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Chapter 3

Probiotics and Its Relationship with the Cardiovascular System

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Abstract

Cardiovascular disease is a major health issue worldwide. Individuals who have cardiovascular disease, are often at risk or already have other diseases, which together can lead to metabolic syndromes and possibly increase the risk of morbidity and mortality. Gut microbial balance is increasingly being recognized as a possible risk factor in cardiovascular illnesses. Studies published so far have shown a possible link to hypertension, hyperlipidemia and associated cardiac illnesses. Balance of the colonic flora seems to improve these co-morbid conditions. Probiotics have been studied in several studies to determine if their use provides a beneficial non-pharmacological treatment option for diseases such as diabetes, obesity, hypercholesterolemia, hypertension, chronic kidney disease, cardiomyopathy and atherosclerosis. Placebo, double blinded controlled studies are s needed to determine if these perceived beneficial effects exists and to what extent probiotics play in the overall outcome in cardiovascular diseases.

Keywords: probiotics, cardiovascular health, hypertension, obesity, diabetes mellitus

1. Introduction

Cardiovascular disease (CVD) is a major cause of death worldwide. There are disease-associated risks that can be either modifiable or unmodifiable factors and examples are low-density lipoprotein (LDL) cholesterol, increased triglyceride-rich lipoproteins, and low levels of high-density lipoprotein (HDL) cholesterol [13]. An individual's personal gene makeup, body composition, health, and having certain preexisting disease states can also influence their risk of having a CVD. These factors often contribute to a group of conditions leading to metabolic

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syndrome. Metabolic syndrome increases an individual's chance of having a disease such as CVD and/or diabetes.

Gut microbes are thought to be responsible for healthy outcomes in terms of the gastrointestinal (GI) tract, as well as positive health benefits distant to the GI tract. The alteration to dietary macronutrient ingestion has increased the prevalence of metabolic disorders which has been shown to be related to microbial imbalance to the gut as part of the pathogenesis [7, 9]. A meta-analysis of several studies found about 1100 bacteria species and their related properties in relation to diseases such as diabetes mellitus, cardiovascular disease, obesity, and cancer [7]. The change in gut microbe related to a disease state can often be associated with an individual's diet. Diets that are high in fat and/or sugar and low in fiber have a negative effect on gut ecosystem [18]. Therefore, diet modification to alter the composition of gut bacteria is vital for either prophylaxis or the treatment of some diseases. This makes gut microenvironment a focus point in the prevention of unhealthy state and improvement to a healthy state in order to avoid metabolic syndrome-related diseases such as cardiovascular disease and diabetes.

Modifying gut microbiota with probiotics has been in practice for centuries and is now being studied in relation to treatment and/or prophylaxis for metabolic syndrome and related diseases such as cardiovascular disease [9]. The more recent metagenomics studies are those that have demonstrated that probiotics are involved in host immune modulation and influence the development and physiology of organs. Therefore, they have been identified as the possible medical therapies to treat GI disorders and to restore an impaired gut ecosystem [8]. Studies have strengthened the idea of the importance of probiotics in aiding the prevention and prophylaxis of gut disorders, urogenital, and respiratory infections with their results [8]. The hypothesis that they could aid in the fight against metabolic disorders is based on them having an effect on the modulation of composition and function of interstitial microbiota [7]. Background information on probiotics, as well as current studies that have observed the gut microbiota in cardiovascular disease-related conditions such as obesity, diabetic, hypercholesterolemia, hypertension, cardio-arterial disease, and cardiomyopathy based on past studies, has been analyzed.

2. Probiotics

Individuals using probiotics for the improvement of health have a well-known history, especially lactic acid bacteria (LAB) and *Bifidobacteria*, as well as prebiotics as part of food or fermented food [7, 20]. Dating back to 76 BC, there was the recommendation of ingestion of fermented milk products for those who had gastroenteritis [7]. The idea behind probiotics being used as a way to alter interstitial microbial balance started in the twentieth century from the work of Metchnikoff [7, 9]. With new advance techniques such as DNA-based analyses, there have been a significant number of research that observed different bacteria and their properties that are related to both positive and negative influences on the human body in the disease and healthy state [7]. The following has been stated to be important in probiotic research: identification, maintenance, and characterization of probiotic strains in live conditions, so potency is preserved, and they arrive alive in a state of action which varies [25].

Probiotics have been observed to have a positive effect on gut microbial and are often studied in a combined relationship with prebiotics termed symbiotic.

Some examples of the positive outcome from probiotics have been an improved immune system through immunoglobulin production, trigger cell-mediated immune response, and help in the treatment of gut disorders such as irritable bowel syndrome (IBS), *Clostridium difficile* colitis, gastric ulcers lactose intolerance, and antibiotic-associated diarrhea (AAD). Positive results from probiotics are caused by the multifactorial process related to them that results in the production of organic acids, hydrogen peroxide, bacteriocins, bacteriocin-link inhibitory substances, short-chain fatty acid (SCFA)-conjugated linoleic acid, and ϒ-amino butyric acid [8]. These can cause improvements that range from improved bone density, anxiety, hyperammonemia, and improved blood lipid profile to name a few [3]. This is based on the proven functions of probiotics such as balancing intestinal microbiota, modulating the immune system, and exerting metabolic influences [4].

Prebiotics often provided with probiotics can contribute to the influences on the bacteria population in the human gut [7, 9]. Prebiotics is a type of nondigestible fiber compound, which is able to bypass the upper gastrointestinal tract, remain undigested, and reach the colon where they are fermented by the gut microflora. It is a type of food source for probiotics (microbiota) and it regulates the growth and activity of gut microbiota, resulting in an improved gut health and strengthened immune system [7, 14]. In order for prebiotics to provide a beneficial role, they must have the following three characteristics: "resistance to gastric acidity, hydrolysis by mammalian enzyme, and gastrointestinal absorption, fermentation by intestinal microflora and selective stimulation of growth and/or activity of intestinal bacteria associated with health and well-being." Various chain-length oligosaccharides are the most common that are studied and those include fructo-oligosaccharide and galacto-oligosaccharide/transgalacto-oligosaccharides [2, 7]. Tri-, di-, and some monosaccharides may also be used as prebiotics if they have host-indigestible bonds.

Prebiotics mode of action is taking advantage of the commensals that are already in the host; they use this to degrade their otherwise indigestible bonds, which support the microbial survival [1]. They are used as fermented ingredients that induce the growth or activity of microorganism. *Bifidobacterium* and *Lactobacillus* have been identified for responding to the administration of prebiotics, for example, oligofructose (OFS) stimulates the growth of *Bifidobacterium*. Prebiotics beneficial properties are not just limited to the GI system. Once prebiotics have been selective fermentation, there will be an increase in the number of commensals while lowering other neutral/harmful organisms which support symbiotic gut microbiota composition. It has been shown that though the "gut-brain axis," some such as fructo-oligosaccharide and galacto-oligosaccharide are able to modulate neural growth factors such as brain-derived neurotrophic factors and synaptic proteins [2]. This can affect memory, attention, learning, and mood. When prebiotics and probiotics are used together, it is called synbiotics.

Fermented foods consist of microorganisms that are either functioning or nonfunctioning. One of the functioning actions is to stimulate probiotic function [6]. *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, and *Weissella* are lactic acid bacteria associated with fermented food along with species of *Bacillus*, *Bifidobacterium*, *Brachybacterium*, *Brevibacterium*,

and *Probacterium* [6]. *Lactobacillus* and *Enterococcus* are LABs, which with *Bifidobacterium* are the most commonly used probiotics. The most common traditional source of the probiotic *Lactobacilli* is fermented milk [6]. These microorganisms have several properties such as probiotic, antimicrobial, antioxidant, peptide production, fibrinolytic activity, poly-glutamic acid, degradation of antinutritive compounds, and ambrotose complex memory [6]. *Bifidobacterium* and *Lactobacilli* will selectively ferment prebiotics which cause an increase of these commensals while displacing other pathogenic or neutral organisms [2].

Probiotics containing a live microorganism should be used with caution in patients that are immunocompromised because they can cause infection or pathogenic colonization [27]. This has been supported by several studies. A study that observed renal-transplant patients with AIDS found that Lactobacillemia, which is not a common cause of bacteremia, occurred. Lactobacillemia was found in other patients who were immunocompromised with the following conditions: cancer, organ transplantation, diabetes mellitus, and recent surgery. Out of these patients, fever was presented in all of them and 15% developed sepsis but it is important to note that Lactobacillemia can have a wide range of clinical features. A probiotic consumed by a patient who had advanced and severe bicuspid aortic valve stenosis developed *L. paracasei* endocarditis. *Lactobacillus* may be under recorded because it is not observed as a pathogen and is also usually determined as part of a polymicrobial infection [33]. These are just a few cases in which an infection was caused, and overall, there have been studies that support the safety of probiotics consumed by groups of immunocompromised patients [33]. Probiotics can also affect some interaction with other drugs, for example, they could interfere with the production of vitamin K and therefore could affect the sensitivity to some drugs like warfarin [27].

Lactic acid bacteria tend to produce bioactive compounds, which are frequently found in fermented products due to LAB-elective habitant food, especially in diary. Biogenic amines are the main health risk in fermented food [5]. These compounds can sometimes cause allergies, hypertensive crises, and headaches. Also, it is important to make sure that probiotics, which are used to aid in the control of LDL levels, do not affect cardiac myocyte function, increase fat deposition, or cause cancer [20]. Cancer is a risk because secondary bile salts may disrupt DNA repair pathway. This disruption can lead to oxidative stress in epithelial cells which can start tumor formation [21]. These adverse effects on human are usually not a concern in generally healthy individuals [6].

3. Relationship of CVS to probiotic use

3.1. Obesity

Obesity, which causes a low-grade inflammation, is a risk factor for cardiovascular disease, diabetes, dyslipidemia, premature death, hepatobiliary disease, and several cancers. There is an estimate of 1.7 billion people in the world that are overweight. Obese individuals tend to have an altered composition of intestinal microbiota, which suggest that intestinal microbiocenosis can be considered the environmental factor that creates the development of obesity

[5]. Some of the effects of altered bacteria composition in the gut is linked to obesity due to several changes such as downregulated activity of FIAF and AMK, impaired production of SCFAs, increased inflammation, altered LPS-endocannabinoid (eCB) system regulatory loops, and bile acid metabolism [5]. The cause of the alteration is believed to be linked through the host's diet. An example of this is that there was a reduction in *Lactobacillus* and *Bifidobacterium* and was observed in mice when they consumed high-fat diets [5]. This change of environment is the basis of studies that have shown that gut microbiota plays a role in energy homeostasis and bodyweight, therefore affecting the pathophysiology of obesity [5, 18].

In obese individuals, the different microorganism environment is believed to affect adiposity and alter the regulation to fat storage [7]. Insulin-type fructan affects the gut ecology and stimulates immune cells leading to a decrease in the weight gain and fat mass in obese individuals [7]. In a meta-analysis, several studies found that there was an increased prevalence of *Firmicutes* shown with obesity phenotypes. These bacteria interfere in a negative relation with metabolism and insulin sensitivity [26]. Probiotics, while resulting in more subtle effects in humans versus mice studies, are now being studied as a way to modulate gut microbiota in relation to obesity [20]. This is because certain traits in probiotic cultures such as exopolysaccharides, CLA, and GABA production were found to have a positive effect on host lipid metabolism and gut microbial composition [8].

An increased number of *Lachnospiraceae* family in obese female microbiota were altered when probiotics containing *L. rhamnosus* CGMCC1.3724 (which reduces *Lachnospiraceae* family) were administered along with an energy-strict diet [38]. However, the probiotics that were related to fat mass in Ref. [38] also caused a decrease of leptin levels, which may lead to a need for the supplementation of leptin in order to maintain weight loss. Probiotics and weight loss have also been linked to a decrease in ghrelin, which could assist in maintaining the weight loss even with the loss of leptin [41]. When *L. gasseri* strain was given in fermented milk for 12 weeks, there was a decrease in abdominal visceral fat in adults with large visceral fat areas [18]. Supporting this, there have been other studies that when looked at the outcome of probiotic consumption, there was a decrease in both body mass index (BMI) and waist circumferences [13]. However, those were a limited number of studies, and additional studies are required, including those that will observe the effect of probiotics on energy balance-related hormones.

In multi-strain probiotic therapies, with 8 weeks of treatment, obese individuals showed a decreased weight, waist circumference, and serum cholesterol levels. This study also supported the idea that probiotics caused results not only by their own metabolism but through probiotic alteration of the gut microbe with an increase of *L. plantarum* population and other Gram-negative bacteria [20]. When prebiotics were added, there was control of overexpression of several host genes that have been known to be related to both adiposity and inflammation [27]. However, the altered level in gut microbe with one probiotic only had a subtle effect, and more studies are necessary to understand if and what probiotics provide a change to obese individual's gut microbe.

Gut bacteria also play a role in obesity through the regulation of inflammation. The relation between low-grade systemic inflammation and obesity is weakened through peptides produced in the gut. These peptides' synthesis is affected by the composition of gut microbiota [7].

An example of this is the serum amyloid A3 protein where the expression in adipose tissue is regulated by gut microbiota [7]. Any alteration to the gut microbiota could then also potentially play a role in body weight due to intestinal microbiota effects on adiposity and the regulation of fat storages.

3.2. Diabetes

Having diabetes or having the risk of diabetes is often associated with a higher risk for cardiovascular disease. This is because of a compensatory action resulting in hyperinsulinemia which leads to a variety of metabolic abnormalities. Individuals who have diabetes were found to have altered intestinal microbiota which can cause increased adiposity, B-cell dysfunction, metabolic endotoxemia, systemic inflammation, and oxidative stress related to their disease. SCFA is an important function in type 2 diabetes mellitus (T2DM); however, bacteria producing SCFA numbers are lower in diabetic individual [7]. Probiotics may offer a beneficial therapy for diabetic patients through increasing SCFA and other methods.

Oral supplements, which contained viable and freeze-dried stains, were found to reduce fasting plasma glucose when compared to a placebo group. Fermented food was also noted to not only aid in the prevention of diabetes but also cause favorable changes in those already diagnosed with diabetes [6]. This could be due to some probiotics delaying the glucose intolerance and hyperglycemia state in individuals. For those with diabetes, some probiotics in fermented food decrease insulin requirements and could increase insulin sensitivity for non-diabetics [6].

Diabetes has a connection to long-term inflammation. This is due to the consumption of high fats and high fructose which causes chronic inflammation leading to the induction of insulin resistance (IR) and disruption of gut flora. This is supported by studies, which have found that certain diets, for example, high-fat diets, tend to increase lipopolysaccharide (LPS) contained in gut microbiota which leads to a decrease of *Bifidobacteria*. This leads to an inflammation state which may be associated to insulin resistance and weight gain [1]. Different probiotics have differential immune pro- or anti-inflammatory action through the attenuation of nuclear factor kappa B (NF-kB) [4]. *Lactobacillus* is a lactic acid bacteria that contains immune stimulating properties [28]. Probiotics, *L. reuteri,* and *L. plantarum* have anti-inflammatory and antioxidant effects which can aid in the management of diabetes [9]. For example, C-reactive protein (CRP), an inflammation marker, is noted to decrease when these probiotic supplements are used [13].

In a meta-analysis, there was no statistically significant glucose-lowering effect of probiotics when combined with prebiotics [1]. However, prebiotics may affect the inflammation state due to prebiotics having immunomodulatory benefits. In a study, prebiotics were found to alleviate chronic inflammation, which could lower the risk of development of cardiovascular disease and diabetes [2]. Probiotics may even possibly assist in the prevention of diabetes through bacterial translocation to mesenteric adipose tissue. This is mediated through acetate production and an increase in gut epithelial integrity [26].

Hyperglycemia, which is a property of diabetes, is a term given when a person has continuous high-fasting blood glucose (>6.1) and is associated with different diseases, the main one being

diabetes mellitus [1]. The first line of treatment is proper nutrition and physical activity [1]. Probiotic supplements along with prebiotics were found to improve the hyperglycemia state. When multi-strain probiotics along with symbiotic supplements were provided to individuals in a hyperglycemia state as their baseline, there was an improvement in their blood glucose level (BGL) [1]. Glucose tolerance and increased satiety with weight loss were found when individuals were administered OFS which lead to *Bifidobacterium* and endotoxin levels to be normalized. Butyrate, which has properties of propionate that can lower blood glucose, is produced by several bacteria [4]. Other studies found that with a symbiotic shake of *L. acidophilus*, *Bifidobacterium* and *L. rhamnosus* caused a 38% decrease in blood glucose levels for patients with T2DM. Though these studies demonstrate that supplementation with probiotics with symbiotic may help in the control of hyperglycemia and T2DM, larger studies are needed to confirm. The glucose-lowering effect is due to the metabolites of these bacteria which was shown to affect biological signaling pathways, modulated genes involved in ubiquitination and proteasome process, and altered autonomic nerve activity [1]. It is also vital to note that probiotics or synbiotic alone did not cause a significant reduction in fasting blood glucose levels.

3.3. Hypercholesterolemia

Cardiovascular disease, affecting both blood vessels and/or heart, usually is the result of hypercholesterolemia and dyslipidemia. There have not been direct studies that compare the effect of prebiotic intake on cardiovascular health; however, there has been an observation on the serum lipid profiles, which all have an effect on CV [2]. These experiments have observed the effect of probiotics and/or prebiotics both in vitro and in vivo on lowering cholesterol [7]. In order to use probiotics to help lower cholesterol, the probiotics adhesion property to the human intestinal epithelial cells is a critical characteristic that must be considered [14]. This characteristic is to ensure that there is extended probiotic transit time in the gastrointestinal trace which was found to cause cholesterol-lowering effects in vivo.

Studies have shown a lower low-density lipoprotein and total cholesterol, along with increases in high-density lipoprotein cholesterol, a reduction in systolic blood pressure (SBP), increases in antioxidant activity, and influences on leptin regulation as a result of probiotics [9]. This is done through an enzyme called bile salt hydrolase (BSH) which causes a decrease in the absorption of cholesterol in the blood stream and is an essential criterion for the selection of probacteria [9, 13]. This enzyme unconjugated bile acids, which eventually cause a decrease in circulating triglycerides and plasma LDL and VLDL levels [12, 20]. The most associated BSH active probiotics are *Lactobacillus*, *Lactococcus,* and *Bifidobacterium* [21]. These bacteria have been observed to lower cholesterol both in vitro and in vivo [28].

For example, see [14], which found that *L. fermentum* NCIMB 5221 and NCIMB 2797 were able to lower cholesterol in an in vitro analysis. They found that *L. plantarum* ATC 14917 had the best results [22]. Another study found that the BSH candidate *L. reuteri* NCIMB 30242 had the capabilities to lower cholesterol in otherwise healthy individuals [12]. This is because *Lactobacillus* species are able to colonize and survive in small intestines [21]. These studies have demonstrated why lactic acid bacteria with BSH are being classified as having hypocholesterol effect. More specifically, trials that used multiple strains versus single strains and fermented products

versus capsule found that multi-strain and fermented methods both caused a decrease in total cholesterol and LDL [13].

Probiotic soy products in association with cardiovascular risk factors were observed. The fecal microbiota that was used was *Lactobacillus* spp., *Bifidobacterium* spp., *Enterococcus* spp., *Enterobacteriaceae*, and *Clostridium* spp. populations. Their results showed a negative correlation with *Enterococcus* spp., *Lactobacillus* spp., and *Bifidobacterium* spp. with cholesterol, non-HDL cholesterol, and autoantibody against LDL [29]. However, this study was performed with rabbits, and future studies with human subjects are necessary for a confirmed effect.

High-density cholesterol, HDL, is considered good cholesterol and is important for removing "bad" cholesterol from the blood stream. This study found that there was a positive correlation between *Lactobacillus*, *Bifidobacterium*, *Enterococcus,* and HDL-C levels [29]. However, in relation to T2DM patients, there were some studies, which found that probiotics failed to maintain a significant effect on lipid profiles [7]. Prebiotics, however, were found to maintain hypocholesterolemic effects in the T2DM individuals [7].

Other methods in which probiotics affect blood lipids include binding and incorporating cholesterol to their cell membrane, which decreases the amount of intestinal cholesterol available for absorption, and by producing SCFA which inhibit hydroxymethylglutaryl CoA reductase. *Lactobacillus* species have protease-sensitive receptors on their cell surface. These receptors bind to exogenous cholesterol or phosphatidylcholine vessels, which then incorporate cholesterol into their cell membrane. This is strain- and growth-dependent action [21].

Probiotics, performing the mechanism of a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, was shown with dietary fibers (prebiotics) altering the functionality of gut microbiome including the stimulation of microbial metabolite production such as short-chain fatty acid which impacts cholesterol metabolism. The lowering of cholesterol with prebiotics is believed to occur through two mechanisms. The first one is it lowers cholesterol absorption by enhancing cholesterol excretion via feces and the second is through the production of SCFAs upon selective fermentation by intestinal bacterial microflora. Inulin and arabinoxylan, both prebiotics, can alter gut microbiome to stimulate SCFA production which has been already shown to effect cholesterol metabolism [12]. The mechanism behind this is that cholesterol is removed though the incorporation of cholesterol into cellular membranes in the intestine [13].

In terms of fermented food, *Monascus purpureus* rice was found have similar actions as statin and acted as a HMG-CoA reductase inhibitor, decreasing the makeup of cholesterol [6]. The studies that have conflicting findings could possibly be due to the delivery system. Studies varied whether the probiotics were given in capsule versus fermented foods. However, in a limited number of meta-analysis of studies, it was found that probiotics using fermented foods were more effective in reducing total cholesterol and LDL than in capsule [13]. In the majority of studies that were reviewed, there was no control for individual's lifestyles in human subjects which could alter the findings.

3.4. Hypertension

Hypertension has several risk factors, such as sedentary lifestyle, lipid and hypercholesterolemia, chronic inflammation, inconsistent modulation of renin-angiotensin system (RAS),

sodium sensitivity, personal habits, anxiety, and stress. While dietary strategies have been the focus of target for repairing the disturbed gut microbiota, probiotics have been found to decrease systolic/diastolic pressures (approximately 14–6.9 mm drop) in prehypertensive and hypertensive patients. This blood pressure (BP)-lowering effect through probiotics is due to a decrease in nitrogen oxide production in macrophages, reducing reactive oxygen species and enhancing dietary calcium absorption using different mechanism. These mechanisms have been found to be related to the production of SCFAs, CLA, GA A, and angiotensin-converting enzyme (ACE) inhibitor peptides [8]. Short-chain fatty acids (SCFAs), which have a role in both energy metabolism and adipose tissue expansion, also have two sensory receptors that have been linked to BP regulation. Some of the probiotic strains that were noted to cause a decrease in SBP were *L. casei*, *Streptococcus thermophiles*, *L. plantarum*, and *L. helveticus* [9]. Fermented milk products have been shown to have antihypertensive properties in both animal models and clinical trials [6]. Blood pressure release may also be due to a decrease in blood lipids, body weight, and IR.

On continuing, blood pressure is normally controlled with a variety of biochemical pathways, including the RAS system. The generation of antihypertensive bioactive peptides causes an ACE-inhibitory activity [8]. Different strains of probiotics have varying potencies as ACE inhibitory activity based on different bioactive peptides [18]. When prebiotics were used along with probiotics or the probiotic strains were enhanced via fermentation substrates, the proteolytic activity and ACE inhibition were increased [20]. Fermentation is able to produce bioactive ACE-inhibitory type peptides, casokinins and lactokinins. Probiotics are able to generate these peptides though fermentation having caseinolytic and lactose hydrolyzing enzyme systems [9]. Consuming probiotic soy milk led to a decrease in BP in a limited number of type II diabetic mellitus subject in a clinical trial lasting 8 weeks [15]. This study did not find any alterations of anthropometric measures which had been found in other studies. This could be that there are strain-specific properties [15]. However, subpopulation studies showed no significant difference and there are no definitive recommendations at this time.

3.5. CAD

Cardio-arterial diseases are often associated with hypercholesterolemia, diabetes, and other metabolic-related diseases. Alteration to the gut microbiota can cause a detrimental risk of obtaining a cardio-arterial disease/state such as atherosclerosis. The change in gut microbiota can cause an increase in the level of trimethylamine N-oxide (TMAO), which has been linked to an increased risk of major adverse cardiovascular events observed in large clinical cohorts. However, additional studies are needed to determine the mechanism of CVD through TMAO [7].

Apo A-V deficient mice were found to have increased precursors of small dense LDL, which is a predictor of coronary artery disease [16]. This deficiency has been observed with bile salt hydrolase expressing probiotics to have an important role in not only lipid metabolism but also atherosclerosis development. *L. reuteri* NCIMB 30242 when provided to non-diabetic subjects with hypertriglyceridemia caused a decrease in apolipoprotein B, which is associated with atherogenic VLDL and LDL products [16]. It was also shown to reduce CRP and fibrinogen which are two factors of atherogenesis [12]. However, this study only included small healthy

hypercholesterolemia population, and the probiotic was given either in capsule or in yoghurt format. In mice, *Lactobacillus* species was found to lower arteriosclerosis [20]. When provided through powered supplement, *L. curvatus* and *L. plantarum* caused a significant increase in apo A-V [16]. With varying methods of providing the probiotics, more controlled studies are necessary to understand the relationship between probiotics and cardio-arterial disease.

Fermented products may provide a decrease in the development of atherosclerosis with the activation of G-protein-coupled bile acid receptor [25]. In a study that compared atherosclerotic lesions in the aortic vessel in animals treated with fermented soy product supplements versus a control group, the ones that were provided the supplement was found to have a lower percentage of aortic vessel covered with lesions [29]. Fermented whole grains are also able to lower coronary heart disease [6].

3.6. Heart failure

Heart failure causes a variety of systemic effects on multiple organs. While there are no heart failure changes observed to effect the gut microbial composition, there have been changes that could cause or increase the incidence of heart failures. New research is currently observing probiotics therapy providing direct cardio-protective effect to the heart. This protection would result in a reduced ischemic injury and improve cardiac function after an infarction [20]. TMAO, which is effected by gut microbiota, can be linked to both the development and progression of atherosclerosis and cardiovascular disease and is effected by gut microbiota [21]. However, a majority of studies have only observed the effects in mice. Continuing due to individuals not realizing that they are at risk for infarction, consuming probiotics as prophylaxis is unlikely and the prevalence of heart failure is stagnant.

3.7. Chronic kidney diseases

Patients with chronic kidney disease have an increased risk for cardiovascular disease through having hyperhomocysteinemia, increased lipoprotein, oxidative stress, and inflammation. Vascular dysfunction in both humans and experimental animals with CKD has been discovered to be due to an increased production and impaired renal excretion of p-cresyl sulfate and indoxyl sulfate which pairs CKD with vascular disease. These toxins along with others are normally cleared by the kidneys. When kidney patients were provided probiotics, there was a decrease in those toxins. However, due to the uremic environment of the gut that is often associated with CKD, probiotic may become ineffective or less ineffective [23].

3.8. Relationship to GI system

A population of microbes that assist the host's biochemical metabolic and immunological balance necessary for health maintenance is termed normal microbiota [6]. Both composition and function characterize the biodiversity of microbiota [4]. The gastrointestinal microbiota includes bacteria, archaea, protozoa, fungi, and different viruses, with anaerobic bacteria and the predominant source [4]. The numbers range from 10 to 100 trillion microorganisms in the GI tract, which, based on an individual's genetic age and diet, vary from individual to

individual [9]. From the time an individual is born until his/her death, there will be more than 500 different species of microorganism that are contained in the human body [6, 7]. An individual's microbial diversity changes throughout his/her life span and depends on a person's health-related interaction between gut microbiota and host's overall health [7]. There are even geographic variations that have been found in relation to the type of *Lactobacillus*, varying from the western and eastern hemispheres. The factors that can influence a person's microbiota are genetics, age, diet, and antibiotic use [8].

The colon has the largest variety of microorganism and is the focus part of most studies [4]. *Bifidobacterium*, *Lactobacillus*, *Propionibacterium*, and *Bacteroidetes* are the dominant species of obligate microflora [5]. Lactic acid-producing *Bifidobacterium* and *Lactobacillus* are often the focal points of studies due to their beneficial effects that is caused by their expression of immunomodulatory and pathogen-antagonistic molecules [2]. These bacteria produce butyrate, which highlights some properties of propionate and is observed as the preferred metabolic fuel for colonocytes possessing antineoplastic properties. This contributes to energy production [4]. Propionate affects colonic muscular contraction, relaxation of resistance vessels, and stimulation of colonic electrolyte transport and insulin resistance [4].

There are several ways that a human's microbiota aids overall health; examples of this include endogenous symbiont microorganisms, microbiota, changing not only gene expression but also have an effect on pH, redox balance, and the ratio between pro-inflammatory and anti-inflammatory cytokines. There are also studies which showed normal microbiota effect on brain metabolism, the immune system, and a couple of homeostatic routes [3]. There have been several studies that have noted a change of gut microbiota in several conditions/diseases such as obesity, fatty liver, insulin-resistant diabetes mellitus, and hypertension [11]. Some examples of these changes are an increase in *Firmicutes* and a decrease in *Bacteroidetes* [18]. With recent studies showing gut microbiota related to the pathogenesis of cardiovascular disease, probiotics, which are live microbial food supplements, could balance intestinal microbial resulting in the treatment or prevention of cardiovascular disease [9, 11].

The gut environment also plays a role in the type of bacteria found per location in the tract. The tract varies from an alkaline pH in the small bowel to an acidic pH in the stomach [31, 32]. Using the 16 s ribosomal RNA gene sequence-based metagenomics methods, it has been determined that 90% of bacteria of the gut belong mainly to the *Bacteroidetes* and *Firmicutes* phylum [27]. It has been discovered that both are lactic acid bacteria which are vital to the gastrointestinal track normal residents. These two are commonly used in fermented food for the prevention and treatment of different disorders ranging from constipation to high cholesterol levels [27].

When an individual is healthy, most of the microbiota act symbiotically with the host. The major metabolic function of microbiota is to assist with the harvest of nutrients and energy from different diets that human's consume [4]. The interaction between the gut epithelial cells and the microbes and the metabolites produced is responsible for the maturation of intestinal epithelial cells, enteric nervous system, intestinal vascular system, and the mucosal immune system. However, an imbalance in gut bacteria has been shown in numerous studies to be linked to a variety of diseases. Intestinal disease state can affect the microflora, impair the gut barrier, and/or cause intestinal inflammation which can all lead to imbalance in gut bacteria population

[31]. In order to reestablish a balance, probiotics, prebiotics, and synbiotics have been used and observed. Probiotics are able to affect the GI tract through their interaction with the intestinal epithelial cells, luminal flora, and mucosal immune cell components of the GI tract [28].

Antibiotics usage in early life has been determined to deplete some components of microbiota causing disrupted normal gut microbiota development [4]. Prebiotics such as fructo-oligosaccharides do not support the growth of antibiotic-related pathogens like *C. difficile* [31]. Several studies have observed the efficacy of different probiotic strains in the treatment of antibiotic/*C. difficile*-associated diarrhea. *L. acidophilus*, *L. rhamnosus* GG, *L. delbrueckii*, and *L. fermentum* are several bacteria that have been shown to decrease the occurrence of antibiotic-induced diarrhea [10]. *C. difficile*, a main concern with the usage of antibiotics pathogenesis, is the disruption of indigenous intestinal microbiome. Probiotics were shown in several studies to decrease *C. difficile* risks; those studies had several limitations such as the type of probiotic variation, the duration of use, and different dosages [35]. Therefore, *C. difficile* and probiotic relationship require more in-depth research.

There have been a variety of studies that observe and prove the health benefits and clinical effects of probiotics to GI abnormalities such as irritable bowel syndrome, gastric ulcer, and antibiotic-associated diarrhea and some cancers [8]. *Lactobacillus* and *Bifidobacteria* influence on resident microbiota can range from temporarily replacing missing parts or supplementing certain population, or by stimulating some of the resident microbiota. *Lactobacillus* species, which has been noted in several studies to provide beneficial effects when they are presented, is metabolically active and contains several properties that affect the whole intestinal microbiota biodiversity [4]. Prebiotics have been shown to suppress indigestion and diarrhea that were caused by pathogens [2].

Continuing, they can also aid in preventing the growth of harmful competitors, prevent the growth of exogenous microbes, and lower the substrate availability for pathogens [19]. *L. fermentum* ME-3 has been found able to suppress Gram-negative bacteria. Some probiotics have an antagonistic effect such as *L. paracasei* and *L. plantarum* with *Salmonella* (microaerobic), *L. plantarum* against *C. difficile* colitis (anaerobic), *L. paracasei* against *Helicobacter pylori*, and *B. lactis*/*B. longum* against *Shigella sonnei* and *E. coli*. Inflammatory bowel disease, which consists mainly of ulcerative colitis and Crohn's disease, has been shown related to intestinal flora dysbiosis through clinical and research studies. In an analysis of several studies, probiotics were determined to have a better outcome than non-probiotics therapy for maintenance therapy. However, they did not give benefit in inducing the remission of ulcerative colitis. This could be due to various methods used, different sample sizes, and controlled variables [34].

Prebiotics can also influence the composition of bacteria in human gut [9]. Several studies showed that when given supplements of fructan and inulin, there was an increased number of *Bifidobacteria* [19]. Other types of prebiotics that have been found to positively affect the gut microbe are arabinoxylan and inulin. These two have a modifying ability through affecting the makeup of and function ability of gut microbe [12]. *Bifidobacteria* and *Lactobacilli* selected fermentation of prebiotics have supported symbiotic gut microbiota through improving numbers of these commensals and decreasing the number of neutral

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or pathogenic organisms. It is vital to know that these microbes' preference to coproduce certain fermentation products depend on the prebiotic structures and the bacterial communities [2]. Example of acidic fermentation products are lactate and short-chain fatty acid, butyrate acetate, and propionate [2]. These products can have benefits in the gut, for example, butyrate supports intestinal epithelium, and along with other SCFAs, they have benefits that are distal to the gut system.

4. Current recommendation for its use and types of availability

Before recommendations on probiotics are made, the following are needed to be taken into account: an individual's immunity, genetics, and diet [9]. The type of probiotics being suggested may differ based on goals and shelf life. World Health Organization (WHO) suggests that in order to provide health benefits, probiotics must be able to endure human digestion including gastric juices and bile and be capable of multiplying once they arrive in the GI tract [9]. The focus should be on the origin of the strain, its colonizing ability, and its safety and efficacy [4]. The amount varies based on the goal; however, it must be adequate enough to have colonization and effect [30]. The duration of the effect varies from probiotics. Studies have found that most effects only last as long as they are consumed [31].

There are an increasing number of probiotic products made available to consumers which include yogurt, other fermented milk and food products as well as various forms of dietary supplements [9]. Individual preferences can vary on the method of ingestion of probiotics. These are usually prepared using lactic acid bacteria of four general species, *Lactobacillus*, and *Bifidobacterium*. Probiotics are used in a variety of food sources not only in traditionally fermented food but are now being added to meat products, snacks, fruits, and juices [5]. Functional properties that lead to microorganisms in fermented foods have probiotics properties, antimicrobial properties, fibrolytic activity, and degradation of antinutritive compounds which may be essential when looking into the selection of a starter culture to be used in the makeup of functional foods [5].

In terms of prebiotics, foods such as artichoke, asparagus, garlic, and wheat have a variety of compound types that have been looked at for prebiotic attributes such as various length oligosaccharides and galacto-oligosaccharides/trans-oligosaccharides [2]. Monosaccharides, di-, and tri- may be used for prebiotics if they have host-indigestible bonds. Other examples of what have been used are sugar alcohol, cycle disaccharide difructose, and hydride II [2]. In order to have a beneficial effect from prebiotics, usually an individual will need 5 g or more to produce enough fermentation [1]. However, to avoid risk related to fermented food, a maximum limit of 100 mg/kg of histamine indicates safe level for consumption [6].

It is vital to recognize that there are no standard guidelines currently existing for oral administration, and the individual use of probiotic and prebiotics should be carefully monitored in order to determine potential adverse reaction [7]. More long-term well-controlled double-blinded studies are needed.

5. Summary

Gut microbial is essential for the balance of pathogens and the control of disease not only at the gastrointestinal tract but also distal to the tract as well. Metabolism and energy balance are major components of cardio-metabolic health [24]. Disease state has been determined to be one cause of an alteration to gut microbial that can affect the stated components. This was observed through different types of microbial environments in patients who are obese or diabetic. This change in gut microbial increases the disease state through the support of its pathogenesis.

Dietary supplements, including probiotics, could lower the risk of diseases such as CVD [17]. Probiotics have been known to cause a positive alteration in the gut microbial. They are often provided with prebiotics in fermented food and are termed synbiotic. Several studies have observed probiotics, its effect on gut microbial, and its relationship to cardiovascular diseases and risks. Probiotics may offer an alternative treatment for diabetes, obesity, hypercholesterolemia, hypertension, CKD, cardiomyopathy, atherosclerosis (**Table 1**). In order for a better understanding on how probiotics can lower the risks for diseases and treat, more studies need to be performed.

	Microorganism	**Results**	**Authors**
Obesity	***Lactobacillus rhamosus***	Mean weight loss in women was significantly higher than that in women in placebo group ($p = 0.02$)	Sanchez et al. [38]
Diabetes	***L. acidophilus*****,** *L. rhamnosus* **and *B. bifidum***	Decline in blood glucose levels by 38% in T2DM subjects	Moroti et al. [39]
	L. acidophilus **and *Bifidobacterium lactis* Bb12**	Significantly lowered fasting blood glucose hemoglobin A1c and malondialdehyde and increased erythrocyte superoxide dismutase and glutathione peroxidase activities and total antioxidant states	Ejtahed et al. [37]
Cholesterol	***L. acidophilus*** w. *B. longum*	Elevation of HDL cholesterol level by 0.3 mmol L-1 and reduction in the ratio of LDL/HDL cholesterol from 3.24 to 2.38	Kiessling et al. [42]
	L. reuteri	A significant reduction in LDL cholesterol 8.92%, total cholesterol 4.81%, non-HDL cholesterol 6.01%	Jones et al. [40]
	L. curvatus **and** *L. plantarum*	An increase of 21.1 and 15.6% in plasma apo A-V levels and LDL particles size	Ahn et al. [16]
Hypertension	***L. casei*** w/*Streptococcus thermophiles*	Systolic pressure lowered significantly ($p < 0.05$)	Kawase et al. [36]

Table 1. Main probiotic effect on cardiovascular disease risk-related states.

Each single strain of multiple strains must be observed individually. This is in order to directly compare the effectiveness of individual strain versus multi-strain [1]. Also, a synergistic effect in the bioactivity of probiotics could result in multi-strain, which can lead to a mutual inhibition by a component strain. This could possibly decrease probiotic efficacy [1]. While there are several probiotics that are available, only some have been shown to be effective and able to colonize [30].

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