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PROBIOTICS: THEIR INFLUENCE ON THE INFLAMMATORY PROCESSES AND OTHER CARDIOVASCULAR DISEASE FACTORS

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Summary. *Probiotic microorganisms have historically been used to rebalance disturbed intestinal microbiota and diminish gastrointestinal disorders, such as diarrhea, or inflammatory bowel disease (e.g. Crohn disease and ulcerative colitis). Recent studies explore the potentioal for expanded uses of probiotics on medical disorders that increase the risk of developing cardiovascular diseases and diabetes, such as obesity, hypercholesterolemia, arterial hypertension, and metabolic disturbances such as hyperhomocysteinemia and oxidative stress. This analythical review aims at summarizing the molecular and cellular mechanisms involved in probiotic-host interaction and to identify the nature of the resulting beneficial effects. Specific probiotic strains can act by modulating immune response, by producing particular molecules or releasing biopeptides and by modulating autonomous nervous system activity.*
Key words: probiotic bacteria, cardiovascular diseases, inflammation, obesity, lipid metabolism, cholesterol, oxidative stress

Introduction. The concept of creating beneficial health effects through the ingestion of living bacteria has been derived primarily from original studies made by Metchnikoff in 1907 [79]. He suggested that the good health and longevity of certain ethnic groups were due to their frequent ingestion of fermented dairy products. A joint working group, combining the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) (FAO/WHO) [34], has defined these probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".

These microorganisms, usually bacteria, are especially involved in improving general gut health and positively influencing the development and activity of the immune system [39, 62]. Microorganisms commonly used as probiotics are bifidobacteria [4], lactobacilli [136], lactococci [87], streptococci [93], enterococci, Escherichia coli [67], and yeasts, particularly saccharomyces boulardii [46].

If there good evidence that probiotics are effective in preventing gastrointestinal disorders, the efficacy of probiotics have not been proven in the treatment of diseases and a number of questions remain unanswered [58, 59, 98, 111]. The specifics of probiotic mechanisms of action remain largely unknown. The emergence of appropriate genetic tools [98], however, allows us to better study these effects and to improve on the selection of new probiotic strains. A number of previous studies addressing these concerns have proceeded along three major themes: 1) production of specific molecules (vitamins, enzymes) [101]; 2) interaction with indigenous microbiota (competition with pathogens, production of bacteriocins [21, 22], and 3) interaction with host cells, particularly those of the immune system [23, 97]. This last area involves particularly the induction of cytokines (pro- and anti-inflammatory) at the origin of specific immune responses.

Recent studies performed in vitro or in rodents, have demonstrated the potential positive effects of probiotics on lifestyle-derived disorders, characterized by nutritional imbalances [65, 90]. Stress, overworking, and smoking, in conjunction with high-calories and low-nutrition diet, may disrupt intestinal homeostasis and weaken the body's natural defenses. In the long term, this can lead to metabolic syndrome, which is a combination of heart attack risk factors [32, 45]: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, proinflammatary state, and protrombotic state [2, 32].

Several key dietary factors can lower the risk of cardiovascular diseases, including lowering of low-density lipoproteins (ldl) cholesterol by reducing saturated fats intake, lowering of triglyceride concentration by reducing sugar and processed food consumption, reducing homocystein concentration by supplementation with vitamins B6 and B12 and folic acid, or increasing antioxidant activity by higher consumption of fruit and vegetables [53]. In this context it is necessary to determine whether bacterial action on the intestinal epithelium might also play a role in the risk of cardiovascular diseases.

The purpose of this review is to examine the impact of food consumption of probiotic strains on medical disorders (obesity, diabetes, arterial hypertension,

hypercholesterolemia and inflammation implicated in elevated the risk of developing cardiovascular disease. Two metabolic disturbances (hyperhomocysteinemia and oxidative stress) also examined because of their close relationship with metabolic syndrome.

Probiotic effects on abdominal obesity. Abdominal obesity is a medical condition defined as an abnormal or excessive fat accumulation that might impair health and which can be associated with an inflammation of the adipose tissue [1, 128]. Environmental, behavioral, and genetic factors have been shown to contribute to the development and progression of obesity. In general terms, obesity results from a disequilibrium in energy balance (energy intake, expenditures, and storage) [26] and can lead to secondary metabolic complications such as Type 2 diabetes, cardiac disease, and cancer. Reduced physical activity or increased caloric intake both contribute significantly to the energy balance in an individuals. This regulation can be controlled by the hormonal system (leptin) and / or perhaps by intestinal bacteria.

Recent evidence suggests that some bacteria normally found as part of the gut microbiota positively affect nutrient uptake and energy regulation [117]. These findings suggest that gut microbiota could play an important role in regulating weight and may be responsible for the development of obesity in some people [26]. In support of this reasoning, Turnbaugh et al [119] demonstated that the microbiota of obese mice has an increased capacity to absorb energy from a given diet. Vijay-Kumar et al [122] futher postulated that alterations in the gut microbiota resulting from a loss of toll-like receptor 5 (TLR 5) could promote the development of metabolic syndrome in mice. Moreover, the increased caloric needs of germ-free animals have been used by researcher to demonstrate mechanisms involved in energy metabolism and maintenance of body weight. Indeed, the presence of intestinal microbiota contributes to an increase in the absorption of carbohydrates and lipids, by fermenting substrates passing through the colon but otherwise unavailable to the host [11], and also helps to regulate fat storage [10].

Shortly after birth, germ-free mice have reduced adipose tissue volume compared with conventional mice. The subsequent colonization of germ-free mice with intestinal microbiota can lead to a 60 % increase in body fat and 30 % reduction in food intake. Several mechanisms have been proposed to explain this phenomenon: an increase in monosaccharide absorption in the intestine leading to hepatic lipogenesis, an increase in available calories in the form of energy liberated through bacterial fementation of nondigestable food, or an increase in insulin concentrations, which contributes to anabolism [10, 17].

The intestinal microbiota might also inhibit the expression of an essential metabolic protein, the fasting-induced adipose factor (FIAF), which specially inhibits lipoprotein lipase. In this case the presence of gut microbiota leads to increased lipoprotein lipase activity, which in turn results in the accumulation of fat in the adipose tissue [10]. It has also been observed that the gut microbiota of obese mice has a higher proportion of bacteria belonging to the Firmicute phylum and a proportionally lower population of Bacteriodetes [71], and recently extended to obese children [61]. These data sugges the existence of a link between the composition of the intestinal microbiota, as measured by Firmicutes:Bacteroidetes ratio, seems to have an impact on the health of the host. However, it is yet unclear as to whether these compositional differences exist as a cause or the consequence of obesity [36, 94].

Immunomodulatory properties of probiotics. Clinical obesity, in addition to its obvious outward phenotype, is now recognized as a low-grade inflammatory condition associated with increased macrophage infiltration of the adipose tissue. The compositional alterations in the intestinal microbiota, and particularly the decrease in bifidobacteria, in obese individuals leads to an increase in the lipopolysaccharide plasma concentration. This elevated level of lipopolysaccharides in turn stimulates the synthesis and secretion of proinflammatory cytokines [17]. The adipose tissue itself also contributes to inflammation through the production of proinflammatory cytokines (IL-6, TNF-α, adiponectin) and other compounds such as leptin, which contribute to insulin resistance [26].

Given the measurable perturbations in the microbiota associated with obesity, the consumption of some probiotics potentially represent a novel tool of risk reduction. Indeed, probiotic use would seem particularly suited to restoring resilent microbiota and reducing inflammation which is left untreated could induce a nonreversible disruption and a potential increased sensitivity to infections. Some strains such as E. coli, Nissle 1917, Lactobacillus rhamnosus GG, and Faecalibacterium prausnitzii can act on the immune system with anti-inflammatory effect [66, 100, 104]. Some bacterial strains have been shown to interact with nuclear receptors (α, β, γ), and especially PRARγ [64], which plays an important role in lipid storage stimulation [128]. However as this point, a direct link between the gut microbiota and the endocrine system remains tentative [7].

Modulation of probiotics enzymatic activity and lipid metabolism. The influence of probiotics on obesity can also be tied to bile salts metabolism and to the reduction in fat absorption by the host [13]. A study in mice has demonstrated the influence on lipid metabolism of the strains L. paracasei NCC2461 and L. rhamnosus NCC4007 (10^8 CFU/day). A decrease in the plasma concentrations of very-low-density lipoproteins (VLDL) and LDL was observed under this

regime, along with a complementary increase in triglyceride concentrations. These observed changes were likely due to the induced modification in the enterohepatic recirculation of bile acids, which have been shown to lower cholesterol and systemic concentration of blood lipids [75].

Other studies have also reported on the ability of some probiotics (L. acidophilus CCRC14079, L. acidophilus LA-5, L. casei NCDC19, and Bifidobacterium animalis BB-12) to produce conjugated dienes of linolic acid (CLA) through linolic acid isomerase [6, 73, 134]. CLA compounds have been reported to possess antiobesity activity [74, 116, 127, 130]. However, the decrease in body fat due to the consumption of exogenous CLA is associated with insulin resistance, hyperinsulinemia, and severe hepatic steatosis [15]. Nevertheless, a recent study taking into account the potential risks of CLA showed that ingestion of L. rhamnosus PL60 over 8 weeks ($1 \cdot 10^7$ CFU/day) reduced the weght of obese mice without a reduction of food intake.

Most importantly, this weight and adipose tissue reduction was achieved without the development of hepatic steatosis [70]. Along the same lines, the use of microorganisms with specific enzymatic activity known for their anti-obesity effects (e.g., δ-6-desaturase, an enzyme required for the synthesis of highly unsaturated fatty acids) could have potential benefits and should also be studied.

Impact of probiotics on diabetes. Diabetes is a chronic disease that occurs when the pancreas does not produce any insulin (Type 1 diabetes) or when the body cannot effectively use the insulin produced, and/or when the pancreas does not produce enough insulin (type 2 diabetes) [131]. Type 1 diabetes is an autoimmune disease resulting in total destruction of insulin-secreting β-cells of the Langerhans islets in the pancreas. The destruction of β-cells leads to a lack of insulin in blood, leading to an increase in glycemia and the necessity of daily insulin treatments. Since ~90% of Type 1 diabetes cases are autoimmune in nature, caused by an overactive immune response, the use of immunomodulatory probiotic strains has been proposed as a method of treatment.

To this end Wen et al. [129] have shown that the interaction of the microbiota with the immune systeme is an important factor modifying predisposition to Type 1 diabetes. Probiotics can prevent destruction of β-cells by their anti-inflammatory properties, increase insulin production, or suppress adrenal sympathetic nerve activity.

The oral administration of L. casei during 8 weeks in mice significantly reduced blood glucose concentrations after 12 weeks and also inhibited the production of T-lymphocytes (CD4+) and proinflammatory cytokines (IFN-γ and IL-2) molecules implicated in Type 1 diabetes progression [78]. Furthermore, oral administration of L. casei to mice treated with alloxan (a molecule that specifically targets -cells of Langerhans islets and thus mimics Type 1 diabetes) can inhibit the destruction of the β-cells [76, 77]. A more recent study [112] has shown that hyperglycemia may by significantly attenuated by the administration of L. rhamnosus GG over a 10-week period, where an effect on insulin production and glucose tolerance was observed. Yamano et al. [135] have carrying out studies on rats supplied water supplemented with a probiotic strain (L.johnsonii La1 ~$1{,}9 \cdot 10^9$ CFU/cm^3) and have demonstrated a decrease in glucose and glucagon amounts, along with an increase in insulin concentrations in the blood.

After having administrated probiotics by intraduodenal injection in rats ($2 \cdot 10^{10}$ CFU/cm^3) authors [135] have revealed a suppression of adrenal sympathetic nerve activity which could improve glucose tolerance by redusing glucagon secretion. A further research was also undertaken into the application of the probiotic strain L. acidophilus (~$1{,}89 \cdot 10^9$ CFU/cm^3) with the goal of restoring nitric oxide concentrations in rats, which is an important regulator of many physiological processes. Importantly, nitric oxide bioactivity is known to be low in Type 1 diabetes [49].

This noninsulin dependent diabetes is a metabolic disorder affecting glucose regulation and eventually causing diabetes mellitus characterized by insulin resistance and reactive hyperinsulinemia. Rats placed on a high fructose diet for 8 weeks suffered from glucose intolerance and an increase in glucose, cholesterol [high-density lipoprotein (HDL) and LDL], and triglycerides amounts in the blood stream [133]. This effect of a fermented milk product containing probiotic strains (L. acidophilus and L. casei) demonstrated that a number of diabetes-associated parameters (i.e., glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress) could by ingestion of the probiotic strains be controlled. Probiotics from a number of reports have been shown to influence Type 1 diabetes at three levels: 1) by regulating immune system activity and thus reducing destruction of pancreatic cells, 2) by simulating insulin production, thereby aiding the reabsorbtion of circulating glucose, and 3) by decreasing glucagon production via modulation of adrenal sympathetic nerve activity [43]. Understanding the relationship between microorganisms and neural modulation is vital to find new probiotic applications, yet very studies exist that address this issue.

Impact of probiotics on hypertension. Nearly a quarter of the population in developed countries suffers from hypertension, another of risk factors for cardiovascular disease. Even though there are no direct causes of hypertension, there are many risk factorssuch as sedentary lifestyle, obesity (more than 85% cases occur in those with a body mass index greater than 25), sodium sensitivity, alcohol intake, and vitamin D deficiency [99, 124]. As a result prevail-

ing modern trends the percentage of individuals affected by this condition continues to increase.

Since an overactive renin-angiotensin system (RAS) leads to vasoconstriction and retention of sodium and water, a way to reduce hypertension is to ACE (angiotensin-converting enzyme) inhibitors [16]: ACE is responsible for increasing blood pressure and blood volume by converting angiotensin I to angiotensin SS, a potent vasoconstrictor, and degrading bradykinin, a potent vasodilatator, and other vasoactive peptides.

Very few studies are currently available on the use of probiotic microorganisms in reducing hypertension and its concordant risk of developing cardiovascular disease. However, beneficial effects of probiotic strains on blood pressurehave been publicized in some report. Kawase et al. [31] have observed a systolic pressure reduction of 6 mm Hg in rats after 8 weeks of L.casei TNC0409 ($\sim$2,4$\cdot 10^{11}$ CFU/day) and Streptococcus thermophilus TMC1543 ($\sim 10^{10}$ CFU/day) ingestion. The atherogenic index of plasma after 4 weeks was also significantly lowered. Tanida et al. [114] have suggested that the probiotic strain L.johnsonii La1 (intraduodenal injection $1\cdot 10^9$ CFU/day), or its metabolites, might lower hypertension by changing autonomic neurotransmission via the central histaminergic nerves and the suprahiasmatic nucleus in rats.

Probiotic strain L. plantarum 299v ($2\cdot 10^{10}$ CFU/day) when administered to 36 smokers over 6 weeks (controlled, randomized, double-blind trial), was shown to lower systolic blood pressure (13 mmHg) [85]. L. plantarum 299 v also induced a significant increase in HDL (+10 %) and a decrease in leptin concentration (-37 %), LDL (-12%), fibrinogen (-21%), IL-6 (-41 %), and F2-isoprostanes (-31%), which are biochemical markers of lipid peroxidation and oxidative stress. All these modifications could help to reduce the cardiovascular risk. Similarly, in a randomized placebo-controlled study with 39 hypertensive patients showed that consumption of the strain L. helveticus LBK-16H during 21 weeks led to a significant reduction of 6-7 mmHg in systolic pressure [102]. These results were confirmed in a randomized, placebo-controlled study involving 40 subjects with high normal blood pressure and 40 subjects with mild hypertension, each receiving L. helveticus CM4 over a 4-week period [5]. Despite these positive results, Simons et al. [103] failed to observe a significant reduction in blood pressure after ingestion of L. fermentum for 10 weeks ($4\cdot 10^9$ CFU/day). This single-center, double-blind, placebo-controlled, parallel design trial was conducted with 46 volunteers with elevated serum cholesterol. It has been proposed that microorganisms are able, through their proteolytic activity, to release bioactive peptide that exhibit antihypertensive properties (e/g/ casokinine from milk casein or lactokinine from α-lactalbumin or β-lactoglobulin) and inhibit ACE activity [27]. These properties are currently limited to certain strains of lactobacilli with specific cell wall enzymes (proteinases) [35, 86, 110].

Impact of probiotics on hypercholesterolemia. For over two centuries, the role of cholesterol in the risk of developing inflammatory diseases such as atherosclerosis has been noted [54]. Cholesterol is carried in the blood stream by lipoproteins such as LDL, VLDL, HDL, and chylomicrons. VLDL and LDL transport cholesterol from the liver to other cells in the body. An increase in the amount of circulating LDL will eventually result in the formation of atherosclerotic plaques (deposits of cholesterol in the arteries), increasing the risk of cardiovascular diseases when associated with oxidative stress [29]. HDL, in the reverse role, collects cholesterol from the arteries and atheromas and returns it to the liver [44].

Drouault et al. [28] attempted to establish a relationship between the structure of the gut microbiota and its ability to influence on fat metabolism and assimilate cholesterol. Three mechanisms of action have been proposed: 1) degradation of bile acids through the enzyme bile salt hydrolase (BSH) which deconjugates bile salts and reduces their reabsorbtion by the body [42], 2) membrane incorporation of cholesterol, e.g. by the strain L. acidophilis ATCC43121 [88], and 3) conversion of cholesterol to coprostanol, which is easily assimilated and excreted in feces [18, 41, 120]. Other researchers believe that probiotics could decrease the synthesis of cholesterol in the liver itself [20, 38, 63]. Most studies to date show a beneficial effect of probiotics on cholesterol concentration. Kawase et al. [63] observed an increase in HDL (+28 %) and a decrease in triglyceride concentration (-20 %) in rats supplemented with L. casei TMC1543 ($\sim 10^{10}$ CFU/day) for 4 weeks.

Similarly a positive effect on LDL concentration has been observed with the strain Bifidobacterium longum BL1 [132], where a significant decrease in the concentration of LDL was observed (-41 %) in a group fed with probiotics in comparison with a control group. Wang et al. [125] evaluated the effects of L. plantarum MA2 (10^{11} CFU/day) in mice during 5 weeks and revealed a significantly lowered serum total cholesterol (-21%), LDL (-20 %) and triglyceride concentration (-25 %), while observing no changes in HDL.

Meta-analysis of data from 425 healthy volunteers revealed a significant and beneficial effect of probiotics on reducing cholesterol concentration (a 4 % decrease in total cholesterol and a 5 % decrease in LDL cholesterol) [3]. Additionally, ingestion of Enterococcus faecium M-74 ($2\cdot 10^9$ CFU/day) in 43 volunteers over 56 weeks of a randomized double-blind, and placebo-controlled study was associated with a 12 % reduction in total cholesterol, a decrease in LDL (-19 %), and no change in HDL and triglycerides [54]. Recently, Andrade and Borges [8] tested

the effects of the L. acidophilus 145 and B. longum BB536 on 34 women and observed a significant reduction in LDL (double-blind, placebo-controlled, crossover study). Similarly, Ataie-Jafari et al. [9] demonstrated that the consumption of yogurt containing L. acidophilus and B. lactis for 4 weeks was associated with a significant decrease in total serum cholesterol in comparison with ordinary yogurt.

Impact of probiotics on hyperhomocysteinemia. Many studies have marked a correlation between nutrient deficiencies (mainly due to B-vitamin deficiencies [108]) and a high plasma homocysteine concentration, which is considered as a risk factor for cardiovascular diseases. Hyperhomocysteinemia can have an impact on oxidative stress, hemostasis and endothelial dysfunction, decreased nitic oxide production, and can affect vascular smooth muscles [55]. After having focused on the production by microorganisms of vitamin K [83], a vitamin involved in blood clotting atherosclerotic plaques [89], researchers recently proposed the use of probiotic strains to reduce hyperhomocysteinemia.

Studies have shown that some lactic acid bacteria and species of Bifidobacterium are able to produce folates in fermented milk [25, 92]. However, some lactobacilli strains used in the production of fermented milk have also been shown to depress the concentration of folic acid in milk [25]. Certain strains of S. thermophilus are very good producers of folates, resulting in a four-fold increase in milk [25]. Moreover, a mix of different strains can greatly increase the amount of folates in milk. This increased concentration of folate is due to the metabolic activity of lactic acid bacteria and Bifidobacterium species [96]. During the fermentation process some probiotics also produce vitamin B_{12} [52, 82, 115], and vitamin B_2 [56].

A comparative genome analysis aimed at identifying new biochemical pathways suggested that the ability of some probiotic strains, especially L. reuteri, to produce vitamin B_{12} is due to an adaptive evolutionary response [84]. The production of И vitamins by probiotics has also been examined in vivo. Pompei et al. [91] showed that administration of three bifidobacteria (B. adolescentis MB 227, B. adolescentis MB 239, and B. pseudocatenulatum MB 116) at $2 \cdot 10^8$ CFU/day for 2 weeks increased folate concentration in the liver and serum in rats.

A randomized nutritional supplementation trial showed that the consumption by children of both sexes (11 years old) of L. acidophilus La1 during 6 weeks in a yogurt matrix (10^{12} CFU/day) was associated with increased folic acid and vitamin B_{12} and decreased homocysteine in the plasma [81]. The ability of probiotics to produce folic acid in humans has been confirmed in three bifidobacterium strains (B. adolescentis DSM18350, B. adolescentis DSM18352, and B. pseudocatenulatum DSM18353) consumed by 23 healthy volunteers (randomly divided into three groups) at $5 \cdot 10^9$ CFU/day during 30 days in a randomized study [109]. These authors have documented the ability of these probiotic strains to colonize the human intestine and to synthesize, de novo, significant amont of folic acid.

The positive effect of the administration of bifidobacteria has also been studied on the homocysteine levels of hemodialysis patients [113]. Vitamin-producing probiotics may provide a complementary endogenous source of biomolecules that are not synthesized by mammalian cells. Probiotics are especially useful for homeostasis of human body, and unlike oral administration of the vitamins, ensures a constant bioavailability [109].

Impact of probiotics on oxidative stress. Oxidation reactions are essential for energy production in living cells. However, oxygen can lead to formation of reactive oxygen or nitrogen species (ROS or RNS), which alter lipids, proteins, nucleic acids, and carbohydrates an can provoke cell and tissue damage [107]. Oxidative stress is caused by an imbalance between ROS production and a biological system's ability to readily detoxify the reactive intermediates or to easily repair the resulting damage [37].

Even as ROS production is used by the immune system as a means of neutralizing pathogens [118]. Oxidative stress is implemented in many diseases such as gastrointestinal inflammation [i.e., inflammatory bowel disease (IBD)], colitis disorders, atherosclerosis, myocardial infarction, stroke, Alzheimer's disease, Parkinson's disease, cirrhosis, dermatitis, diabetes mellitus or Type 2 diabetes, age-related macular degeneration and retinopathy [12, 65, 80]. Metabolic syndrome, obesity, accelerated aging, and the development of certain tumors have also been linked to oxidative stress [24, 123]. Increased ROS initiated several processes involved in atherogenesis [121], including expression of adhesion molecules, stimulation of vascular smooth muscle proliferation and migration, apoptosis in the endothelium, oxidation of lipids, activation of matrix metalloproteinase, and altered vasomotor activity [50, 52]. A recent publication has demonstrated that the intake of antioxidants may lead to the reduced impact of oxidative stress on the human body [52, 72].

Probiotic strains have been explored for their ability to reduce oxidative stress. In vitro, some probiotic strains can reduce oxidative stress. This is the case for L. fermentum ME-3 DSM14241, possessing a manganese superoxide dismutase (SOD), which can increase the antioxidative defensives (TAA, the total antioxidative activity; TAS, the total antioxidative status; and glutathione reductase) and scavenge prooxidant metals [70, 80]. Some lactobacilli and bifidobacteria also possess in vitro antioxidant capacity [126]. These strains are notably able to limit lipid peroxidation and to enhance free radical scavenging. In

vivo the proof of the concept of antioxidative strains protecting mice from inflammation has been shown in several studies using either recombinant lactococci [47, 48] or recombinant lactobacilli [47, 69].

These recombinant strains producing SOD or catalase were able to reduce damages induced in TNBS — (trinitrobenzene sulfonic acid) and DSS — (dextran sulfate sodium) induced colitis murine models, suggesting a potential interest in antioxidative probiotic strains for the prevention and the treatment of IBD. Recently, it has been shown that probiotic strains S. boulardii when administered to rats allowed an upregulation of SOD and glutathione peroxidase [30].

Volunteers (n=21) were selected for a 3-week trial in order to assess the effect of the probiotic L. fermentum ME-3 [68]. Administration of fermented goat milk increased the protection against atherogenicity in the participants. In clinical study reported on the beneficial effects on oxidative stress of probiotics consumption in healthy individuals [105]. Consumption of L. fermentum ME-3 in fermented milk (6,3 109 CFU/day, open, placebo-controlled, n=21) or capsules (1,6 109 CFU/day, double-blind, randomized, placebo-controlled, n=24) over 3 weeks was shown to significantly improve the blood TAA and TAS value: 6 % and 9 % for fermented milk, and 4 % and 2,5 % for capsules, respectively.

The increase in TAA value by ingestion of L. fermentum ME-3 has also been shown in vitro [106]. A crossover, randomized clinical trial was carried out with conventional yoghurt and probiotic yoghurt containing L. casei on 33 healthy female volunteers [33]. The results showed a a significant reduction in total antioxidant capacity values and increase in malondialdehyde and conjugated dienes value in both tested groups.

Summary. Many studies on probiotics have highlighted the importance of the gut microbiota in gastrointestinal disorders and have more recently begun to focus on associated cardiovascular risks. Probiotics show positive effects on the six disorders/disturbances in in vitro and in vivo studies, most notably due to their anti-inflammatory properties or their enzymatic capacities. However, the lack of double-blind randomized clinical trials, especially for obesity, diabetes, and oxidative stress, makes definitive conclusions impossible at this time. Furthermore, no studies to date have directly addressed the impact of probiotics on risk factors for cardiovascular diseases, which include aneurysm, angina pectoris, atherosclerosis, cerebrovascular accident, cerebrovascular disease, congestive heart failure, coronary artery disease, myocardial infarction, and peripheral vascular disease.

In this review we attempt to highlight the links made between medical disorders and mechanism of probiotics action. In the future, recombinant probiotics [14, 95] and the determination of microbiota composition in patients suffering from specific medical disorders [104] represent new avenues of research.

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Пробиотики:влияние на течение воспалительных процессов и на другие факторы, вызывающие развитие сердечно-сосудистых заболеваний

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***Резюме**. Пробиотики – биологически активные вещества, содержащие в своем составе живые бактерии, близкие по строению к бактериям нормальной микрофлоры кишечника. Попадая в организм, пробиотики способствуют нормализации работы желудочно-кишечного тракта и снижают вероятность развития воспалительных заболеваний ЖКТ, болезни Крона, язвенного колита и т.д. Они так же способствуют профилактике появления многих патологических состояний, которые являются факторами риска развития сердечно-сосудистых заболеваний (ожирение, гиперхолестеринемия, окислительный стресс, диабет, метаболические нарушения). В данном аналитическом обзоре показано положительное действие пробиотиков на макроорганизм на молекулярно-клеточном уровне за счёт продукции специфических регуляторных молекул и высвобождения биологически активных пептидов, регулирующих функционирование вегетативной нервной системы.*
Ключевые слова: пробиотики, сердечно-сосудистые заболевания, ожирение, метаболизм лепидов, холестерин, окислительный стресс, воспаление.

Пробіотики: вплив на перебіг запальних процесів та на інші фактори, що спричиняють розвиток серцево-судинних захворювань

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Резюме. Пробіотики – біологічно активні сполуки, які у своєму складі мають живі бактерії, подібні за будовою до бактерій нормальної мікрофлори кишківника. Потрапляючи до організму, пробіотики сприяють нормалізації роботи шлунково-кишкового тракту та знижують вірогідність розвитку запальних захворювань ЖКТ, хвороби Крона, виразкового коліту та ін. У процесі численних досліджень з'ясовується профілактична спроможність пробіотиків щодо розвитку багатьох патологічних станів – факторів ризику розвитку серцево-судинних захворювань (ожиріння, гіперхолестеринемія, окислювальний стрес, діабет, метаболічні зрушення). У даному аналітичному огляді показана позитивна дія пробіотиків на макроорганізм на молекулярно-клітинному рівні за рахунок поліпшення кишкового мікробіому. Більшість пробіотиків сприяють модуляції адекватної імунної відповіді організму завдяки продукції специфічних регуляторних молекул і вивільнення біологічно активних пептидів, що регулюють функціонування вегетативної нервової системи.
Ключові слова: пробіотики, серцево-судинні захворювання, ожиріння, метаболізм ліпідів, холестерин, окислювальний стрес, запалення.