Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
July 2022, Volume 16, Number 3

Research Paper

Lactobacillus paracasei Has Anti-Inflammatory Effect on the Heart Failure Induced by Isoproterenol in Rats

Zohreh Hesari[1] Khatereh Kafshdoozan[1*], Parviz Kokhaei[2], Bahador Bagheri[3], Sahar Ghaffari Khaligh[1]

1. Department of Pathobiology, Faculty of Veterinary Medicine, Semnan University, Semnan, Iran.
2. Department of Immunology, Cancer Research Center, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.
3. Department of Pharmacology, Cancer Research Center, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

Use your device to scan and read the article online

How to cite this paper Hesari Z, Kafshdoozan K, Kokhaei P, Bagheri B, Ghaffari Khaligh S. *Lactobacillus Paracasei* Has Anti-Inflammatory Effect on the Heart Failure Induced by Isoproterenol in Rats. Iranian Journal of Toxicology. 2022; 16(3):195-202. http://dx.doi.org/10.32598/IJT.16.3.922.1

http://dx.doi.org/10.32598/IJT.16.3.922.1

Article info:
Received: 10 Dec 2021
Accepted: 09 Mar 2022
Online Published: 01 Jul 2022

*** Corresponding author:**
Khatereh Kafshdoozan, PhD.
Address: *Department of Pathobiology, Faculty of Veterinary Medicine, Semnan University, Semnan, Iran..*
E-mail: *kafshdouzan@semnan.ac.ir*

ABSTRACT

Background: Heart Failure (HF) has become one of the most prevalent cardiovascular problems worldwide. Considering the beneficial effects of probiotics on human health, we aimed to investigate the anti-inflammatory effect of oral administration of *Lactobacillus paracasei* in HF induced by isoproterenol.

Methods: Forty Wistar male rats weighing 80g on average were randomly assigned to five groups of eight each: control, probiotic, HF model, prophylaxis including probiotic + HF, and treatment (HF+probiotic). The rats were treated and examined over 30 days. Heart failure was induced by the subcutaneous injection of isoproterenol (5 mg/kg) once daily for 10 days. At the completion of the study, the ratios of Body, Heart, and Left Ventricle Weights (BW, HW & LVW), serum TNF-α levels, measured by ELISA, myocardial histopathological lesions were determined and compared among the groups. Cardiac hypertrophy was defined by comparing the LVW to total body weight for each animal.

Results: The LVW and LVW/HW ratio were significantly increased in the rats with HF ($P<0.05$). In the treatment group, the LVW/HW and serum TNF-α level were lower compared to those in the HF group. Also, the infiltration of inflammatory cells, necrosis, and myocardial hypertrophy were remarkably lower than those in the HF group.

Conclusion: The study findings indicate that the oral administration of *Lactobacillus paracasei* subsp. paracasei-8700: 2 can reduce the cardiac hypertrophy, failure and inflammation induced by the administration of isoproterenol in rats. Therefore, the study results suggest a novel approach for the management and potential prevention of heart failure.

Keywords: Cardiovascular disease, Cytokines, Dysbiosis, Inflammation, Probiotics, Tumor

Introduction

Heart Failure (HF) is a complex syndrome that is often associated with several concomitant cardiac problems. Cardio-Vascular Disease (CVD), which include Myocardial Infarction (MI), high blood pressure, and chronic inflammatory conditions can affect heart function, leading to a clinical syndrome known as heart failure. Despite new approaches in the pharma-cotherapy, such as angiotensin-converting enzyme and improved lifestyle, CVD remains the leading cause of death and disability in the developed countries [1, 2]. The intestinal microbiota is composed of a complex and

diverse microbial community that plays a significant role in the human health.

Recent studies have shown that any change in the intestinal microbiota may lead to acute or chronic conditions of the host functions. Additionally, on the basis of strong evidence, possible links between HF and intestinal health have been proposed [3, 4]. There are three possible mechanisms that may cause HF secondary to changes in the intestinal microbiota [4, 5]:

a) An increase in harmful intestinal metabolites, such as Trimethylamine N-Oxide (TMAO); which is an endogenous toxin known to be associated with CVD, b) Via endotoxemia caused by a rise in the blood Lipopolysaccharide (LPS) level, and c) Chronic inflammation and cardiometabolic risk factors.

Maintaining or restoring a healthy intestinal microbiota is believed to be a promising intervention that protects against cardiovascular diseases [1]. Probiotics are live organisms that provide beneficial health effects if used appropriately [6]. Studies have shown that probiotics can significantly affect the composition of the intestinal microbiota, diversity, and function [3, 5, 6]. Several probiotic strains are shown to modulate the intestinal immune system by regulating certain metabolites, which promote the growth and function of intestinal epithelial cells [4].

In this context, it has long been known that probiotics have the ability to reduce metabolic disorders and cardiovascular risk factors, such as hypertension and elevated blood cholesterol [4]. In addition, several studies have demonstrated that probiotics reduce inflammation and inhibit myocardial hypertrophy [4-7]. Lactobacillus strains are commonly used as probiotics to treat many clinical conditions. *Lactobacillus paracasei* belongs to the *L. casei* family, and is predominantly isolated from milk and dairy products [8]. Multiple in vitro studies have demonstrated that the molecular mechanisms responsible for the probiotics' immunomodulatory effects are strain-dependent. Thus, these positive effects are not applicable to other strains in the absence of experimental evidence [9].

Aim of the study: Given the beneficial effects of probiotics as discussed above, we aimed to evaluate the effect of *L. paracasei* subsp. 8700:2 on HF induced by isoproterenol, based on serum Tumour Necrosis Factor-α (TNF-α) level and specific histopathological parameters in male Wistar rats.

Materials and Methods

Animal experiments: Forty adult male Wistar rats, weighing 185±15 grams, were obtained from Tehran University of Medical Sciences. Rats were housed in standard stainless-steel cages at an ambient temperature of 23.5±1.5°C and 12 hours of alternating light and dark cycles in the animal house of Semnan University of Medical Sciences, Semnan, Iran. The animals were left undisturbed for one week to be acclimated before starting the experiments. They had free access to tap water and commercial pelleted food. All experimental protocols were performed according to the National Institutes of Health's guidelines (Bethesda, USA), and approved by the Ethics Committee of Semnan University of Medical Sciences (Code: IR.SU.REC.1399.3).

Chemical reagents: *Lactobacillus paracasei* subsp. paracasei 8700:2 was a generous gift provided by Takgene Probiotic Products Company (Tehran, Iran). Isoproterenol and TNF-α Elisa kits were purchased from Sigma Chemical Co. (St. Louis, MO, USA; CAS No. 51-30-9) and Biolegend, (San Diego, USA), respectively.

Experimental design and protocols: Rats were randomly assigned to five groups of eight each (Table 1). We used *Lactobacillus paracasei* subsp. Paracasei-8700:2 (*L. paracasei* subsp-8700:2) at 10^9 CFU count, which were prepared in Takgene probiotic products (Tehran, Iran). The probiotic (500mg) was dissolved in 250mL saline to prepare 2×10^6 CFU/ml. From this solution, A 1ml aliquot was administrated to each rat via gastric gavage (Table 1). The heart failure was induced by isoproterenol, dissolved in normal saline and injected into the rats subcutaneously (5mg/kg) once daily over 10 days [10]. Isoproterenol stimulates both β1 and β2 adrenergic receptors, and lowers peripheral vascular resistance in skeletal muscles, and in renal and mesenteric vasculature [11].

By the end of 4th week, all of the rats were treated with sodium thiopental, and blood samples were collected from their jugular veins. The blood samples were centrifuged at 4000 g for 10 min at 25°C and the sera were separated and stored at -70°C. Subsequently, the animals were sacrificed and the hearts were removed and weighed. The induced cardiac hypertrophy was measured by comparing the weight of the Left Ventricle Weight (LVW) relative to that of the whole Heart Weight (HW). A significant increase in LVW/HW ratio was considered as left ventricular hypertrophy [11].

Measurement of Tumor Necrosis Factor- α (TNF-α): At the end of the study, the TNF-α was quantified in the sera of all rats, using the TNF-α Elisa kit based on the manufacturer's instructions.

Histopathological measurement: After sacrificing the rats, the hearts were removed, weight and fixed in 10% formalin overnight at room temperature. After the fixation, all heart samples were sectioned in transverse and parallel, and were processed and stained with Hematoxylin and Eosin (H&E). The heart tissue slides were prepared and examined by two pathologists, and the data were analyzed in a double-blinded fashion.

All heart slides were examined under light microscopy at both 100X and 400X magnifications. For each myocardial sample, the histological evidence of myocarditis and inflammation was classified by the degree of cellular infiltration; myocardial cell necrosis; extent of calcification and fibrosis, and were graded on a zero to 4+ scales as follows: 0=No or suspicious presence of lesions; 1+ = Limited focally lesion; 2+ to 3+ = Intermediate to severe multiple lesions; and 4+ = Heart failure with extensive tissue lesions.

Statistical analyses: Initially, the data were tested for normality by one sample Kolmogorov-Smirnov. Next, the data were tabulated as the Mean±SE. All data, except those for the serum levels of TNF-α, were analyzed by one-way Analysis of Variance (ANOVA). The TNF-α values were analyzed, using Kruskal-Wallis' test. A $P<0.05$ was considered as significant for the statistical differences. The data analyses were performed on SPSS software, v. 19.

Results

Effect on Body Weight (BW): Table 2 represents the effect of oral administration of *L. paracasei* subsp-8700:2 on the rats' body weight over four weeks. In the group treated with the probiotics, the body weight increased significantly ($P<0.05$). However, the body weight decreased significantly after treatment with probiotic in HF rats compared to those in the probiotics and control groups ($P<0.05$). The rats in the prophylaxis and HF-model maintained similar body weights.

Effect on Heart Weight (HW): There was no statistically significant differences in the Heart Weights (HW) among the study groups.

Effect on Left Ventricular Weight (LVW): The induction of HF markedly increased the LVW in the HF-models as compared to those in the probiotics group ($P<0.05$; Table 2).

Effect on LVW/HW ratio: There was a significant increase in the left ventricle to heart weight ratio in the HF-models ($P<0.05$) as compared to those in the probiotics and prophylaxis groups. The LVW/HW ratio was decreased in the treatment group and reached that of the control group (Table 2).

Effect on pro-inflammatory cytokine TNF-α: As presented in Figure 1, the TNF-α level in rats with heart failure induced by the isoproterenol was higher than those in other groups. The oral intake of *L. paracasei* subsp-8700:2 in the treatment and prophylaxis groups reduced the serum level of TNF-α. However, no significant differences were found in this respect among the study groups.

Effect of probiotics on histopathological scores: The evaluation of the heart tissue samples showed normal shape and arrangement of the myofibrils in the control group. As shown in Figure 2, there was no evidence of hyperemia, hypertrophy, necrosis or fibrosis. The grade assigned to the control group was considered zero.

In the control group, all cardiomyocytes were normal without hyperemia, inflammation or necrosis. In all histopathological sections from the probiotics model group, we observed hyperemia and fatty degeneration. However, the heart myofibrils were arranged normally without hypertrophy, necrosis or fibrosis. Besides, there was no evidence of immune cells infiltration. The grade assigned to the probiotic treatment group was 1+. In the induced HF group (isoproterenol group), there were marked hyperemia, myofibrils hypertrophy, and scattered necrosis with irregular arrangements. Also, mononuclear inflammatory cells were present in these slides. The grade assigned to this group was 4+. In all histopathological sections of the hearts from the prophylaxis group (probiotics + isoproterenol), there were extensive hyperemia, necrosis, fibrosis, and mononuclear inflammatory cells. Thus, the grades assigned to this group were from 3+ to 4+. Finally, myofibrils were arranged normally and the fibrosis was significantly sparse in the treatment group. Also, few mononuclear cell infiltrations were present. Thus, the grade assigned to the treatment group was 2+.

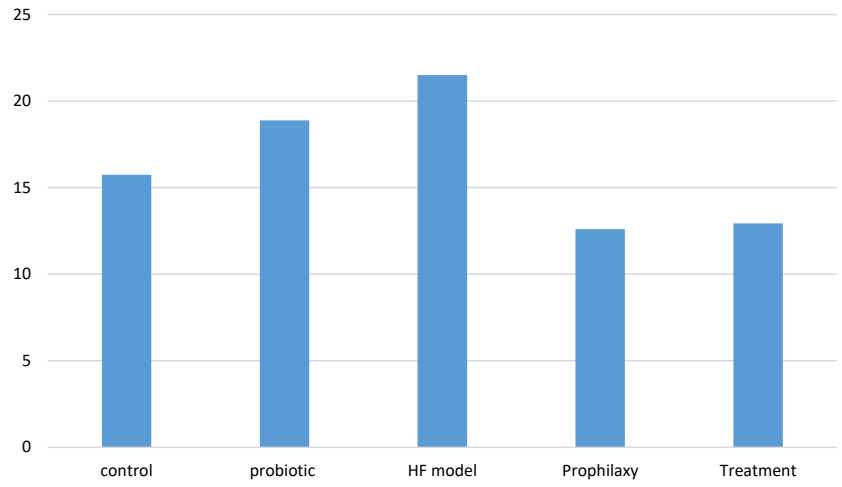

Figure 1. Serum TNF-α levels (pg/ml) among the study groups.

Data are shown as the Mean±SE

Discussion

In light of the widespread incidence of cardiovascular disease, there is a need for innovative prevention and treatment strategies. The etiology of heart failure has been expanded to include multiple pathological conditions that are controlled by numerous cytokines, such as TNF-α. In recent years, intestinal microorganisms have been suggested to be responsible for the development of metabolic diseases, including heart failure. Therefore, any factor that enhances the balance of gut microorganisms is likely to be beneficial for the prevention and management of this condition. In this regard, there is growing evidence on the beneficial effects of the administration of probiotics on the cardiovascular system [3, 4, 6, 7].

Induction of heart failure: In this study, we induced HF through the subcutaneous injection of isoproterenol (5 mg/kg) in rats. Isoproterenol is a synthetic catecholamine β-adrenergic agonist, which in high doses results in severe stress on the rat myocardium. Isoproterenol-induced myocardial injury is caused by the production of highly reactive free radicals, which deplete endogenous antioxidants, damage the lipid membranes, and ultimately cause apoptosis and necrosis of the heart muscle. This approach is acceptable as a universally standard method for assessing cardiac dysfunction [11, 12]. In some studies, coronary ligation has been used to induce myocardial infarction [13, 14]. However, the induction of heart failure through coronary ligation is a complex approach and is associated with high morbidity and mortality. Therefore, we used isoproterenol as an effective and reliable agent to induce infarct-like myocardial injury, mimicking acute heart failure in humans [10, 14].

Lactic acid bacteria are the most commonly used probiotics [8]. More studies have documented the beneficial effects of these bacteria on preventing and/or treating metabolic diseases [5, 9, 12]. As expected, the results of this study showed the administration of *L. paracasei* subsp-8700:2 increased the rats' body weights. However,

Table 1. Organization of study groups

Groups	Days 1-10	Days 11-20	Days 21-30
Normal control	¤	§	§
Probiotic control	ŧ		
Isoproterenol control	❣		
Prophylaxis	ŧ	ŧ	❣
Treatment	❣	ŧ	ŧ

¤=Normal saline (5 mg/kg/day, subcutaneous), §= Normalsaline (1 ml/day, oral), ❣= Isoproterenol (5 mg/kg/day, subcutaneous), ŧ= Probiotic (1 ml/day, oral)

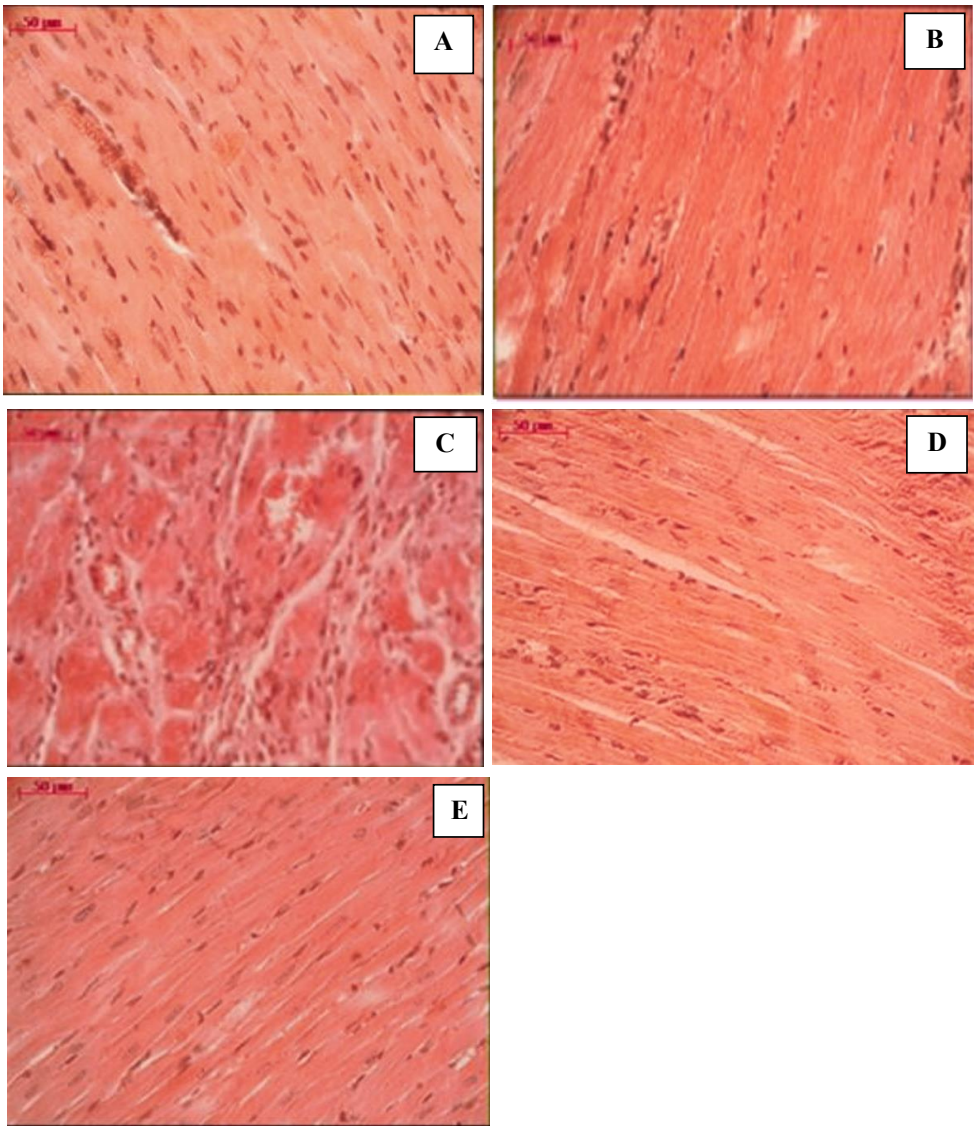

Figure 2. Photomicrographs of rat cardiac apex sections stained with H&E (400X), showing the histopathological changes in the rats' heart tissue samples.

A. Control, B. Heart failure induced by isoproterenol, C. Prophylaxis, D. Probiotic, and E. Treatment.

Table 2. The effect of *L. paracasei* sub spp.paracasie 8700:2 on tissue weight ratios

Groups	Mean±SE				
	Baseline BW (g)	ΔBW (g)	HW (g)	LVW (g)	LVW to HW (g/g)
Control	181.83±12.9	99.16±30.29[a]	0.8142±0.05971	0.4308±0.07485	0.52692±0.065688
Probiotic control	180.25±8.46	117.25±27.82[b]	0.8457±0.10865	0.3879±0.04974[a]	0.45892±0.020623[a]
Heart failure	180.42±18.68	85.28±19.62	0.8175±0.089	0.4657 ±0.040[a]	0.574±0.064927[a,b]
Prophylaxy	180.4±15.04	87.6±36.59	0.8768±0.03312	0.4085±0.04751	0.46532±0.043311[b]
Treatment	181.0±8.81	55.28±11.32[a,b]	0.7742±0.11203	0.3990±0.09466	0.52046±0.116548

Values with similar superscripted letters in each column were significantly different (P<0.05).

the weight gain was significantly lower in the treatment group than those of the control and probiotics groups. Similarly, it has been shown that probiotics can cause weight gain in both animal and human models by modulating the gut microbiota. Million et al. [15] conducted a comparative meta-analysis and assessed the effect of lactobacillus-containing probiotics on weight gain. Their results revealed that the administration of *Lactobacillus acidophilus* resulted in significant weight gain in animals and humans, while *L. ingluviei* and *L. fermentum* contributed to weight gains in animals [15, 16].

In order to determine whether L paracasei subsp-8700:2 reduces certain cardiac changes induced by HF in the rat model, we measured the left ventricular weight ratio relative to the heart weight (LVW/HW) in each group. An increase in this ratio reflected myocardial hypertrophy [11]. As shown in Table 2, the increase in the LVW/HW ratio in the HF group indicated a strong hypertrophic reaction induced by isoproterenol. However, the rats treated with *L. paracasei* showed a ratio resembling that of the control group. Interestingly, the ratio was also similar to those noted in the probiotics and prophylaxis groups. These findings suggest that *L. paracasei* has beneficial effects on the prevention and treatment of the heart failure due to isoproterenol. However, the histological evaluations in the prophylaxis group showed hyperemia, necrosis, fibrosis, and infiltration of mononuclear inflammatory cells, although the degree of tissue damages were not as large as those observed in the heart failure group. Considering the tissue alterations in the prophylaxis group, it was likely that isoproterenol induced myocardial damages shortly after injection into the rats.

Therefore, the administration of L. parascasei did not result in beneficial effects based on the histopathological findings. Further, the changes in the bodyweight of rats in the prophylaxis and HF groups were similar. Consistent with these results, Gan et al. [7] have evaluated the role of *L. rhamnosus* in the development of myocardial hypertrophy in rat model. Their results indicated that rats under the probiotic regimen showed remarkable attenuation of left ventricular hypertrophy and the gene expression for atrial natriuretic peptide [7]. Additionally, another study in rats [14] has shown that the oral consumption of four probiotic strains causes significant reductions in myocardial necrosis, edema, and infiltration of inflammatory cells. These probiotics are *L. casei*, *L. acidophilus*, *L. rhamnosus*, and *L. bulgaricus*. These findings were documented after inducing heart failure with isoproterenol compared to those noted in the normal group.

Abd-el Hamid et al. [17] claimed that probiotics mitigated skeletal muscle atrophy in isoproterenol-induced heart failure rats by lowering the angiotensin-II, thus providing antioxidant, anti-fibrotic, anti-hypertrophic, and hyperglycemic effects [17]. Since isoproterenol causes myocardial infarction by producing highly cytotoxic free radicals, as observed in the current study, it is believed that the mechanism for the beneficial effects of L. parascasei is linked to its antioxidant activity [14]. Even though the antioxidant mechanisms are not fully understood, the production of antioxidant metabolites and enzymes, such as glutathione, folate, superoxide dismutase, and catalase are thought to be implicated. In addition, probiotics are likely to have antioxidant property through which they chelate metal ions [18].

Considering that normal cardiomyocytes do not release TNF-α, this factor is an essential pro-inflammatory cytokine that leads to HF via pathophysiologic pathways. It is known that mononuclear macrophages and cardiomyocytes release large amounts of TNF-α in response to heart attacks, anoxia, and cardiac ischemia. Moreover, it has been observed that a direct correlation exists between serum TNF-α levels and the HF severity [19, 20].

Cardiomyocyte hypertrophy increases the release of TNF-α and collagen production [21]. In the present study, the TNF-α levels increased in the HF group compared to that noted in the control group, in which treatment with *L. paracasei* decreased the serum TNF-α level. This finding is consistent with that reported by previous studies that described the immunomodulatory mechanism of action of probiotics [21, 22]. One explanation is that L. paracasei can reduce persistent reperfusion injury mediated by the inflammatory response, interfere with the activation of Nuclear transcription Factor κB (NF-κB), and prevent the expression of pro-inflammatory cytokine, TNF-α. Nuclear transcription factor κB is a proinflammatory mediator that plays an important role in the production of cytokines. Besides, TNF-α upregulates the expression of NF-κB, Cyclooxygenase 2 (COX-2), and inducible Nitric Oxide Synthase (iNOS), leading to the progression of HF [21-25].

Although strong evidence has revealed that excessive expression of TNF after MI causes adaptive myocardial hypertrophy, the role of TNF in the pathogenesis of HF is not fully understood. Thus, the potential utilization of TNF for therapeutic purposes requires further studies [20]. In this context, it should be noted that despite the known beneficial effect of probiotics, serious infections have been reported in children from the use of probiotics recently especially in cases of immunodeficiency [26].

Conclusion

The results of this study demonstrated that the oral administration of *Lactobacillus paracasei* subsp-8700:2 possessed cardioprotective effects due to its ability to decrease the inflammatory response and to reduce the serum TNF-α levels in isoproterenol-induced heart failure in rat model. These results suggest that using viable probiotic supplements may be useful in the management of cardiac injury in cases carrying the risk of myocardial infarction. However, more studies are warranted to confirm this hypothesis. The findings of this study provide new insights into the development of novel therapeutic strategies toward the management of cardiovascular disease.

Ethical Considerations

Compliance with ethical guidelines

All experimental protocols were performed according to the National Health Guidelines, USA, and approved by the Ethics Committee of Semnan University of Medical Sciences (Code: IR.SU.REC.1399.3).

Funding

The present manuscript was extracted from the DVM thesis of the first author at the Department of Pathobiology, Faculty of Veterinary Medicine, Semnan University of Medical Sciences.

Authors' contributions

Conceptualization and supervision: Parviz Kokhaei, Khatereh Kafshdouzan; Methodology: Bahador Bagheri; Histopathological examinations: Sahar Ghaffari Khaligh; Data collection, investigation and writng of original draft: Zohreh Hesari; Data analysis and writing, review and editing: Khatereh Kafshdouzan.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgements

We would like to thank the faculty and staff of the Physiology Research Center of Medical Sciences for their assistance with this project.

References

[1] Moludi J, Alizadeh M, Davari M, Golmohammadi A, Maleki V. The efficacy and safety of probiotics intervention in attenuating cardiac remodeling following myocardial infraction: Literature review and study protocol for a randomized, double-blinded, placebo-controlled trial. Contemp Clin Trials Commun. 2019; 15:100364. [DOI:10.1016/j.conctc.2019.100364] [PMID] [PMCID]

[2] DiRienzo DB. Effect of probiotics on biomarkers of cardiovascular disease: Implications for heart-healthy diets. Nutr Rev. 2014; 72(1):18-29. [DOI:10.1111/nure.12084] [PMID]

[3] Costanza AC, Moscavitch SD, Faria Neto HC, Mesquita ET. Probiotic therapy with Saccharomyces boulardii for heart failure patients: A randomized, double-blind, placebo-controlled pilot trial. Int J Cardiol. 2015; 179:348-50. [PMID]

[4] Vasquez EC, Pereira TMC, Peotta VA, Baldo MP, Campos-Toimil M. Probiotics as beneficial dietary supplements to prevent and treat cardiovascular diseases: Uncovering their impact on oxidative stress. Oxid Med Cell Longev. 2019; 2019:3086270. [PMID] [PMCID]

[5] Liu Y, Fatheree NY, Mangalat N, Rhoads JM. Lactobacillus reuteri strains reduce incidence and severity of experimental necrotizing enterocolitis via modulation of TLR4 and NF-κB signaling in the intestine. Am J Physiol Gastrointest Liver Physiol. 2012; 302(6):G608-17. [PMID] [PMCID]

[6] Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. Therap Adv Gastroenterol. 2013; 6(1):39-51. [DOI:10.1177/1756283X12459294] [PMID] [PMCID]

[7] Gan XT, Ettinger G, Huang CX, Burton JP, Haist JV, Rajapurohitam V, et al. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. Circ Heart Fail. 2014; 7(3):491-9. [PMID]

[8] Batt CA, Tortorello L, Patel P. Encyclopedia of food microbiology. Amsterdam: Elsevier Science; 2014. https://www.google.com/books/edition/Encyclopedia_of_Food_Microbiology/1b1CAgAAQBAJ?hl=en&gbpv=0

[9] Xu Y, Tian Y, Cao Y, Li J, Guo H, Su Y, et al. Probiotic properties of Lactobacillus paracasei subsp. Paracasei L1 and its growth performance-promotion in chicken by improving the intestinal microflora. Front Physiol. 2019; 10:937. [DOI:10.3389/fphys.2019.00937] [PMID] [PMCID]

[10] Siddiqui MA, Ahmad U, Khan AA, Ahmad M, Badruddeen KM, Akhtar J. Isoprenaline: A tool for inducing myocardial infarction in experimental animals. Int J Pharm. 2016; 6(2):138-44. https://www.researchgate.net/publication/301214358

[11] Sun JM, Wang CM, Guo Z, Hao YY, Xie YJ, Gu J, et al. Reduction of isoproterenol-induced cardiac hypertrophy and modulation of myocardial connexin43 by a KATP channel agonist. Mol Med Rep. 2015; 11(3):1845-50. [DOI:10.3892/mmr.2014.2988] [PMID]

[12] Lobo Filho HG, Ferreira NL, Sousa RB, Carvalho ER, Lobo PL, Lobo Filho JG. Experimental model of myocardial infarction induced by isoproterenol in rats. Rev Bras Cir Cardiovasc. 2011; 26(3):469-76. [PMID]

[13] Goldman S, Raya TE. Rat infarct model of myocardial infarction and heart failure. J Card Fail. 1995; 1(2):169-77. [DOI:10.1016/1071-9164(95)90019-5]

[14] Sadeghzadeh J, Vakili A, Sameni HR, Shadnoush M, Bandegi AR, Zahedi Khorasani M. The effect of oral consumption of probiotics in prevention of heart injury in a rat myocardial infarction model: A histopathological, hemodynamic and biochemical evaluation. Iran Biomed J. 2017; 21(3):174-81. [DOI:10.18869/acadpub.ibj.21.3.174] [PMID] [PMCID]

[15] Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. Microb Pathog. 2012; 53(2):100-8. [DOI:10.1016/j.micpath.2012.05.007] [PMID]

[16] Angelakis E, Raoult D. Gut microbiota modifications and weight gain in early life. Hum Microbiome J. 2018; 7:10-4. [DOI:10.1016/j.humic.2018.01.002]

[17] Abd-El Hamid MS, Mohamed AE. Probiotics mitigates skeletal muscle atrophy in isoproterenol-induced heart failure adult rats; by increasing IGF-I Gene expression and improving insulin sensitivity. Med J Cairo Univ. 2019; 87(5):2907-24. [DOI:10.21608/mjcu.2019.59330]

[18] Lee J, Hwang KT, Chung MY, Cho DH, Park CS. Resistance of lactobacillus casei KCTC 3260 to reactive oxygen species (ROS): Role for a metal ion chelating effect. J Food Sci. 2005; 70(8):m388-91. [DOI:10.1111/j.1365-2621.2005.tb11524.x]

[19] Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: The Framingham Heart Study. Circulation. 2003; 107(11):1486-91. [DOI:10.1161/01.CIR.0000057810.48709.F6] [PMID]

[20] Anker SD, Von Haehling S. Inflammatory mediators in chronic heart failure: An overview. Heart. 2004; 90(4):464-70. [DOI:10.1136/hrt.2002.007005] [PMID] [PMCID]

[21] Tian M, Yuan YC, Li JY, Gionfriddo MR, Huang RC. Tumor necrosis factor-α and its role as a mediator in myocardial infarction: A brief review. Chronic Dis Transl Med. 2015; 1(1):18-26. [DOI:10.1016/j.cdtm.2015.02.002]

[22] Lescheid DW. Probiotics as regulators of inflammation: A review. Funct Foods Health Dis. 2014; 4(7):299-311. [DOI:10.31989/ffhd.v4i7.2]

[23] Bartekova M, Radosinska J, Jelemensky M, Dhalla NS. Role of cytokines and inflammation in heart function during health and disease. Heart Fail Rev. 2018; 23(5):733-58. [DOI:10.1007/s10741-018-9716-x] [PMID]

[24] Boarescu PM, Chirilă I, Bulboacă AE, Bocșan IC, Pop RM, Gheban D, et al. Effects of curcumin nanoparticles in isoproterenol-induced myocardial infarction. Oxid Med Cell Longev. 2019; 2019:7847142. [DOI:10.1155/2019/7847142] [PMID] [PMCID]

[25] Hajighorbani M, Ahmadi-Hamedani M, Shahab E, Hayati F, Kafshdoozan K, Keramati K, et al. Evaluation of the protective effect of pentoxifylline on carrageenan-induced chronic non-bacterial prostatitis in rats. Inflammopharmacology. 2017; 25(3):343-50. [DOI:10.1007/s10787-017-0335-2] [PMID]

[26] Pruccoli G, Silvestro E, Pace Napoleone C, Aidala E, Garazzino S, Scolfaro C. Are probiotics safe? Bifidobacterium bacteremia in a child with severe heart failure. Infez Med. 2019; 27:175-8. https://www.researchgate.net/profile/Carlo-Pace-Napoleone/publication/333853508_Are_probiotics_safe_Bifidobacterium_bacteremia_in_a_child_with_severe_heart_failure/links/5d259d4e92851cf44074e41d/Are-probiotics-safe-Bifidobacterium-bacteremia-in-a-child-with-severe-heart-failure.pdf