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# HEALTH BENEFITS OF TAKING PROBIOTICS IN PEOPLE WITH METABOLIC SYNDROME

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***Abstract.*** *Metabolic syndrome is a complex condition that includes dyslipidemia, impaired glucose homeostasis, elevated blood pressure, overweight, abdominal obesity, and/or insulin resistance, increasing the risk of heart disease, stroke, and type 2 diabetes. It is the result of an energy imbalance that favors the accumulation of fat in tissues. Molecular changes include reduced mitochondrial oxidative capacity, damaged cellular redox state, and altered insulin signaling leading to impaired glucose transport and lipolysis. Probiotics are recognized as powerful dietary components with numerous health-promoting functions that can also help fight certain diseases. This paper provides an overview of the effects and mechanisms of action of probiotics (mainly Lactobacillus strains) in the prevention and treatment of metabolic syndrome. Despite the observed benefits of Lactobacillus administration, the exact mechanism of action is not yet clear, but it is most likely related to the reduction of endoplasmic reticulum stress and suppressed macrophage activation, leading to increased insulin sensitivity. An analysis of nine clinical trials, six of which were randomized, has shown that in some cases the use of probiotics in patients with metabolic syndrome leads to an improvement in body mass index, blood pressure, glucose metabolism, and lipid profile. Probiotics also had a positive effect on inflammatory biomarkers such as soluble vascular cell adhesion molecule-1, interleukin-6, tumor necrosis factor-alpha, vascular endothelial growth factor, and thrombomodulin. Although the use of probiotics may lead to a discrete improvement in some clinical features and a reduction in inflammatory biomarkers, these beneficial effects appear to be marginal compared to the effects of drug therapy and a healthy lifestyle. Disruption of the gut microbiota also influences various risk factors for metabolic syndrome. Thus, maintaining a healthy microbiota is as important as restoring a disturbed microbiota.*

***Key words:*** *probiotics, Lactobacillus, metabolic syndrome*

## Introduction

Metabolic syndrome refers to a group of conditions that can lead to cardiovascular disease, diabetes, stroke, and other health problems (Figure 1). It primarily affects the heart, liver, pancreas, blood vessels, and visceral adipose tissue [1] and is associated with mitochondrial and insulin signaling dysfunction [2, 3]. The main risk factors for metabolic syndrome are abdominal obesity, insulin resistance, physical inactivity, aging, and hormonal imbalance [4]. It is diagnosed when someone has three or more signs: high blood glucose level (≥ 100 mg/dL), low blood high-density cholesterol level (< 50 mg/dL in women and < 40 mg/dL in men), high blood triglyceride level (≥ 150 mg/dL), large waist circumference (≥ 88 cm in women and ≥ 102 cm in men), and high blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) [5]. In recent years, the prevalence of metabolic syndrome has increased, especially in the United States, largely due to unhealthy lifestyles and associated diseases, and in some countries, it is as high as 30% [5]. According to the World Health Organization (WHO), there are 890 million adults with obesity [6], 1.28 billion adults with hypertension [7], and 422 million adults with diabetes [8].

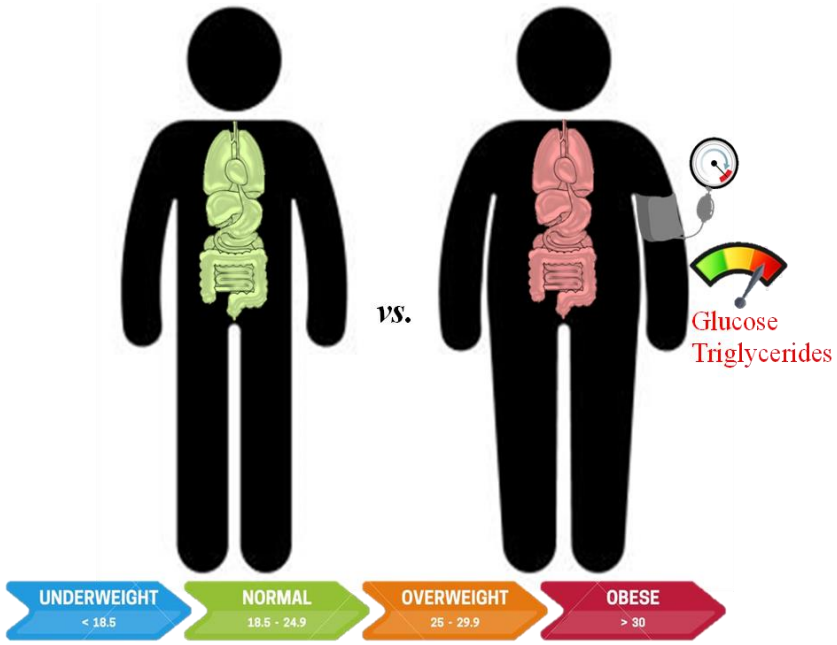


Figure 1. Probiotic-promoted health *vs.* metabolic syndrome

Obesity is a major health risk for metabolic syndrome. Globally, it has doubled in adults and quadrupled in adolescents in the last 30 years. In 2022, 2.5 billion adults (aged 18 and over), 37 million children under the age of 5, and 390 million children and adolescents aged 5 to 19 were overweight [6]. There is increasing evidence of a

causal relationship between the gut microbiota and obesity/obesity-related diseases [9]. Thus, one of the alternative strategies in the fight against obesity and therefore the metabolic syndrome is the use of probiotics in food, as a dietary supplement, and rarely as a drug. The traditional bacteria *Lactobacillus* is the best-studied probiotic with a long tradition of use to maintain and improve human health. The bacteria *Bifidobacterium*, the yeast *Saccharomyces cerevisiae*, and more recently an innovative beneficial bacteria (next-generation probiotics, NGP) have also been recognized as useful and subjected to extensive research.

## *Lactobacillus*

*Lactobacillus* is a group of lactic acid-producing bacteria that are divided into 23 genera, more than 250 species, and 57 subspecies, and are widely found in nature, humans, and food. Some of them are effective in the prevention and treatment of various diseases, including metabolic syndrome, and are therefore used as probiotics with dose- and strain-specific effects. The mechanism of action is not yet fully understood, but it is probably associated with increased insulin sensitivity, due to a reduction in endoplasmic reticulum stress and suppressed macrophage activation [10]. No less important mechanisms of action is the modulation of the gastrointestinal microbiota and the immune system [11].

In high-fat diet-induced obese rodents, the use of *Lb. rhamnosus* PL60 ($1 \times 10^7$ or $1 \times 10^9$ CFU/day for 8 weeks), *Lb. plantarum* LG42 ($1 \times 10^7$ or $1 \times 10^9$ CFU/day for 12 weeks), *Lb. plantarum* Q180 ($1 \times 10^9$ CFU/mL for 8 weeks), *Lb. plantarum* TN8 ($1 \times 10^9$ CFU/day for 30 days), *Lb. plantarum* KY1032 and *Lb. curvatus* HY7601 (each $1 \times 10^{10}$ CFU/day for 9 weeks, singly or in combination) or *Lb. gasseri* SBT2055 ($5 \times 10^8$ CFU/g for 24 weeks) was associated with a reduction in adipose tissue, body weight, glucose, insulin, leptin, cholesterol and triglyceride levels, insulin resistance, and pro-inflammatory interleukin-12, interferon-gama and tumor necrosis factor-alpha cytokine production, as well as a concomitant increase in interleukin-10 and improvement in fatty liver index [12-17]. Commercial probiotic strains *Lb. rhamnosus* Rosell 11 and *Lb. helveticus* Rosell 52 ($1 \times 10^7$, $1 \times 10^8$, and $1 \times 10^9$ CFU/mL for 2 months) also had beneficial effects in mice fed a high-fat high-sucrose diet, which were reflected in significantly decreased blood glucose and serum triglyceride levels, improved glucose tolerance, and promoted body weight loss, especially at a concentration of $10^9$ CFU/mL [18].

In clinical trials with overweight or obese individuals, supplementation with *Lb. gasseri* BNR17 ($1 \times 10^9$ or $1 \times 10^{10}$ CFU/day over 12 weeks), *Lb. rhamnosus* strain CGMCC1.3724 ($1.6 \times 10^8$ CFU/day over 24 weeks), *Lb. plantarum* TENSIA ($1.5 \times 10^{11}$ CFU/g over 3 weeks), *Lb. reuteri* V3401 ($5 \times 10^9$ CFU/day over 12 weeks) or *Lb. plantarum* K50 ($4 \times 10^9$ CFU/day over 12 weeks) reduced visceral adipose tissue, weight, body mass index, blood pressure, cholesterol and triglyceride levels, interleukin-6, and soluble vascular cell adhesion molecule-1 [19-23]. A meta-analysis of nine clinical trials of *Lactobacillus* supplementation showed positive effects on total cholesterol and low-density lipoprotein concentrations, fasting glucose and

triglycerides in these individuals [24]. Finally, a multispecies probiotic containing different strains of *Lactobacillus* (*Lb. acidophilus* W37, *Lb. brevis* W63, *Lb. casei* W56, *Lb. salivarius* W24), *Lactococcus* (*L. lactis* W19, *L. lactis* W58), and *Bifidobacterium* (*B. bifidum* W23, *B. lactis* W51, *B. lactis* W52) administered over 12 weeks decreased the systolic blood pressure and interleukin-6 levels at a dose of $2.5 \times 10^9$ or $1 \times 10^{10}$ CFU/day, and the vascular endothelial growth factor, tumor necrosis factor-alpha, and thrombomodulin at a dose of $1 \times 10^{10}$ CFU/day [25].

In addition to probiotics, postbiotics (cell-free supernatants, exopolysaccharides, enzymes, cell wall fragments, short-chain fatty acids, bacterial lysates) can also play a role in lipid metabolism and reduce the risk of obesity and obesity-related diseases such as metabolic syndrome [26, 27]. Postbiotics include all substances released or produced by the metabolic activity of a microorganism that have a direct or indirect positive effect on the host. Since postbiotics do not contain live microorganisms, the risks associated with their intake are low. Thus, in high-fat diet-induced obese rodents, the cell-free extract of *Lb. paracasei* (100 and 200 mg/kg for 9 weeks) reduced body weight, total serum lipids and triglycerides [28], exopolysaccharides from *Lb. rhamnosus* GG (50 mg/kg every two days for 2 weeks) reduced triacylglycerol and cholesterol ester levels in the liver and down-regulated inflammation in adipose tissue and liver [29], and heat-killed *Lb. plantarum* L-137, administered for 4 to 20 weeks, reduced weight gain, plasma glucose, cholesterol, alanine aminotransferase, and aspartate transaminase [30].

## *Bifidobacterium*

*Bifidobacterium* is a group of bacteria normally found in the gut that contribute to health by immunomodulating, strengthening the intestinal epithelial barrier, preventing the adhesion of pathogens and producing antimicrobial compounds [31].

Treatment with *Bifidobacterium* strains led to improvements in high-fat diet-induced obese rodents. *B. breve* B-3 ($1 \times 10^8$ or $1 \times 10^9$ CFU/day for 8 weeks) or *B. longum* BR-108 (200 or 400 mg/kg/day for 4 weeks) reduced visceral fat, decreased glucose, triglyceride and cholesterol levels, improved glucose tolerance, and diminished insulin resistance [32, 33]. In another study, the administration of *Bifidobacteria* strains FS31-12, L66-5, M13-4, and L75-4 ($1 \times 10^8$ CFU/mL for 6 weeks) reduced serum triglycerides and liver fat content, with only the administration of strain L66-5 leading to body weight loss [34].

The probiotic *B. lactis* HN019 reduced body mass index, total cholesterol, and low-density lipoprotein, as well as the pro-inflammatory cytokines tumor necrosis factor-alpha and interleukin-6 in patients with metabolic syndrome ($2.72 \times 10^{10}$ CFU/day over 45 days) [35], while the daily administration of capsules containing *B. longum* BB536 ($1 \times 10^{10}$ CFU) and *B. breve* MCC1274 ($5 \times 10^9$ CFU) decreased abdominal visceral fat area, total abdominal fat area, serum triglyceride levels, and body mass index in overweight adults [36]. A meta-analysis found that supplementation with a probiotic bifidobacteria formulation (*B. bifidum*, *B. breve*, *B. longum*, *B. animalis*

subsp. *lactis*) was also associated with an improvement in adiposity, glycemia, insulin resistance, and fatty liver, with possible species-specific effects [37].

### *Saccharomyces boulardii*

The only probiotic yeast on the market is *S. cerevisiae* var. *boulardii* (formerly *S. boulardii*), which is most commonly recommended for diarrhea caused by *Clostridium difficile* [38] and/or in combination with the use of antibiotics to promote recolonization of the microbiota [39]. *S. boulardii* and its metabolites act as regulators of the intestinal microbiota [40]. The bioactive metabolite products (2-hydroxyisocaproic acid, gamma-aminobutyric acid, shikimic acid, p-aminobenzoic acid, tyrosol, and lactic acid) have antioxidant, antibacterial, antitumor, and anti-inflammatory properties [41]. The advantage over probiotic bacteria is the impossibility of acquisition, i.e. the absence of resistance to antibiotics [40], which may facilitate their use in the development of functional foods [42]. Oral ingestion of *S. boulardii* is considered safe and well tolerated, but there are several reports of fungemia in patients with severe intestinal and general diseases [43, 44]. Preparations containing *S. boulardii* have been on the market since 1950 and have been used in clinical trials since 1977, indicating their relatively safe nature [45].

To evaluate the risk factors for the occurrence of metabolic syndrome and the beneficial effect of *S. boulardii* in its treatment, eight studies were reviewed based on defined inclusion criteria, of which five were animal studies (preclinical studies) and three were human studies (clinical trials). The results showed regulation of lipid profile, modulation of intestinal microbiota and gene expression, and reduction of body weight as positive outcomes of *S. boulardii* ingestion. Although further experiments are required to confirm these results, there is a trend towards a reduction in metabolic syndrome risk factors with *S. boulardii* ingestion. *S. boulardii* appears to show a renoprotective effect by reducing albuminuria and proteinuria and improving histologic changes in animals with type 1 diabetes [5].

## Innovative beneficial bacteria

Innovative beneficial bacteria such as *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Anaerobutyricum hallii*, *Bacteroides uniformis*, *Bacteroides coprocola*, *Parabacteroides distasonis*, *Parabacteroides goldsteinii*, *Hafnia alvei*, *Odoribacter laneus*, and *Christensenella minuta*, identified in the gut microbiome by novel next-generation sequencing techniques, appear to be the main components of NGP. Their mechanisms of action include modulation of gut microbiota and secretion of gut peptides, improvement of gut function, and maintenance of gut integrity [46]. The beneficial effects of these probiotics and the safety of their use in obesity and obesity-related diseases have not yet been extensively studied and have so far been demonstrated mainly for *A. muciniphila* and *H. alvei*.

It has been shown that the administration of *A. muciniphila* strains EB-AMDK 10, EB-AMDK 19 and EB-AMDK 27 ($1 \times 10^8$ CFU/day for 12 weeks) or BAA835 ($2 \times 10^8$ CFU/day for 4 weeks) and *H. alvei* strains HA4597 ($3 \times 10^8$ and $4 \times 10^7$ CFU/day for 18 and 46 days; $1.4 \times 10^{10}$ CFU/day for 38 days) reduced body weight, food intake, fat mass, adipogenesis/lipogenesis, serum total cholesterol, inflammation, and insulin resistance, restored damaged gut structure and integrity, and improved liver function and glucose homeostasis in a mouse model of high-fat diet-induced obesity [47-50]. Clinical trials have confirmed that the administration of *A. muciniphila* ($1 \times 10^{10}$ CFU/day over 3 months) and *H. alvei* HA4597 ($1 \times 10^{11}$ CFU/day over 12 weeks) in overweight/obese individuals is safe and well-tolerated, and is associated with a reduction in body weight, fat mass, hip circumference, insulinemia, and plasma total cholesterol level, and an improvement in insulin sensitivity, liver dysfunction, and inflammation [51, 52].

## Conclusion

The efficacy and positive effects of probiotics on the characteristic signs of metabolic syndrome have already been demonstrated in numerous animal studies and clinical trials. However, further research is needed to explain more precisely and specifically the observed effects and mechanisms of action of probiotics, especially considering that they are still marginal compared to the effects of drug therapy and a healthy lifestyle.

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# ZDRAVSTVENE KORISTI PRIMENE PROBIOTIKA KOD LJUDI SA METABOLIČKIM SINDROMOM

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***Sažetak.*** *Metabolički sindrom je kompleksno stanje koje uključuje dislipidemiju, poremećenu homeostazu glukoze, povišen krvni pritisak, prekomjernu težinu, abdominalnu gojaznost i/ili insulinsku rezistenciju, i samim tim povećava rizik od srčanih oboljenja, moždanog udara i dijabetesa tipa 2. Posljedica je energetskog disbalansa koji pogoduje akumulaciji masti u tkivima, dok molekularne promjene uključuju smanjen oksidativni kapacitet mitohondrija, oštećeno ćelijsko redoks stanje i izmijenjenu signalizaciju insulina koja dovodi do poremećenog transporta glukoze i lipolize. Probiotici su prepoznati kao moćni sastojci u ishrani sa višestrukim funkcijama za unapređenje zdravlja, zajedno sa njihovom sposobnošću da pomažu u borbi protiv specifičnih bolesti. U ovom radu je dat pregled efekata i mehanizama djelovanja probiotika (uglavnom Lactobacillus sojeva) u prevenciji i pri terapiji metaboličkog sindroma. Bez obzira na pokazane koristi primjene Lactobacillus, još uvijek nije razjašnjen tačan mehanizam djelovanja, ali je najvjerovatnije povezan sa smanjenjem stresa endoplazmatskog retikuluma i potisnutom aktivacijom makrofaga, što dovodi do povećane osjetljivosti na insulin. Analiza devet kliničkih studija, od kojih je šest randomiziranih, pokazala je da primjena probiotika kod pacijenata sa metaboličkim sindromom u nekim slučajevima dovodi do poboljšanja indeksa tjelesne mase, krvnog pritiska, metabolizma glukoze i lipidnog profila. Probiotici su takođe imali pozitivan efekat na inflamatorne biomarkere kao što su rastvorljivi molekul adhezije vaskularnih ćelija-1, interleukin-6, faktor nekroze tumora-alfa, faktor rasta vaskularnog endotela i trombomodulin. Iako upotreba probiotika može dovesti do diskretnog poboljšanja nekih kliničkih karakteristika i smanjenja inflamatornih biomarkera, čini se da su ovi korisni efekti marginalni u poređenju sa efektima terapije lijekovima i zdravim načinom života. Takođe, i poremećaj mikrobiote crijeva utiče na različite faktore rizika za metabolički sindrom. Stoga je održavanje zdrave mikrobiote važno kao i obnavljanje poremećene mikrobiote.*

***Ključne riječi****: probiotici, Lactobacillus, metabolički sindrom*