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Probiotics and prebiotics in arterial hypertension

Probiotici i prebiotici kod arterijske hipertenzije

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ABSTRACT

There is growing evidence that a disturbed microbiota, a complex ecosystem, is associated with the development of numerous diseases, including arterial hypertension. This complex cardiovascular disease is the result of not sufficiently clear role that genetic and environmental factors play in it. Not only does the treatment of hypertension include a drug therapy, but also it includes a variety of non-pharmacological measures based on dietary intervention. Probiotics and prebiotics are besides the nutrition the most commonly used substances that are aimed at maintaining a healthy microbiome or restoring the balance in case of disturbed bacterial homeostasis in disease. Although many studies have confirmed the effects of an imbalance in the gut microbiota (dysbiosis) in the last decade, the benefits of dietary intervention with probiotics in people with hypertension need to be supported by stronger evidence and further clinical trials in order to be ultimately confirmed.

Keywords: microbiota, probiotics, prebiotics, arterial hypertension

SAŽETAK

Sve je više dokaza da je narušen sustav ljudske mikrobiote, kompleksnog eko sistema, povezan s patogenezom brojnih bolesti, među ostalim i arterijske hipertenzije (AH). Ova kompleksna kardiovaskularna bolest rezultat je još uvijek nepotpuno jasne uloge genetskih i okolišnih čimbenika. Liječenje AH pored medikamentnog liječenja obuhvaća i višestruke nefarmakološke mjere čiji temelj predstavljaju dijetalne intervencije. Najčešće korištene tvari kojima se nastoji održati zdrav mikrobiom ili uspostaviti ravnoteža pri poremećenoj bakterijskoj homeostazi u bolesti su, osim prehrane, probiotici i prebiotici. Iako mnoga istraživanja u zadnjem desetljeću potvrđuju učinak disbalansa crijevne mikrobiote (tzv. disbioze), za definitivnu potvrdu dobrobiti dijetalne intervencije probioticima kod osoba s AH, potrebni su snažniji dokazi te daljnja klinička istraživanja.

Ključne riječi: mikrobiota, probiotici, prebiotici, arterijska hipertenzija

INTRODUCTION

Not only do the foods have the purpose of supplying the organism with nutrients for the fundamental functions of growth and development nowadays, but also it is becoming an increasingly important component in maintaining health and everyday quality of life (Shori, 2015; Markowiak and Śliżewska, 2017). The improvement of technological processes of food production and processing as well as new scientific insights related to nutrition have led to a reduction of incidence of diseases caused by lack of nutrients. However, we are facing the challenges of malnutrition at the same time (Shao et al., 2017). An increasing number of citizens in the European countries practice the so-called the Western pattern diet, which is characterized by a high intake of red meat, animal fat, sweets and desserts, as well as a low intake of fresh fruits and vegetables and low-fat dairy products, and in general we eat too much processed food and too little fermented food, which results in a lower diversity of microbiota. This diet accompanied by reduced physical activity increases the risk of nutritional deficits, obesity and chronic diseases (Hariharan et al., 2015; Furman et al., 2019). Food and lifestyle have thus become the leading factors that affect the economic and social status, life expectancy and quality of life of the inhabitants of Europe (Granato et al., 2010). Ultra-processed foods with a high glycemic index, which are highly present in such foods, stimulate oxidative stress, which causes the activation of various inflammatory processes (Furman et al., 2019). In contrast, meals rich in fresh fruits and vegetables with little red meat, and foods included in the Mediterranean diet, can reduce the risk of chronic diseases (Hariharan et al., 2015) This is the reason why a great attention is paid to the composition of food, and great efforts are made in developing the so-called functional products that will meet the nutritional needs of consumers, and at the same time have a beneficial effect on their health.

USE OF PROBIOTICS AND PREBIOTICS

In addition to nutrition, probiotics and prebiotics are the most commonly used substances taken with an aim to maintain a healthy microbiome or to establish a balance when bacterial homeostasis is believed to be disturbed in a disease (Quigley, 2019; Tousoulis et al., 2022). Probiotics are living microorganisms that, when administered in appropriate amounts, confer the health benefit on the host (Cremon et al., 2018).

A wide variety of fermented products, such as yogurt, kefir, sauerkraut, tempeh, and kimchi, which serve as sources of probiotic strains, are part of the human nutrition in different cultures (Kothari et al., 2019). An increasing importance is also being paid to the interaction between probiotics and various food matrices as well as the challenges in developing such products (Min et al., 2019). The most commonly used commercially available strains belong to different species of the genera *Lactobacillus (acidophilus*, *gasseri*, *johnsonii)*, *Lacticaseibacillus (casei*, *paracasei*, *rhamnosus)*, *Lactiplantibacillus (plantarum)*, *Limosilactobacillus (reuteri*, *fermentum)*, *Ligilactobacillus (salivarius)* and *Bifidobacterium (adolescentis*, *animalis*, *bifidum*, *breve* and *longum*) and are considered to have positive effects on health through different mechanisms (Vitali Čepo et al., 2020). Probiotics are associated with various health functions such as the prevention of intestinal tract infections, improvement of lactose metabolism, lowering of the elevated serum cholesterol levels, boosting of the immunity system, stimulation of calcium absorption, improvement of protein digestibility, synthesis of vitamins (vitamin B, nicotinic acid and folic acid) and suppression of effects of foodborne pathogens (Panghal et al., 2018).

The functional food sector has shown tremendous growth in recent years owing to the use of probiotic bacteria referred to as "food additives". The administration of probiotic bacteria in food poses numerous challenges related to their growth, survival, sustainability, stability and functionality in food processing, storage and consumption, as well as changes in the sensory characteristics of probiotic foods (Min et al., 2019). However, the viability of probiotics is affected by several parameters such as oxygen, pH, storage temperature, hydrogen peroxide and many other parameters (Reque and Brandelli, 2021). The efficacy of probiotic bacteria in unrefrigerated food with low pH or high water activity, a

potential loss of bacterial vitality, additionally undesired fermentation and changes in the sensory features of food products can result in poor microbiological quality and poor acceptability to consumers (Min et al., 2019).

Since fermented dairy products are not the only source of probiotics, but can be consumed with other fermented foods such as sauerkraut and plant-based beverages, research and development of non-dairy probiotics have been intensified, which is especially important for people who are lactose intolerant (Mridula and Sharma, 2015; Panghal et al., 2018). It is already known that many foods of plant origin have exceptional nutritional and health values and have a positive effect on overall human health (Palfi et al., 2014; Palfi and Tomić-Obrdalj, 2014; Hrg, 2017; Palfi and Knežević, 2018; Knežević et al. 2020).

Non-dairy plant food matrices such as fruits, vegetables, plant "milk", cereals and legumes have proven to be successful carriers in the delivery of probiotics to humans. Lactobacilli and bifidobacteria in these plant matrices have especially showed the ability of maintaining the appropriate probiotic number (10^6 – 10^8 cfu/mL or g of food product - carrier) during the shelf life of the product (Rasika et al., 2021).

Prebiotics, compared to probiotics, which can introduce exogenous bacteria into the colonic microflora, aim to selectively stimulate the growth and/or activity of some groups of beneficial bacteria in the large intestine, thus positively affecting the host's health (Prasanna and Rastall, 2017; Delgado and Tamashiro, 2018; Ashwini et al., 2019). Prebiotics are non-digestible carbohydrate molecules, including sugar polyols, poly- and oligosaccharides, and resistant starches, as well as fiber (Lockyer and Stanner, 2019). There are also artificially synthesized prebiotics such as lactulose, lactosucrose and cyclodextrins (Chong et al., 2019).

In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) expanded the definition of prebiotics to include a substrate that is selectively utilized by host microorganisms conferring a health benefit. Prebiotics are therefore not only limited to food or carbohydrate substances and are no longer limited to the gastrointestinal tract. They now include non-nutritive components and are applied to extraintestinal tissues. This definition now also applies to animals (Gibson et al., 2017). They are, generally, found in various food sources, such as chicory, chia seeds, dandelion, flax seeds, onions, leeks, garlic, almonds, artichokes, oats, chicory, barley and many other plants (Davani-Davari et al., 2019; Green and et al., 2020). By feeding intestinal microbes, prebiotics significantly improve their metabolic activity, improve digestion, the ability of absorbing nutrients and the state of the immune system, while simultaneously suppressing the growth of pathogenic microbes (Lockyer and Stanner, 2019) and increase the bioavailability of minerals, especially calcium and magnesium (Chong et al., 2019; Patel et al., 2014; Karakan et al., 2021). All these features of prebiotics allow them to be used as functional food ingredients in various foods. Prebiotics are thus administered in a wide range of products, including dairy products, beverages and healthy drinks, infant food, meat products (Ashwini et al., 2019).

A synbiotic is a combination of probiotic and prebiotic components where the presence of prebiotics enhances the activity of the probiotic microbial strain (Kumari et al., 2020). Prebiotics such as FOS, GOS, XOS, inulin, fructans are the most commonly used fibers which, when used together with probiotics, are referred to as synbiotics and can improve the viability of probiotics (Pandey et al., 2015). A synbiotic, originally designed as a combination of probiotics and prebiotics, is now defined as a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host (Swanson et al., 2020).

Unlike probiotics, which are live cultures of bacteria or other microorganisms with a beneficial effect on human health, postbiotics include molecules generated as a result of the probiotic metabolism. In 2019, ISAPP defines a postbiotic as a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host. Effective postbiotics must contain inactivated microbial cells or cell components, with or without metabolites that contribute to observed health benefits (Salminen et al., 2021). Since postbiotics

do not contain live microorganisms, they show a beneficial effect on health like probiotics, while minimizing the risks associated with their intake at the same time (Żółkiewicz et al., 2021).

IMPACT OF PROBIOTICS AND PREBIOTICS ON HEALTH AND THE HEALTH CONDITION OF THE ORGANISM

The human body is colonized by a large number of microbes that peacefully coexist with their host. The most colonized site is the gastrointestinal tract, with Bacteroidetes and Firmicutes largely dominating the intestinal microbial flora (Schippa and Conte, 2014; Pushpanathan et al., 2019). Gradual microbial colonization of the gut begins at birth and continues throughout the early stages of life to form a gut microbiota that is different for each individual (Salminen and Isolauri, 2006). The microbiota has important metabolic functions, and regulates the inflammatory response by stimulating the immune system. An imbalance of gut microbes (dysbiosis) is associated with important human diseases such as inflammation-related disorders (Schippa and Conte, 2014; Antal et al., 2019). Nutrition, although it is not the only factor that can affect the gut microbiota, is one of the most important factors that can cause dysbiosis, that is, any change in the composition of bacteria in the intestines, compared to that found in healthy individuals (Mota de Carvalho et al., 2018).

Research on the human microbiota, especially the gut microbiota, has become one of the most common areas of innovation when the study of various pathologies is concerned (Turnbaugh et al., 2006). Changes in the gut microbiota play an important role in the pathogenesis of many diseases. Many scientific and clinical trials have verified the positive effect of probiotics on numerous diseases, especially the gastrointestinal tract diseases. Their positive effects on allergic diseases (e.g. atopic dermatitis), treatment of metabolic diseases such as obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease, prevention of various types of urogenital infections, etc. have also been identified (Markowiak and Śliżewska, 2017.; Albano et al., 2018). The positive effects of probiotics were also observed when establishing normal intestinal microflora following the treatment by antibiotics (Šušković et al., 2009). Liu et al. (2018) believe that the strongest evidence in favor of probiotics lies in the prevention or treatment of five conditions: necrotizing enterocolitis, acute infectious diarrhea, acute respiratory tract infections, antibiotic-associated diarrhea and infant colic. In times of pandemic and lack of proven effective therapy for COVID-19, probiotics may be a potential therapeutic strategy, but further research needs to be conducted (Angurana and Bansal, 2021; Batista et al., 2021).

It is necessary to emphasize that the way the probiotics function can depend on a strain, dose and components used to produce a given probiotic product (Markowiak and Śliżewska, 2017). Based on a limited number of studies, some scientists report that multi-strain probiotics are more efficient than single strains (Chapman et al., 2011). However, taking disease and strain specificity into account, in most cases multi-strain mixtures were not significantly more efficient than single-strain probiotics (McFarland, 2021). Besides, strains can interact and act antagonistically.

Although they have a beneficial effect on health, the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) find that probiotics may have some-side effects as well as potential problems due to the use of live microbial cells (Yeşilyurt et al., 2021).

A growing body of evidence supports the role of prebiotics in reducing the risk and severity of gastrointestinal infections and inflammation, including diarrhea, inflammatory bowel disease, ulcerative colitis and irritable bowel syndrome. Data shows that they reduce the risk of obesity by stimulating the satiety and weight loss (Brownawell et al., 2012; Lockyer and Stanner, 2019). Some studies have shown that people who consume large amounts of fiber or other types of prebiotics show a significantly lower risk of diabetes, and a reduced prevalence of colon cancer (Slavin, 2008; Hijová et al., 2013). The clinical administration of prebiotics seems promising considering a very low risk

of serious-side effects, ease of administration and strong potential of affecting the composition and function of the microbiota in the intestines and beyond (Miqdady et al., 2020).

According to current data, postbiotics show pleiotropic effects that include immunomodulating, anti-inflammatory, antioxidant and anticancer properties. The further research into the biological activities of these metabolites is expected to reveal new possibilities of using the postbiotics. The potential administration of postbiotics could include an attractive therapeutic and preventive strategy in modern medicine (Żółkiewicz et al., 2021).

Observations of whether gut microbiota can potentially be a new therapeutic approach and new targets in the development of innovative drugs have led to making suggestions for options for individual treatment that will be based on the genetics, biological response and functional profile of the microbiota of an individual (Leone et al., 2013). Fecal microbiome transplantation has been successful in treating several gastrointestinal diseases and restoring the composition of the gut microbiota (Gupta et al., 2016), especially in people suffering from chronic inflammatory bowel diseases (Lee and Chang., 2021).

Future research should be focused on identifying optimal probiotics, doses for treating specific diseases, the efficacy of adding prebiotics on their action, as well as determining whether defined microbial communities would provide greater benefit than that of single-species probiotics (Liu et al., 2018).

LABELING OF PROBIOTICS ON FOOD PRODUCTS - LEGAL REGULATION

The global probiotics market is estimated at USD 61.1 billion in 2021 and is projected to reach USD 91.1 billion by 2026. The key drivers of market growth are the increasing use of nutrient-dense foods as a result of increased consumer awareness of healthy nutrition accompanied by technological progress in the production of probiotics at the same time (Research and Markets, 2021).

Probiotics are mainly registered as food supplements or food for special medical needs (Vitali Čepo et al., 2020). The only health claim approved for probiotics in the European Union is that consumption of yogurt alleviates the symptoms of lactose intolerance (Smug et al., 2014). The European Food Safety Authority (EFSA) has indicated that it will allow health claims based on the capacity of probiotics to reduce intestinal and respiratory infections. Thus the difference between health claims and medical claims would be eliminated to a certain extent (Katan, 2012). According to the currently valid legislation in EU countries, food products may not be labeled with health claims not approved by EFSA, while the term "probiotic" is considered a health claim. Compliance with and strict application of legal regulations on food safety and control is one of the most important prerequisites for preserving and improving consumer health (Knežević et al., 2013). In order to facilitate the selection of an appropriate product, dose and formulation for a specific indication, physicians in the United States of America and Canada have developed clinical guides to probiotic products (Clinical Guide to Probiotic Products Available in Canada, 2022; Clinical Guide to Probiotic Products Available in USA, 2022).

ARTERIAL HYPERTENSION AND PROBIOTICS

Arterial hypertension (AH) is the most common cardiovascular (CVD) disease and is the most important modifiable CV risk factor and the leading cause of premature death (Krstačić et al., 2014). The disease is defined by elevated levels of systolic (≥ 140 mmHg) and/or diastolic (≥ 90 mmHg) pressure. WHO data indicates that as many as 1.26 billion persons aged from 30 to 79 suffer from AH, and as many as 46% of them are unaware of the disease (NCD-RisC, 2021). In addition to medical treatment, non-pharmacological treatment also plays an important role in normalizing elevated blood pressure (BP) levels and preventing the consequences of the disease. It includes the correction of an unhealthy lifestyle (insufficient level of physical activity, cigarette smoking, obesity, stressful lifestyle, modern Western pattern diet that includes a lot of salt, sugar, saturated fats and animal

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proteins, etc.). Combined treatment of AH by applying non-pharmacological measures and several groups of antihypertensive drugs are more efficient in achieving the BP target values and reducing the CV risk (Brouwers et al., 2021).

The microbiota, a set of microorganisms that colonize the digestive tract and communicate with the endocrine, neurological and immune systems, is the regulator of homeostasis in the body. Numerous trials based on animal models and humans have found that the disturbance of the gut microbiota plays a significant role in the development of AH. The trials have shown the existence of an interaction between long-term use of antihypertensive drugs and gut microbiota, which can affect the metabolism and pharmacokinetics of this group of drugs that is biotransformed in the digestive tract (Verhaar et al., 2020). Nutrition also has an important impact on the modulation of gut microbiota. Fermented dairy products (yogurt, kefir, etc.), vegetables and food supplements are sources of probiotic microorganisms. They are usually produced with the help of lactic acid bacteria, the most common of which are *Lactobacillus* sp., *Bifidobacterium* sp., *Enterococcus* sp. and *Streptococcus* sp.. The trials suggest that their number is many times lower in a gram of fermented products than in modern dietary supplements such as tablets and capsules, where the number of lactic acid bacteria can be up to $10^{10\text{-}12}$.

Meta-analysis conducted by Khalesi et al. (2014) found that the consumption of probiotics results in lowering the systolic pressure by 3.56 mmHg and diastolic pressure by 2.38 mmHg. The effect of probiotics is higher if the initial BP levels are higher, more probiotics are administered throughout a period of ≥8 weeks, or the daily dose is $\geq 10^{11}$ units of colony-forming bacteria. Although this effect on BP levels seems to be modest, it is comparable to the effect of one of the most prescribed antihypertensive drugs. As a matter of fact, the administration of the ACE inhibitor Ramipril in the HOPE (Heart Outcomes Prevention Evaluation) study has led to lowering of systolic blood pressure by 3.3 mmHg and diastolic blood pressure by 1.4 mmHg, which was associated with reducing a relative risk of CV mortality, myocardial infarction or stroke by 22% (Sleight, 2000). Buendia et al. (2018) found that in subjects diagnosed with AH, the consumption of ≥2 servings of yogurt per week significantly reduces CV risk (myocardial infarction and stroke). Similar results were found by Elias et al. (2018). The molecular mechanism of the antihypertensive effect of probiotics in patients with AH has not been fully clarified and is the subject of current research. A potential explanation for lowering the BP levels may lie in the remodeling of the gut microbiome by increasing the release of organic (short-chain) fatty acids.

Soybean is the fourth most represented field crop in the world, and it ranks third in Croatia (Andrijanić et al., 2022). It is one of the leading export products in the United States of America. In addition to food production, it is also used as a raw material in the chemical and pharmaceutical industries. In the last 30 years, soybean and soy products have been increasingly mentioned as a source of positive effects on health. As a matter of fact, soybean and soy products contain isoflavones that exhibit antioxidant, anti-inflammatory, hypolipemic and hypoglycemic properties (Huang et al., 2016).

Owing to the probiotic effect, daily consumption of a fermented soy drink may result not only in positive changes in the composition of the microbiota, but it can also lower elevated BP levels. Owing to meta-analysis conducted, Mosallanezhad et al. (2021) found a beneficial effect of soybean and soy products on BP level, which is more effective in people with AH at the age of 56, as well as in subjects with lower diastolic pressure levels. They found that systolic pressure was lowered by 1.70 mmHg and diastolic pressure was lowered by 1.27 mmHg. The antihypertensive effect of soybean is according to a meta-analysis by Kou et al. (2017) higher in postmenopausal women and it depends on a dose. The use of ≥2 5 g of soybean per day lowered systolic blood pressure by 4.62 mmHg and diastolic blood pressure by 1.63 mmHg. A possible explanation for lowering BP levels by using soybean and soy products lies the vasodilator effect via arginine, which promotes the formation of nitric oxide.

Beetoot has also been the subject of research recently, especially the fermented beetroot juice that has a probiotic effect. According to the European Society for Hypertension, beetroot has the strongest antihypertensive effect in comparison to other types of vegetables, and it has an effect on the formation of nitric oxide. The same Society draws attention to the fact that the use of nutraceuticals - food that provides medical or health benefits must be based on research results and must not replace the administration of antihypertensive drugs (Borghi et al., 2020).

CONCLUSION

Apart from nutrition, probiotics and prebiotics are the most commonly used substances aimed at maintaining a healthy microbiota or restoring the balance in case of disturbed bacterial homeostasis in disease. A significant growth of the global probiotics market is predicted due to the increased awareness of consumers about healthy foods and the use of nutrient-dense foods.

Although many trials confirm the negative effect of gut microbiota disturbance in the last decade, stronger evidence and further clinical trials are needed to definitively confirm the benefits of dietary intervention with probiotics in people with AH.

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