Role of *Lactobacillus plantarum* to Attenuate Cardiac Disorder

Maham Fatima[1], Sabahat Amin[1], Fatima Iftikhar[2], Maryam Amanullah[1], Muzna Abid[1], Nimra Arshad[1], Iqra Ahram[1], Muhammad Saeed[1,*], Mian Kamran Sharif[1,*] and Faneela Sajjad[1]

[1]National Institute of Food Science and Technology, University of Agriculture Faisalabad, Pakistan
[2]Department of Food and Nutritional Sciences, Arid Agriculture University, Rawalpindi, Pakistan
*Corresponding author: drmsaeed@uaf.edu.pk; mks@uaf.edu.pk

Abstract

Cardiac disorder (CD) is a significant global health issue, with 17.9 million deaths in 2019. Probiotics and prebiotic foods have emerged as a potential solution to protect individuals against CD. *Lactobacillus spp*., a potentially probiotic strain, can help maintain lipid levels, blood pressure, and blood glucose equilibrium and normalize metabolic disorders, exhibiting anti-cardiac potential. *Lb. plantarum* can be used as a fermentation strain for various food categories, including cereals, dairy, meat, vegetables, and fruits. Studies show that fermented meals with *Lb. plantarum* have enhanced health profits, including improved antioxidant capacity and increased active ingredient substance. *Lb. plantarum* can also reduce blood pressure by obstructing angiotensin-converting enzyme (ACE) activity and γ-aminobutyric acid (GABA) activity. It can also modulate serum glucose levels and impede diabetes by affecting the comparative abundance of gut microbial species. *Lb. plantarum* can also modulate signaling pathways via gut microbiota, enhancing glucose utilization and acclimating to glucose-limited environments. Elevated cholesterol is a risk factor for cardiac disorders, and probiotics derived from food sources or intestinal flora have significant therapeutic properties. *Lb. plantarum* has shown substantial lowering-cholesterol efficacy in vitro and in vivo, modulating lipid metabolism via signaling pathways and enhancing the presence of beneficial microbes.

Keywords: Cardiac disorder, Probiotics, *Lactobacillus plantarum*, Cholesterol, Blood Pressure

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Introduction

Cardiac disorder (CD) has become increasingly frequent and complex with the advancement of modern life. CD significantly contributes to worldwide mortality, with an anticipated 17.9 million deaths (32.13%) attributed in 2015, compared to 12.3 million fatalities (25.8%) in 1990 (WHO, 2021). According to Global Burden of Disease (GBD) data for Pakistan, there was a 29% rise in death and disability attributable to ischemic heart disease (IHD) between 2009 and 2019. Stroke-related mortality and disability rose by 20%. As depicted in Figure 1, cardiac health depends on a variety of complex factors. Diseases, illnesses, individual lifestyles, as well as living environments, all influence our cardiac health. It is the predominant complication in specific conditions, such as diabetes, and has now emerged as a primary reason for mortality among individuals with diabetes mellitus (Khanal et al., 2022).

Given these circumstances, alongside the pressing demand for novel effective medications, the advancement of probiotics and prebiotic foods has emerged as a viable method to safeguard individuals against cardiac disorder (CD). Probiotics are defined as "live microorganisms that, when administered in sufficient quantities, provide a health benefit to the host" (Fenster et al., 2019). *Lactobacillus spp.* are broadly recognized as probiotics due to their characteristic probiotic attributes (Rasika et al., 2021). *Lactobacillus plantarum* (*Lb. plantarum*) also called *Lactiplantibacillus plantarum* is a species within the *Lactobacillus* genus, that has been considered to have probiotic potential. Certain strains of *Lb. plantarum* may assist in maintaining the equilibrium of blood pressure along with its glucose and lipids levels, as well as regulating metabolic disorders (Wu et al., 2019), thereby exhibiting anti-cardiac potential. Probiotics must be introduced into the human gastrointestinal system using carriers, which typically include food products and capsules. Food products offer superior marketing and acceptance than encapsulation technology. An efficient technique for the production of probiotic foods is fermentation. Given its potential as a probiotic, some foods, including cereals, dairy products, meat, vegetables, and fruits, can be fermented using *Lactobacillus plantarum*. Research indicates that the meals fermented using *Lb. plantarum* possesses enhanced health advantages, including improved antioxidant capacity and increased active ingredient content (Kimoto-Nira et al., 2019; Oh et al., 2020).

2. Possible Mechanism of *Lb. plantarum* in Counteracting Cardiac Disorder

2.1. Antioxidant Properties

Research has associated free radical production with the onset of cardiac disorder (CD). Multiple strains of *Lb. plantarum* possesses a free radical scavenging ability that shows its antioxidant potential. The process of antioxidation by *Lb. plantarum* is diverse and intricate. For instance, Nrf_2 is a protein that modulates intrinsic antioxidant systems while its corresponding HO-1 gene encodes a principal antioxidant enzyme that mostly promotes the metabolism and breakdown of heme into CO, ferrous ions, and biliverdin. *Lb. plantarum* JM113 has been observed to elevate the mRNA levels of this protein, thereby facilitating antioxidation (Yang et al., 2017). *Lb. plantarum* KCCP11226 is capable of synthesizing the C-30 carotenoid 4,4'-diaponeurosporene, which possesses antioxidant properties (Kim et al., 2021; Kim et al., 2019).

Superoxide anion radical, DPPH radical, and hydroxyl radical have been documented to be directly neutralized by *Lb. plantarum* DM5 (Das and Goyal, 2015). Table 1 summarizes additional pathways through which *Lb. plantarum* exerts its antioxidant effect.

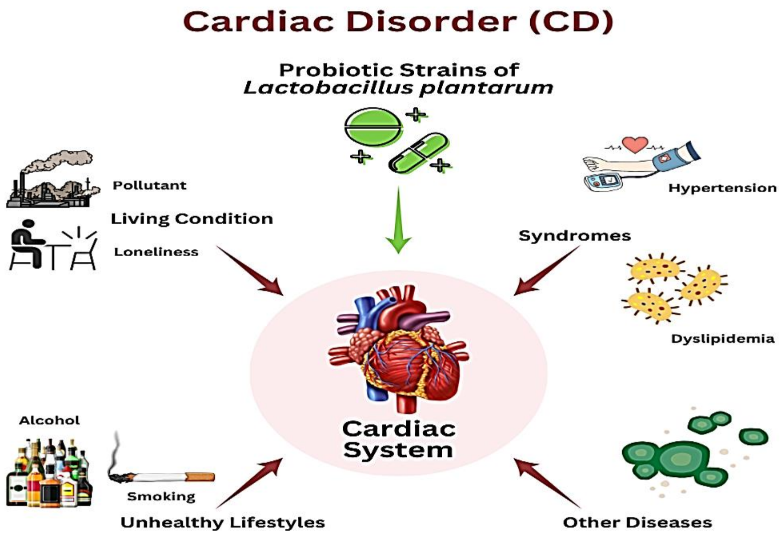

Fig. 1: Determinants of Cardiac Disorder

Table 1: *Lb. plantarum* Pathway Exerts its Antioxidant Properties (Wang et al., 2022)

Strains of *Lb. plantarum*	Resource	In vivo studies (I) or in vitro studies (II)	Mechanism for Antioxidation
Lb. plantarum CCFM10	Various storage facilities (strains of edible fungi)	I	Elevate the levels of CAT, GSH, TOC, and SOD in the serum of oxidatively damaged mice
Lb. plantarum RS15-3	Various storage facilities (strains of edible fungus)	I	Elevate the levels of CAT, GSH, TOC, and SOD in the serum of oxidatively damaged mice
Lb. plantarum CCFM242	Various storage facilities (strains of edible fungi)	I	Boost the liver's overall antioxidant capability
Lb. plantarum Y-20	Naturally fermented chopped pepper	I	Support the Caco-2 cells' enzymatic and non-enzymatic antioxidant mechanisms of defense to prevent damage from oxidative stress and H_2O_2
Lb. plantarum ATCC 14917, NCFM, and NDC 75017		I	Reduce the level of MDA in liver, brain, and serum while increasing GSH-Px activity, SOD activity, and concentration of T-AOC
Lb. plantarum FEED8	Intestinal tract of old people in Guangxi and Bama	I	Elevate glutathione (GSH) levels and other markers
Lb. plantarum JMCC0017	Dairy products fermented traditionally in Xinjiang	I	Metabolites exhibit strong antioxidant properties
Lb. plantarum CBB	Tofu prepared from traditionally fermented milk in Inner Mongolia	I	Modulate the activity of intracellular antioxidant enzymes in Caco-2 cells damaged from oxidative stress
Lb. plantarum KM1	Naturally fermented products	I	Scavenge DPPH radical, hydroxyl radical, and superoxide onion radical
Lb. plantarum AR501		I	Scavenge superoxide onion radical, DPPH, and hydroxyl radical
Lb. plantarum SM4	Kimchi fermented with *Taraxacum coreanum*	I	Increase the mRNA levels of Nrf_2 and its corresponding downstream HO-1 gene
Lb. plantarum NCB		I	Increased expression of antioxidant genes
Lb. plantarum KLDS1.0202	Cheese like cheddar cheese	II	Generate C-30 carotenoid 4,4'-diaponeurosporene
Lb. plantarum ZLP001		II	Develop a *T. coreanum* white fermented product with improved oxidation resistance and bioactive capacities
Lb. plantarum from traditional sourdough	Traditionally prepared sourdough	I	*Lb. plantarum* ZLP001 supplementation raises serum levels of glutathione peroxidase ($p<0.01$), superoxide dismutase ($p<0.05$), and catalase ($p<0.10$) while lowering malondialdehyde ($p<0.05$)

Another *Lb. plantarum* strain, however, may possess multiple distinct antioxidant pathways. For example, NJAU-01 strain of *Lb. plantarum* can modulate the diversity of gut microflora and alter the protein expression in various pathways of metabolism to protect the organism from oxidative stress. Additionally, its extracts exhibit strong antioxidant properties (Ge et al., 2021). This gives an idea of the possibility for antioxidant effects sourced from *Lb. plantarum* in humans.

2.2. Blood Pressure Reduction

Hypertension is defined by a blood pressure (BP) of ≥130mmHg in systolic and/or a BP of ≥80mmHg in diastolic (Welton et al., 2018). Over the past couple of years, this condition has experienced a substantial increase in prevalence. Unhealthy lifestyles that are composed of high-salt diets, low intake of potassium, alcohol consumption, overweight, hypertension, and not having any routine exercise, have been one of the leading causes of CD (Mills et al., 2020). According to Statistics from Forouzanfar et al. (2017). Hypertension was responsible for 7.8 million fatalities which accounted for 14% of the total deaths during 2015.

Angiotensin-converting enzyme (ACE) is involved in the regulation of blood pressure. Enhanced activity of ACE increases blood pressure because it causes stimulation of angiotensin production, leading to vasoconstriction. According to the recent research, the fermented food using *Lb. plantarum* may have a potential effect on lowering the blood pressure of the patients. A comprehensive review and analysis of relevant independent studies revealed that hypertension patients who consumed supplementation of *Lb. plantarum* experienced an obvious reduction in diastolic blood pressure as compared to non-hypertensive individuals (Lewis-Mikhael et al., 2020). Furthermore, Chen et al. (2018) reported that the use of *Lb. plantarum* 69 to ferment goat milk could prevent ACE activity, achieving an 88.91% inhibition rate. The mechanism by which *Lb. plantarum* lowers blood pressure and reduces ACE activity is illustrated in Figure 2. Nonetheless, the influence of gastric enzymes is occasionally disregarded by scientists in in-vitro studies; hence, certain findings from these trials will be further elucidated through in vivo examinations.

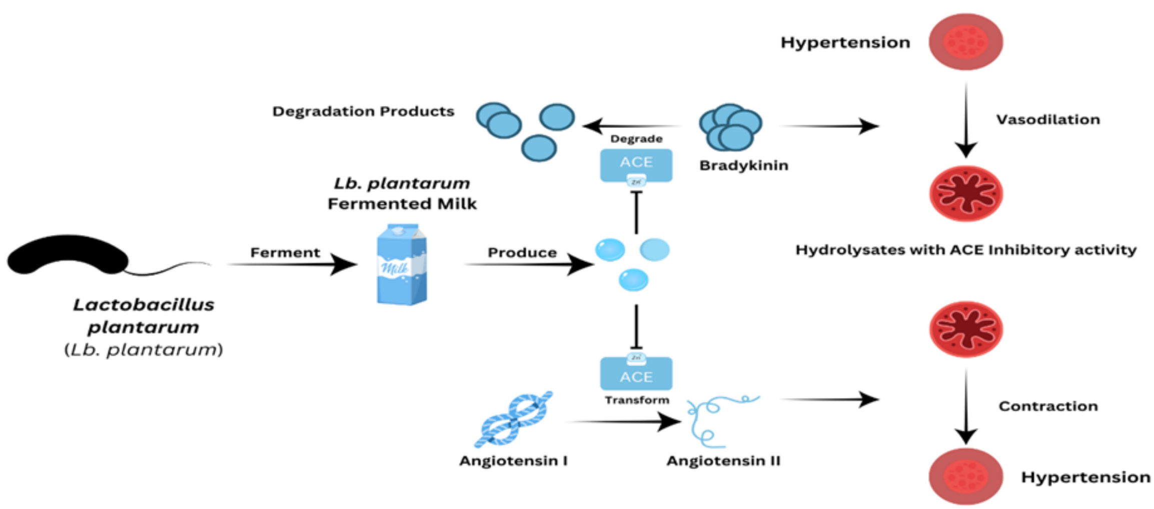

Fig. 2: *Lactobacillus plantarum* Fermented Food Lowers Blood Pressure

In the meantime, γ-aminobutyric acid (GABA), a non-protein amino acid, can reduce blood pressure. According to some research studies, GABA can lower high levels of blood pressure in both humans and animals (Diana et al., 2014). LAB cells produce significant quantities of GABA because the GAD enzyme, which is essential for the synthesis of GABA, is very active in their cells. According to Zareian et al. (2015), fermenting the batter of dosa, wheat-based rice, for 120 hours with *Lb. plantarum* MNZ can increase the GABA levels of the dosa (by roughly 143mg/kg). Use of different strains of *Lb. plantarum* to ferment lentils and milk can also give some concentration of GABA.

2.3. Lowering Glucose

The blood glucose level is referred to as the glucose level of the blood serum. A normal level of serum glucose in the blood is crucial for sustaining the metabolism of the body as well as the fundamental operations of all body organs. Consequently, abnormal glucose levels in the blood, whether elevated or diminished, might adversely affect a person's health. Hyperglycaemia will elevate the chances of diabetes, impair immune function, and contribute to cardiovascular disease. If the body does not promptly consume the glucose level, it may result in diminished energy levels, fatigue, and sadness. *Lb. plantarum* can modulate the glucose levels, impeding diabetes (Hutt et al., 2015).

Many related tests were performed to verify the hypoglycaemic effects of *Lb. plantarum* while investigating the mechanism behind it. The precise mechanism of lowering glucose still needs clarification, but the closest plausible hypothesis pertains to gut bacteria. Lin et al. (2020) demonstrated alterations in glucose levels in *Lb. plantarum*-treated piglets, and further on, they characterized the microbiome in faecal samples. They found that *Lb. plantarum* influence on glucose homeostasis may be related to higher relative variation of microbial species within the gut *Lb. plantarum*. *Lactobacillus* can modify the gut microbiome of the host, *plantarum* which leads to an increase in some glucose forms, reflecting reduced glucose reabsorption and a reduce in glycated haemoglobin (HbA1c) levels and fasting glucose concentrations. Moreover, the improvement in glucose tolerance is also associated with the changes in AMPK and kinase B (Akt) phosphorylation status and with the changes in the mRNA expression levels of G6Phase and PEPCK, thus resulting in decreased glucose production. Figure 3 depicts the hypothetical mechanism by which gut microbes move glucose metabolism.

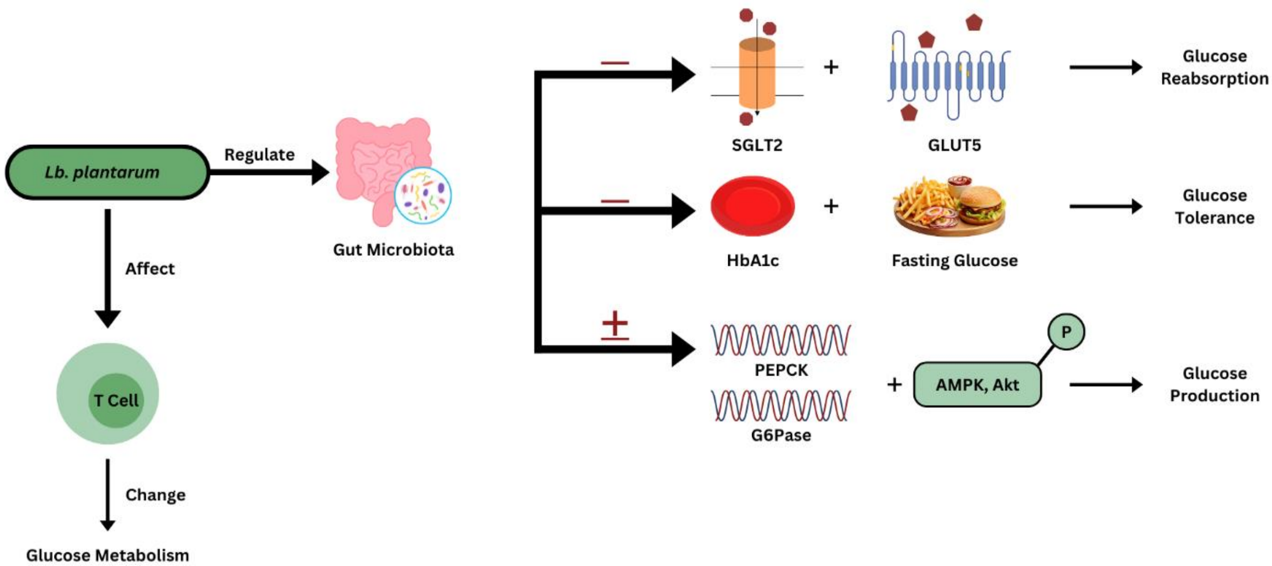

Fig. 3: *Lb. plantarum* Maintaining Glucose Level

It has been established that *Lb. plantarum* can modulate the signalling pathways through gut microbiota (Lee et al., 2018). Mice fed with *Lb. plantarum* HAC01 had reduced the levels of glycated haemoglobin (HbA1c) and fasting glucose and passed the OGTT test well, thereby indicating the action of the strain against hyperglycaemia and its potential to ameliorate glucose intolerance. The proteins involved in glucose metabolism in the liver and gene expression research found that it increases AMPK and Akt phosphorylation, reduces the mRNA expression of G6Pase and PEPCK, and influences the endogenous production of glucose in the liver (Lee et al., 2021). Certain studies demonstrate that *Lb. plantarum* can enhance glucose utilization. Rats subjected to a diet high in fructose demonstrated overexpression of the fructose transporter GLUT5 and the glucose transporter SGLT2, perhaps resulting in elevated fructose levels in their blood and kidneys. The supplementation of *Lb. plantarum* may inhibit glucose reabsorption (Korkmaz et al., 2019). In addition to glucose utilization, *Lb. plantarum* may acclimatize to low-glucose environments. Studies on the proteomic and genotypic changes in *Lb. plantarum* P-8 brought on by three years of glucose deprivation looked at a variety of survival strategies, such as cell envelope modifications, phosphotransferase system activation, amino acid accumulation, and utilization, decreased glucose uptake, and increased ATP or glucose production in response to glucose scarcity (He et al., 2018).

2.4. Lipid Lowering

Elevated cholesterol is a risk factor for a cardiac disorder, which can lead to many high-mortality conditions, including hyperlipidemia and atherosclerosis. Atherosclerosis is a persistent inflammatory condition, frequently associated with endothelial dysfunction, lipid accumulation in the endothelium, apoptosis, necrosis, and proliferation of smooth muscle cells, alongside systemic and localized inflammation including both adaptive and innate immunity (Herrero-Fernandez et al., 2019). Hypercholesterolemia is a pathological condition characterized by low-density lipoprotein (LDL), triglyceride (TG), and total cholesterol (TC) levels surpassing established thresholds, while high-density lipoprotein (HDL) levels fall below the normative range (Zhang et al., 2017). The primary cause of these disorders is the buildup of cholesterol in the arteries. According to research, a 1% decrease in serum cholesterol levels can reduce the incidence of coronary disease (CD) by 2-3%, particularly when HDL cholesterol is increased, and LDL cholesterol is decreased. The goal for LDL-cholesterol (LDL-C) in individuals with atherosclerosis is less than 1.80mmol/L (less than 70mg/dL), or a 50% reduction if the baseline level falls between 1.80 and 3.50mmol/L (between 70 and 135mg/dL) (Hasenfuss et al., 2018).

Consequently, contemporary medicine posits that identifying pharmaceuticals capable of lowering lipid concentrations in the blood and liver is an efficacious strategy for preventing cardiac disorder (CD). Currently, pharmacological interventions, particularly statins, which are 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase inhibitors, are predominant therapies employed to efficiently reduce cholesterol levels, particularly LDL-C. Nonetheless, these medications are costly and include detrimental side effects, including liver enzyme irregularities and rhabdomyolysis (Qu et al., 2020). Consequently, researchers want to identify a safe, naturally derived molecule as a substitute for pharmaceuticals. Probiotics derived from food sources or intestinal flora possess significant therapeutic properties and can serve as functional strains in the prevention and treatment of several diseases. Moreover, the majority of *Lactobacilli* are classified as Generally Recognized as Safe (GRAS) and have a longstanding record of safe utilization, exhibiting fewer adverse effects and a superior safety profile in comparison to pharmaceuticals. Colautti et al. (2022). *Lb. plantarum* exhibits substantial cholesterol-lowering efficacy both *in vivo* and *in vitro*, dramatically enhancing blood cholesterol levels and diminishing illness risk (Wang et al., 2014; Tang et al., 2016; Ding et al., 2017).

Extensive research has established *Lb. plantarum*'s capacity to lower cholesterol levels in vitro, and studies have confirmed its possible processes. Bile salt hydrolase (BSH) enzymatically deconjugates bile acids, cholesterol is integrated into probiotics, cholesterol is integrated into probiotic cell membranes in relation to growth, cholesterol co-precipitates with deconjugated bile, short-chain fatty acids are formed during fermentation, and cholesterol reductase converts cholesterol into coprostanol. (Lye et al., 2010; Ooi and Liong, 2010). Nonetheless, the in vivo mechanism of lipid reduction remains inadequately elucidated. The potential processes are summarized as follows: (1) Modification of lipid metabolism through signalling pathway manipulation; (2) using conjugated linoleic acid (CLA) isomerase to reduce cholesterol; (3) decrease in cholesterol made possible by bile acids; (4) intestinal microbiota modification to control lipid metabolism.

2.4.1. Signalling Pathway

Probiotic *Lactobacillus plantarum* can influence lipid metabolism through multiple signaling pathways; one notable example is the AMPK signalling system (Qu et al., 2016). *Lb. plantarum* can control the production of cholesterol and fatty acids by changing the expression of downstream proteins and activating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK). Lee et al. (2018) found in earlier studies that *Lb. plantarum* does not alter AMPK mRNA expression but covalently modifies the AMPK pathways to activate them. Increasing the phosphorylation levels of AMPK through covalent modification will increase the activity of *Lb. plantarum*. Lipid synthesis is also repressed by AMPK-activated AMPK as the former can stop acetyl-CoA carboxylase (ACC), which in turn is the amplifier of AMPK, hence an enzyme vital for fatty acid synthesis. In addition, due to the AMPK signaling which helps in promoting peroxisome proliferator-activated receptor-alpha (PPARα), the AMPK signaling thereby enhances fatty acid oxidation. It avoids the accumulation of fatty acids as triglycerides (Leung et al., 2016). Studies have demonstrated that *Lb. plantarum* can suppress the expression of lipogenic proteins in hepatic tissue, such as stearoyl-CoA desaturase 1 (SCD-1) and sterol regulatory element-binding protein 1c (SREBP-1c) (Tang et al., 2020). This indicates that *Lb. plantarum* can modulate hepatic lipid metabolism at least partially through the AMPK system, reducing lipid production and enhancing fatty acid oxidation.

Many species of *Lb. plantarum* have been shown to have this mechanism. Teng et al. (2020) tested the LP104 strain of *Lb. plantarum*, which was isolated from kimchi. The mice were randomly divided into one of three groups: NFD, LP104 + HFD, or HFD. The *Lb. plantarum* 104 + HFD group possessed greater AMPK phosphorylation with decreased levels of ACC compared with the HFD group. Concurrently, the expression of PPARα greatly increased, but that of lipogenic proteins, such as SCD-1 and SREBP-1c, dramatically decreased. Correspondingly, data obtained showed that *Lb. plantarum* LP104 supplementation strongly suppressed the elevated levels of TG, LDL, and TC levels induced by a diet rich in fats. Identical results have been seen in *Lb. plantarum* NA136 (Zhao et al., 2019), *Lb. plantarum* S58 (Tang et al., 2020), and *Lb. plantarum* NCU116 (Xu et al., 2020).

2.4.2. Bile Acid

Lactobacillus plantarum can help reduce cholesterol levels in serum by the action of bile acids. One component of bile is bile acid, which is frequently present in alkaline bile as a potassium or sodium salt that is referred to as bile salt. The control of the blood cholesterol levels is closely related to the bile salt. Medical studies indicate that the amount of bile acid is markedly elevated in individuals with fatty liver, hyperlipidaemia, and non-alcoholic steatohepatitis compared to healthy individuals (Rosso et al., 2018). Given that cholesterol serves as a base for the production of bile salts, enhancing bile salts breakdown may reduce the levels of cholesterol effectively. The two methods through which *Lb. plantarum* lowers cholesterol levels and modifies bile acid concentrations are shown in Figure 4.

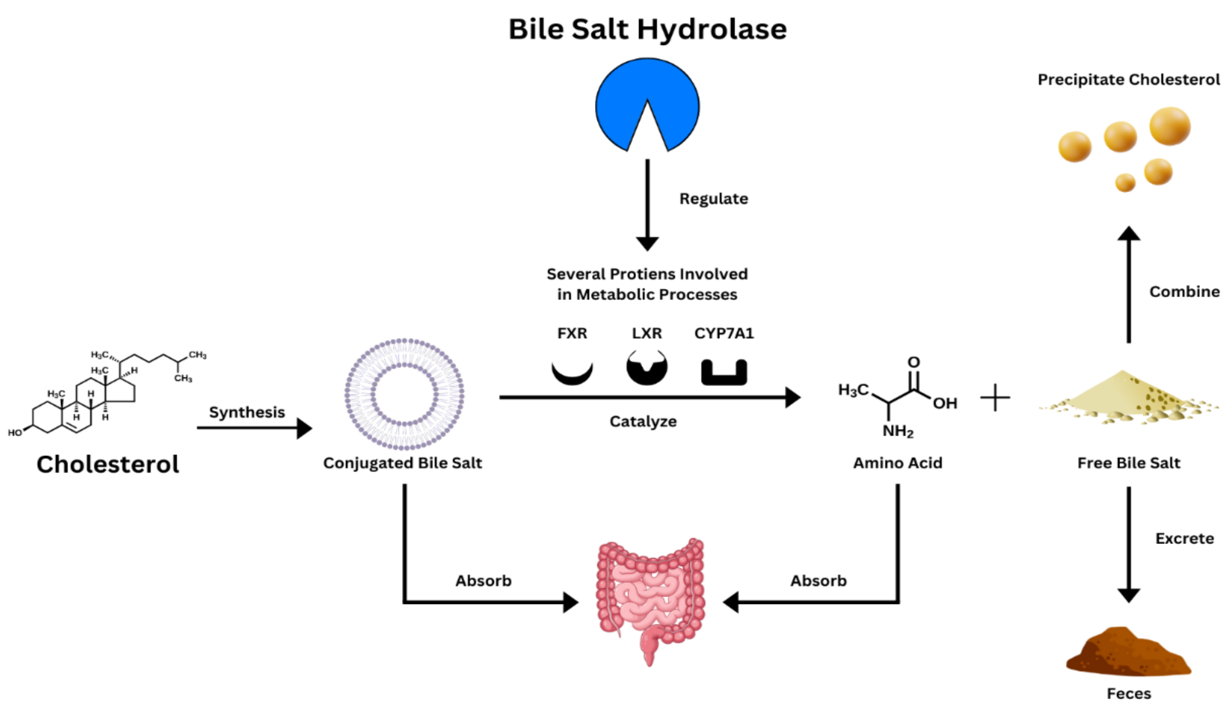

Fig. 4: Role of *Lb. plantarum* to Reduce Bile Acid

This figure 4. suggest *Lb. plantarum* can modulate metabolism of bile acid via BSH and facilitate the binding of free bile salts and cholesterol for diminishing lipid levels. Consequently, the reduction of cholesterol through bile acids may represent a viable strategy for employing *Lb. plantarum* in the management of cardiac disorder (CD).

2.4.3. Intestinal Flora

Recent data indicates that intestinal dysbiosis caused by a diet rich in fat permits the onset of several metabolic disorders, hypercholesterolemia, and obesity. The present study has established the role of gut microbiota in disease modulation and host health (Marchesi et al., 2016). Scientists have suggested the potential of *Lb. Plantarum* increases intestinal flora diversification and species richness, as well as the richness of helpful bacteria and the impoverishment of harmful bacteria. Shao et al. (2017) used metagenomic studies to demonstrate probiotic supplementation of gut microbiota pattern in a patient with hyperlipidaemia. The researcher established that *Faecalibacteria, Bifidobacteria*, and *Akkermansia* showed significant increases at *Lb. plantarum* level. The *plantarum* treated groups, but the genera *Natranaerovirga, Clostridium, Fervidicella, Gemella, Roseburia, Odoribacter,* and *Escherichia/Shigella* were highly increased in hyperlipidaemic individuals. The core mechanism through which gut microbiota reduces lipids is still very poorly understood despite being one of the most actively researched areas. We expect upcoming research results.

2.4.4. Conjugated Linoleic Acid (CLA) Isomerase

Besides CLA production, *Lb. plantarum* can also produce conjugated linoleic acid isomerase, which helps in decreasing hyperlipidaemia and cholesterol treatment. CLA is composed of a group of linoleic acid isomers, including cis-9, trans-11, trans-10, and cis-12, which are synthesized together to play a major role in the metabolic pathways regulating lipid metabolism and fat absorption. The chemical process of linoleic acid synthesis has complex requirements and produces a number of byproducts. An alternate promising approach is to use microorganisms to produce linoleic acid isomerase. Amongst the most effective strains of *Lactobacillus* isolated from traditional Chinese pickles was found to be *Lb. plantarum* ZS2058, which presented notable linoleate isomerase activity. Linoleic acid isomerase localization and purification proved that CLA isomerase catalyzed a hydration reaction in the microbial cells, yielding 10-HOE, which is an intermediate of CLA biosynthesis and subsequently underwent several steps to give biologically active CLA (Yang et al., 2014).

Lb. plantarum AKU1009A possesses a similar conversion pathway (Kishino et al., 2013). Isomerization of linoleic acid through fermentation could be achieved with the use of Acer Truncatum Bunge seed oil, based on a *Lb. plantarum* CGMCC8198 study that identified a homologous sequence to the isomerase gene of *Lb. plantarum* ZS2058. This has provided a basis for microbial production using *Lb. plantarum* (Chen et al., 2017). Further evidence that conjugated CLA is indeed a cholesterol-lowering agent can be gleaned from the work of Chen et al. (2022), which showed that dietary supplementation with the compound increased the prevalence of bacteria associated with lipid metabolism and significantly reduced fat gain in mice.

Conclusion

Given the world's incidence of heart disease, probiotic food has also acquired significance in the form of prevention and management along with orthodox drugs. *Lactobacillus plantarum,* in addition to having high potential for the treatment and prevention of CD, can be potentially produced as a probiotic of importance for human health. Its process includes the increase of antioxidant assays and the maintenance of blood pressure, blood lipid profile, and glucose balance. Cardiac disorder (CD) can be prevented and cured through a range of fermented foods. By researching and improving the properties, technology, composition, and related aspects of foods fermented by *Lb. plantarum*, researchers have the potential to enhance the value of such foods and their probiotic activities, thereby benefiting patients experiencing heart disease symptoms. As a result, functional fermented foods are isolated from *Lactobacillus. Lb.* It has a very good potentiality in the control and management of heart disease. Future incidence of the CD may well be decreased to the lowest percentage along with impact through including this fermented food products by *Lb. plantarum* in everyday life. Again, the functional foods should further be developed more precisely with detailed studies on optimising the different conditions for *Lb. plantarum* culture production.

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