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DIETARY SUPPLEMENTS IN THERAPY TO SUPPORT WEIGHT REDUCTION IN OBESE PATIENTS

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ABSTRACT

Obesity is a pandemic disease that poses a serious problem for the entire world population. Preventative and non-pharmacological treatments for obesity include changing eating habits and increasing physical activity. The use of certain dietary supplements also brings beneficial results in the process of reducing excess body weight. There are many options for the treatment of obesity available on the pharmaceutical market. This study aims to review the latest publications on selected dietary supplements in the treatment of excess body weight. Dietary supplements which support a reduction in excess body weight include capsaicin, bitter orange, white bean seeds, green coffee, berberine, and single and multi-strain probiotics. Some of these supplements have additional health benefits. Bitter orange has antioxidant and anti-ulcer properties. Berberine improves lipid metabolism and reduces blood glucose levels. Capsaicin has found application in the treatment of neurodegenerative diseases. Supplements that do not significantly reduce body weight are chitosan and vitamin D. Chitosan can reduce blood pressure, while vitamin D improves the sensitivity of tissue to insulin. An increase in body mass index (BMI) is associated with an increased risk of many diseases, including cardiovascular disease, diabetes mellitus, musculoskeletal disorders, and certain cancers. Dietary supplements with beneficial effects which support a reduction in excess body weight can be used in the treatment of both obesity and its complications.

Keywords: supplements, obesity treatment, berberine, probiotics

INTRODUCTION

Epidemiological studies have shown that an increase in body mass index (BMI) of 5 kg/m^2 increases the overall risk of death by 29%, the risk of death from cardiovascular disease by 41%, and from diabetes by as much as 210% (Apovian, 2016).

In 2016, approximately 39% of the world's population over 20 years of age were obese, representing approximately 1.9 billion adults. By age 40, the majority of obese patients are male, but this trend is reversed later in life, possibly due to menopause, which is associated with a higher incidence of obesity in women. Over the past 35 years, the incidence of obesity has increased by 80%, while the number of obese people has increased by half. Across the globe, the regions with the highest percentage of obese people are North America and Europe (Chooi et al., 2019).

Obesity is a risk factor for many diseases, including type 2 diabetes, dyslipidemia, or cardiovascular diseases. On the other hand, obesity risk factors mainly include inadequate eating habits and low levels of physical activity. The correction of eating habits may turn out to be an insufficient element in the treatment

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of obesity. For this reason, in obese patients, pharmacotherapy may be part of the treatment for excess body weight. An example of a drug that supports the treatment of obesity is orlistat, which has been approved for use in Europe. This drug reduces the absorption of fats from the gastrointestinal tract. In patients with morbid obesity, pharmacotherapy, improving eating habits and increasing physical activity may not bring the expected results of treating excess body weight, therefore, bariatric surgery is becoming an increasingly more frequent therapeutic choice in these patients (Jackson et al., 2015).

In addition to increasing physical activity and improving the diet, the process of weight reduction can be supported by using dietary supplements. These include a variety of substances that contribute to weight loss. This review presents the characteristics of the most commonly used dietary supplements which support the treatment of obesity and the mechanisms of their action.

CAPSAICIN

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the alkaloid responsible for the spicy, searing taste of chili peppers. The chili pepper and its culinary and medical uses have been known for millennia. It is used in many communities and cultures as a flavor-enhancing spice, but also as a natural preservative (Sharma et al., 2013). Experimental and clinical studies have shown the multidirectional effects of capsaicin on the body. It has analgesic, antioxidant, antihypertensive, anti-aggregating, and anti-angiogenic effects (Adaszek et al., 2019; Zheng et al., 2017). The results of previous research indicate the possibility of using capsaicin in the prevention and therapy of neurodegenerative diseases, such as Alzheimer's disease, and in non-alcoholic fatty liver disease. The beneficial effects of capsaicin consumption on the maintenance of a healthy body weight and reduction of adipose tissue have also been observed (Sharma et al., 2013). Preclinical and clinical studies have shown that the potential mechanism of capsaicin's anti-obesity action includes the inhibition of adipogenesis, activation of brown adipose tissue (BAT) and stimulation of thermogenesis, increased lipolysis, decreased appetite, and increased satiety as a result of the regulation of the nervous system in the hypothalamus and modulation of the functions of the digestive system and the intestinal microbiome (Li et al., 2020b; Rosca et al., 2020; Zheng et al., 2017). The main mechanism of action of capsaicin on the metabolism is the activation of TRPV1 (transient receptor potential vanilloid subfamily 1). These receptors could be a potential target in obesity prevention as they play a key role in the regulation of body weight, glucose, lipid metabolism, and the cardiovascular system. It has been shown that capsaicin can regulate the function of adipocytes through the inactivation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and activation of the PPARy receptor (peroxisome proliferator-activated receptor; Zheng et al., 2017). Randomized clinical trials have shown an association between increased capsaicin intake in the diet and decreased appetite, increased resting energy expenditure, increased fat oxidation, increased BAT activity, and increased thermogenesis (Zheng et al., 2017). In obese subjects, an increase in capsaicin consumption was associated with a decrease in blood glucose, a decrease in tissue insulin resistance, and a favorable lipid profile (Li et al., 2020b). In studies on mice, following the administration of capsaicin, a favorable change in the intestinal microbiota was observed, consisting in the growth of bacteria that synthesize short-chain fatty acids (SCFA) and a reduction in the number of gram-negative bacteria producing LPS (bacterial liposaccharide), which increases the production of pro-inflammatory cytokines (Wang et al., 2020b). The results of many studies suggest that it is possible to use capsaicin in the prevention and treatment of obesity. It has also been found that it is safe to use inpatients with normal and low body weight (Zheng et al., 2017). It should be noted, however, that some studies have not confirmed the beneficial properties of capsaicin towards weight loss in obese people. In other studies, gastrointestinal tract irritation and instances of inflammation were found as a result of the use of an increased supply of capsaicin in the diet (Adaszek et al., 2019).

CHITOSAN

Chitosan is a chain polyaminosaccharide derived from chitin. Its primary source is the shells of crustaceans (Ríos-Hoyo and Gutiérrez-Salmeán, 2016). It is part

of many dietary supplements available on the Polish market intended to support the treatment of obesity, hypercholesterolemia, and hypertension. The main mechanism of action of chitosan in the body is to reduce the absorption of fat and cholesterol. Studies on obese mice have shown that chitosan activates the leptin signaling pathway (JAK2-STAT3), and thus reduces tissue resistance to leptin and inhibits adipogenesis (Wang et al., 2019b). Other studies have shown an increase in BAT and an increase in thermogenesis in obese rats fed a diet supplemented with chitosan (Pan et al., 2018). The results of meta-analyses have shown a decrease in body weight in obese people after using chitosan supplements, but the weight loss in the analyzed studies was not statistically significant. The effectiveness of chitosan in reducing excess body weight was tested in humans at various doses over a short and relatively long period of use and similar results were obtained (Ríos-Hoyo and Gutiérrez-Salmeán, 2016). The comparison of the effects of chitosan and orlistat showed that chitosan did not significantly increase the excretion of fat in the feces. However, it has been observed that its use improves the lipid profile in obese people and lowers blood pressure (Moraru et al., 2018). Based on the results of many clinical studies, it can be concluded that chitosan only has a slight effect on body weight but may reduce cardiometabolic risk in obese people.

BITTER ORANGE

Bitter orange (*Citrus aurantium* L.) is a plant whose extract is used to treat many disorders and diseases. In Chinese medicine, bitter orange is consumed to prevent indigestion, diarrhea, and constipation, while in South America, *C. aurantium* extract is used to treat epilepsy, anxiety, and insomnia. Bitter orange extract is used in weight loss supplements due to its weight loss properties, incl. appetite control and energy conversion. Over 90% of the protoalkaloids contained in bitter orange are *p*-synephrine – a derivative of phenylethylamine structurally similar to ephedrine (a compound prohibited from use in supplements in 2004 due to the occurrence of adverse cardiovascular symptoms). The features that distinguish *p*-synephrine from ephedrine are its physiological properties and pharmacokinetics, as well as the binding of adrenergic receptors. Therefore, when using supplements containing *p*-synephrine, one should not be afraid of similar effects to those of ephedrine (Stohs, 2017). In animal studies, the addition of bitter orange to the diet caused a slight increase in blood pressure and heart rate; these changes worsened when combined with caffeine (Hansen et al., 2012). Clinical studies have shown that pure p-synephrine or bitter orange administered for six to twelve weeks in combination with caffeine increases energy expenditure and resting metabolism, resulting in weight loss (Stohs et al., 2012). The safety of bitter orange was confirmed in a double-blind placebo study. After the use of *p*-synephrine for 60 days at a dose of 98 mg per day, no changes in blood pressure were observed and no significant changes in blood morphological and biochemical parameters were observed (Kaats et al., 2013). Bitter orange extract not only supports weight loss but also has a number of other beneficial properties. *C. aurantium* has antitumor, cytotoxic, sedative, antidiabetic, antioxidant, and anti-ulcer properties (Suntar et al., 2018).

WHITE BEAN SEEDS

White beans belong to the *Phaseolus vulgaris* (common bean) species and are the most widely cultivated legume in the world, especially in tropical countries of the Americas, Asia, Africa, and Europe, and they owe their popularity to their high content of carbohydrates (29–47% by weight of seeds) and protein (22–27%; He et al., 2018). *Phaseolus vulgaris* contains an α-amylase inhibitor whose action leads to the inhibition of starch digestion and reduction of glucose absorption, and, consequently, weight loss (Ríos-Hoyo and Gutiérrez-Salmeán, 2016). Experimental studies have confirmed the effectiveness of the use of white bean seeds in the weight loss process. 12-day administration of *Phaseolus vulgaris* to obese mice and rats resulted in both weight loss and a cardioprotective effect: lowering blood cholesterol and its LDL fraction (Zhu et al., 2012). White bean seed extract also modulates the intestinal microbiota, which results in the increased production of SCFA (Shi et al., 2020). Clinical studies have confirmed the beneficial effects of *P. vulgaris*. After one month of using bean seed extract at a dose of 2,400 mg per day, obese subjects reduced their body weight by an average of 2.24 kg (in the

placebo group – 0.92 kg), with no side effects (Wang et al., 2020a). It was also tested whether *Phaseolus vulgaris* has a beneficial effect on postprandial glycemia and body weight (Carai et al., 2011). The mechanism of action of *P. vulgaris* is related, inter alia, to the inhibition of ghrelin secretion, and thus increases satiety and lowers food consumption (Spadafranca et al., 2013). The anti-adipogenic activity of *P. vulgaris* extract in the process of preadipocyte differentiation and its lipolytic effect were also identified (Castillo et al., 2019). Short-term (up to 12 weeks) supplementation with white beans has been shown to have no side effects (Maunder et al., 2020). However, frequent consumption of bean seeds can cause an allergic and toxic reaction. These symptoms are caused by the content of lectin – a protein of non-immune origin resistant to the action of digestive enzymes with the ability to bind sugars. Lectins also have beneficial properties for the body, including the prevention of mucosal atrophy, anti-cancer effects, or participation in the prevention of obesity. Lectin purification strategies are currently being analyzed in order to obtain a stable and pure form of the protein which may improve or eliminate the bioactivity of the lectins in the future (He et al., 2018).

GREEN COFFEE

One of the bioactive substances in the extract of unroasted green coffee beans is chlorogenic acid – a polyphenol belonging to the subfamily of phenolic acids which shows beneficial effects in the slimming process (Ríos-Hoyo and Gutiérrez-Salmeán, 2016). Green coffee extract has been observed to affect the release of fatty acids from human adipocytes. This effect has been noted during both short-term (2 h) and long-term (192 h) therapy. It is believed that with short exposure to green coffee, residual traces of caffeine may have a greater lipolytic effect on the body, and with prolonged use, the effect of chlorogenic acid on the release of fatty acids is evident (Flanagan et al., 2014). Decaffeinated green coffee prevents the accumulation of adipose tissue and reduces insulin resistance due to the inhibition of the expression of genes related to adipogenesis and inflammation in the perioral adipose tissue (Song et al., 2014). Clinical trials have confirmed weight loss in obese people using green coffee supplements and a low-calorie diet. In the intervention group, a greater reduction was observed in body weight, adipose tissue content and waist-hip ratio (WHR). In people using green coffee, the levels of adiponectin were significantly higher than in the placebo group, in contrast to the levels of leptin. Green coffee extract also improved the lipid profile by lowering the concentration of total cholesterol and LDL fraction, as well as free fatty acids (Haidari et al., 2017). It should be added that in people with a healthy body weight, no effects on body weight were observed from green coffee (Gorji et al., 2019). The studies also showed that chlorogenic acid affects the restoration of the intestinal microbiota caused by the use of a high-fat diet. For this reason, the use of supplements containing green coffee extract is recommended not only to support the weight loss process, but also to regain microbial balance (Wang et al., 2019c).

BERBERINE

Berberine is an alkaloid component of barberry (*Berberis vulgaris* L.) found in the plant's stem, rhizome, roots, and bark. This substance has many proven therapeutic effects, including anti-cancer properties, and protects the digestive system and the central nervous system. Many studies have shown the advantages of using berberine in the weight loss process as it influences the mechanisms of weight loss (Ilyas et al., 2020). The use of berberine increases energy expenditure and glucose tolerance and reduces the expression of pro-inflammatory cytokines in white adipose tissue, which improves metabolic function (Lin et al., 2019).

Adipose tissue is divided into two types: white and brown, while white adipose tissue that turns brown when exposed to environmental stimuli is called beige adipose tissue. White adipose tissue stores triglycerides for energy, while BAT regulates body temperature by burning energy from the oxidation of blood lipids, so the activation of BAT leads to weight loss and is a way to prevent obesity (Li et al., 2020a). A study on mice led to the observation of browning, i.e., the conversion of white adipose tissue to beige, and activation of BAT during a 4-week intake of 5 mg/kg of berberine per day, which increased thermogenesis and energy burning. The mechanism responsible for these processes is the increased phosphorylation of

AMPK (adenosine 5'-monophosphate-activated protein kinase) and the expression of UCP1 (uncoupling protein) and PGC1α (PPARγ coactivator-1α; Zhang et al., 2014). In a human study, a dose of 1.5 g of berberine, also administered for 1 month, activated brown adipose tissue via the AMPK-PRDM16 (PR domain-containing 16) pathway (Wu et al., 2019). Berberine has been observed to inhibit the expression of genes responsible for adipocyte proliferation and differentiation (Chow et al., 2016; Wang et al., 2019a; Wang et al., 2018). *Berberis vulgaris* L. extract also lowers leptin levels in overweight and obese individuals, leading to weight loss (Yang et al., 2012). While there was no significant effect of berberine on BMI, the waist-to-hip ratio (WHR) was significantly reduced. Similar studies have shown conflicting results in waist circumference (Amini et al., 2020; Mirzaee et al., 2020). After 12 weeks of administering 500 mg of berberine three times daily to obese adults, mild weight loss was observed, while the lipid profile improved significantly (a 12.2% decrease in total cholesterol and a 23% decrease in triglycerides). An additional advantage was the nearly 60% increase in blood calcitriol concentration (Hu et al., 2012). In combination with other health-promoting ingredients, such as red yeast rice, berberine lowers total cholesterol and LDL cholesterol (Zanardi et al., 2012). By modulating the gut microbiota, berberine reduces insulin resistance, which results not only in lowered blood glucose but also in weight loss (Xu Hui et al., 2017). Type 2 diabetes mellitus is one of the risk factors for obesity, therefore, the therapeutic effect of berberine on blood glucose levels is very important. Like metformin, berberine has the ability to increase the number of SCFA-producing bacteria in the gut and to compensate for the structural changes in the microbiota caused by a high-fat diet (Zhang et al., 2015). The consumption by diabetics of 1g of berberine daily for three months successfully lowered fasting blood glucose, including after meals (Zhang et al., 2008). Even after a weekly intake of 0.5 g of berberine per day, blood glucose, and hemoglobin A1c levels were significantly reduced (Yin et al., 2008). Berberine also affects the genes responsible for hepatic gluconeogenesis, glucose-6-phosphatase, and phosphoenolpyruvate carboxykinase (PEPCK), leading to de novo inhibition of glucose formation (Xia et al., 2011). Berberine is a safe and effective ingredient in supplements and medications, but its systemic oral bioavailability is low, as demonstrated by pharmacokinetic studies (Wang et al., 2017). Research indicates the positive effects of berberine on the mechanisms related to weight loss; however, low bioavailability may indicate ineffective action of oral slimming supplements containing *Berberis vulgaris* L. extract.

VITAMIN D

Vitamin D is fat-soluble, and its food sources are fatty fish, e.g., mackerel, herring, sardines, salmon, tuna, and fish oil, liver or other offal, shiitake mushrooms, and egg yolks. However, the main source of vitamin D for the body (approx. 90%) is its synthesis in epithelial cells (Chang and Lee, 2019). Vitamin D_3 activated in the skin under the influence of sunlight is converted by the liver into 25-hydroxyvitamin D [25(OH)D] and then in the kidneys into the active form 1,25-dihydroxy--vitamin-D [1,25(OH)2D]. Calcitriol (1.25(OH)2D) is not used to assess the concentration of vitamin in the blood, but calcidiol (25(OH) D) is used due to its longer half-life (3–4 weeks versus 3–4 hours, respectively) and 1000-fold higher concentration in the blood (Lukaszuk and Luebbers, 2017). The optimal concentration of 25 (OH) D in the serum is 32–54 ng/mL (80–135 nmol/L), while in sunny countries it is higher and may reach 90 ng/mL (225 nmol/L). A drop in the concentration to below 30 ng/mL indicates a vitamin D deficiency (Alshahrani and Aljohani, 2013). The role of vitamin D is to increase the transport of calcium in the intestines, kidneys, and bones, and to regulate the activity of osteoblasts and osteoclasts; its action occurs through the stimulation of vitamin D receptors (VDR) found, among other places, in the small intestine, colon, activated B and T lymphocytes, osteoblasts, and in the main organs (heart, brain, gonads, breasts, prostate; Chang and Lee, 2019). The world population is deficient in vitamin D, and risk factors include lack of exposure to sunlight, incorrect use of sunscreen creams, and a diet low in vitamin D. The population groups most at risk are pregnant women, people with increased skin pigmentation (Latin Americans, Blacks), and obese people (Holick, 2017). In people with excess body weight, the prevalence of vitamin D deficiency is higher than in people with normal body

weight (Pereira-Santos et al., 2015). It has been shown that vitamin D deficiency in obese individuals may be due to insufficient supply, low physical activity, limited sun exposure, and decreased absorption, especially in people who have undergone bariatric surgery (Thomas-Valdés et al., 2017). It is believed that the reason for these differences is the vitamin D content in adipose tissue (which is more in obese people) and thus the reduction of serum 25 (OH) D concentration for metabolic purposes (Drincic et al., 2012). It has been observed that in response to supplementation with the same amount of vitamin D, serum 25 (OH) D concentration is higher in subjects with a normal BMI than in obese subjects. Therefore, it is suggested that the dose of vitamin D should be adjusted according to body weight (Gallagher et al., 2013). A weight reduction of 10 kg increases the level of calcidiol in the serum (by 6.4 nmol/L), while reducing the fat tissue content by 10% increases the concentration of 25 (OH) D by 9.1 nmol/L, which confirms the release of vitamin D from adipose tissue in the slimming process (Pannu et al., 2016). Vitamin D status does not result in faster weight loss, but supplementation with vitamin D (2000 IU per day) in the weight loss process has a positive effect on weight loss and body fat percentage (Mason et al., 2014). Studies have shown that serum calcidiol concentration is negatively correlated with the percentage of adipose tissue, while supplementation with vitamin D_3 without the use of a caloric deficit in the diet does not significantly affect body weight and fat content (Golzarand et al., 2018). On the other hand, insufficient levels of vitamin D and zinc may increase the risk of obesity and other metabolic diseases (Poli et al., 2017). After using vitamin D supplementation in obese people, an improvement in insulin sensitivity was observed, which is important in diabetic treatment (Cefalo et al., 2018). It is worth noting that the combination of vitamin D_3 supplements and a low-calorie diet leads to a reduction in body circumference, which is important in the prevention of cardiovascular diseases (Perna, 2019). Despite the lack of spectacular evidence to support the use of vitamin D_3 during weight loss, supplementation is very important in order to normalize the concentration of vitamin D in the body and reduce the risk of developing diseases related to vitamin D deficiency (Amrein et al., 2020).

SUPPLEMENTS WHICH REPLENISH MICRONUTRIENT DEFICIENCIES

In obese people, there may be deficiencies in micronutrients resulting from their insufficient supply, impaired absorption, or increased excretion from the body. Qualitative malnutrition, often observed in obese people, may be related to the occurrence of this disease, as well as being the result of a reducing diet. Nutrition studies of obese people have indicated a low intake of vitamins such as vitamin D, C, E, and folic acid, and the minerals calcium, potassium, iron, zinc, and selenium in their diets. It is worth noting that deficiencies of these micronutrients also persist after the use of nutritional intervention (Hamułka et al., 2019; Poli et al., 2017; Via, 2012). Blood analysis of obese people showed a low concentration of carotenoids and vitamins D, E, B_1, B_6, folic acid, and vitamin C (Thomas-Valdés et al., 2017). In the case of vitamins that are well-soluble in fats (e.g., vitamin A, E), it is suggested that they may be deposited in the adipose tissue of obese people and resulting in them having a low blood concentration. Studies have shown that vitamin A deficiency can lead to the accumulation of body fat and chronic inflammation (Thomas-Valdés et al., 2017). An additional dose of vitamin E in the diet of obese animals increased the synthesis of leptin and anti-inflammatory adipokines (adiponectin) and decreased the concentration of pro-inflammatory cytokines (IL-6). In addition, it should be mentioned that vitamin E is a powerful antioxidant, and supplementation with this vitamin can reduce oxidative stress (Thomas-Valdés et al., 2017). In turn, the use of vitamin B_1 can improve the metabolism of the body as it is necessary for the proper metabolism of carbohydrates and branched-chain amino acids. Supplementation with folic acid and vitamin B_6 improves the metabolism of homocysteine and reduces the risk of developing atherosclerosis and endothelial dysfunction. On the other hand, an increase in the supply of vitamin C has a positive effect on glucose and fat metabolism and protects the vascular endothelium against oxidative stress (Thomas-Valdés et al., 2017). The results of meta-analyses indicate the beneficial effects of calcium supplementation in obese people, which is mainly related to the reduction of adipose tissue without a significant effect on BMI or waist circumference (Hong

et al., 2020). Studies in older people have shown that a low-energy diet can reduce bone density and increase the risk of fractures. A combination of factors such as high body fat, low lean mass, obesity-related inflammation, and micronutrient deficiencies are believed to contribute to bone deterioration in old age. The adverse effects of a low-calorie diet on the skeleton may indicate the need for an increased supply of calcium and vitamin D in the form of supplements in the elderly with obesity (Haywood et al., 2017). Taking into account the relationship between a deficiency of micronutrients and the risk of obesity, and the scientifically proven deficiencies of vitamins and minerals in the diet of obese people, including those undergoing nutritional therapy, the use of dietary supplements should be considered.

PROBIOTICS AND SYNBIOTICS IN THE TREATMENT OF OBESITY

The idea of the relationship between excess body weight and intestinal microbiota abnormalities originated at the beginning of the 21st century; in 2005, R. E. Ley et al. showed that in the caecum of obese mice with a homozygous aberration of the leptin gene, the population size of *Bacteroidetes* decreased by 50% and the population of *Firmicutes* increased proportionally (Ley et al., 2005). This publication contributed to an exponential increase in the number of studies, both in humans and in animal models, on the abnormalities of the intestinal microbiota in obese patients. The second milestone in the research on the relationship between the intestinal microbiota and obesity was the demonstration that in the population of bacteria inhabiting the gut of obese mice, the expression of genes related to energy intake from food increases. This study demonstrated the obesogenic effect of abnormal gut microbiota and identified a new potential target for future prevention and treatment strategies (Turnbaugh et al., 2006). Numerous human studies have confirmed a decline in the number of *Bacteroidetes* and an increase in the number of *Firmicutes* in obese patients (Abenavoli et al., 2019). Further work revealed further relationships between the intestinal microbiota and body weight: a high content of *Lactobacillus paracasei* in lean people, and a high content of *L. reuteri*, *L. gasseri*, *Prevotellaceae* bacteria combined with a low content of *Ruminococcus flavefaciens*, *Clostridium leptum*, and *Bifidobacterium* in obese patients (Husen et al., 2009; Million et al., 2012; Schwiertz et al., 2010). Scientific research conducted over the last decade has brought ample evidence of the beneficial effects of probiotic supplementation on the health of patients with excess body weight. Most of them concerned single-strain preparations. Currently, however, there is an increasing amount of work on the supply of multi-strain supplements. Probiotic supplementation affects a number of anthropometric and biochemical parameters in obese patients. A 12-week supply of *Pediococcus pentosaceus* and *Bifidobacterium animals* subsp. Lactis CECT 8145 leads to a reduction in BMI (body mass index) and waist circumference in obese adults, which, in the case of the supply of *B. animals* subsp. Lactis CECT 8145, leads to a decrease in the waist-to-height ratio (Higashikawa et al., 2016; Pedret et al., 2019). The supply of probiotics also significantly affects the body composition of obese patients. Supplementation with *L. curvatus* HY7601 and *L. plantarum* KY1032, apart from a decrease in body weight and waist circumference, leads to a reduction in body fat content (Jung et al., 2015). A similar effect can be observed as a result of supplementation with *Bifidobacterium breve* B-3 (Minami et al., 2018), *Lactobacillus gasseri* SBT2055 (Kadooka et al., 2010), and *Lactobacillus gasseri* BNR17 (Kim et al., 2018). The action of the last two strains is particularly beneficial – the result of their supplementation is a decrease in the content of visceral fat, an excessive amount of which is one of the causes of chronic inflammation in obese patients. Probiotic supplementation as a method of prevention and treatment for excess body weight shows beneficial effects not only as an independent intervention but also as one of the elements of a comprehensive obesity prevention and treatment program. This use of the supply of probiotic preparations was investigated, among others, by Sánchez et al., who showed a significant decrease in body weight in obese adults using *L. rhamnosus* CGMCC1.3724 supplementation with dietary intervention (Sanchez et al., 2017). Probiotic supplementation is effective in the treatment of excess body weight not only in adults, but also in children and adolescents. It has been shown that an eight-week supply of *Lactobacillus rhamnosus* GG in obese adolescents with hypertransaminasemia and

ultrasound markers of liver damage leads to a decrease in blood transaminases, a decrease in BMI, and a decrease in the content of visceral adipose tissue (Vajro et al., 2011). In the group of children and adolescents, probiotic supplementation also showed a favorable clinical effect in patients with obesity coexisting with insulin resistance; a thirteen-week supply of *B. pseudocatenulatum* CECT 7765 leads to weight loss in this group of patients (Sanchis-Chordà et al., 2019).

Recently, there has been an increasing amount of research on the use of multi-strain probiotic preparations in the treatment of obesity. It has been shown that the supply of a multi-strain probiotic preparation consisting of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus* W56, *Lactobacillus* W56, *Lactobacillus lacticus lacticus* W56, *Lactobacillus* W56, and *Lactobacillus salivarius* may reduce body weight, BMI, and body fat content, and improve the lipid profile in obese postmenopausal women (Szulińska et al., 2018). Obesity is a significant risk factor for disturbances in iron metabolism (Skrypnik et al., 2019b). The intestinal microbiota significantly affects the body's mineral balance, including iron metabolism (Skrypnik and Suliburska, 2018). It has been shown that a multi-strain probiotic preparation containing *Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19, and *Lc. lactis* W58 may have a positive effect on iron bioavailability and iron absorption in the duodenum (Skrypnik et al., 2019a). This preparation does not disturb the biochemical mechanisms of iron homeostasis (Skrypnik et al., 2020); however, it may have a positive effect on liver function and lipid profile (Skrypnik et al., 2018). Probiotic supplementation is also an effective intervention for preventing obesity in people with normal body weight. It has been shown that the supply of probiotic bacteria such as *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium animalis* subspecies *lactis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Lactobacillus helvetius* reduces the increase in body mass and adipose tissue mass during the use of a high-fat diet in young adults with a normal body weight (Osterberg et al., 2015).

Previous studies on the mechanisms of the influence that a supply of probiotic preparations has on the health of obese patients have shown the significant therapeutic potential of this intervention in the treatment of not only excess body weight, but also of its complications, such as insulin resistance and type 2 diabetes (Markowiak and Śliżewska, 2017).

One of the factors causing obesity is the excessive permeability of the intestinal barrier to bacteria and the substances they produce, such as lipopolysaccharides. Excessive intestinal permeability leads to an increase in oxidative stress, insulin resistance, and chronic subclinical inflammation: pathologies directly related to the development of obesity and its complications (Cerdó et al., 2019). The use of probiotics prevents the occurrence of intestinal dysbiosis and supports the reconstruction of the intestinal barrier by modulating the phosphorylation of cytoskeletal proteins and intercellular connections and by stimulating the secretion of mucus 25. *Bifidobacterium infantis* and *Lactobacillus acidophilus* normalize the synthesis of occludin and claudin 1, while *Lactobacillus bacteria* intensify the synthesis of mucin, which prevents the adhesion of *E. coli* bacteria and reduces the excessive permeability of the intestinal barrier (Cerdó et al., 2019; Guo et al., 2017). The second mechanism of action of probiotics in the prevention and treatment of obesity is their ability to reduce chronic inflammation. This property is demonstrated primarily by the bacteria *L. brevis*, *L. plantarum*, *L. casei*, and *B. infantis* (Osman et al., 2008; Ueno et al., 2011; Zakostelska et al., 2011). In addition, probiotics have the ability to modify the synthesis of pro-inflammatory cytokines and have a positive effect on the cells of the immune system, e.g., Th1 lymphocytes. Thus, probiotic bacteria exhibit immunomodulatory properties. Probiotics have also been shown to prevent chronic and acute colitis (Cerdó et al., 2019).

It has been shown that the supply of probiotic preparations has a positive effect on the lipid profile of obese patients and reduces the concentration of glucose and insulin in the blood (Szulińska et al., 2018). *Akkermansia muciniphila* reduces the expression of glucose-6-phosphatase mRNA, thus reducing gluconeogenesis and preventing fasting hyperglycemia (Everard et al., 2013).

Synbiotics are preparations containing a mixture of prebiotics and probiotics. Prebiotics are defined as

foods that can cause beneficial changes in the gut microbiota (Barengolts, 2016).

So far, a small amount of research has been carried out on the use of synbiotics in the prevention and treatment of obesity. In vitro studies have shown that synbiotics are more effective in modulating the gut microbiota than prebiotics or probiotics alone. On the other hand, a significant number of studies have failed to show the synergistic effects of synbiotics in the treatment and prevention of obesity. The use of probiotic strains of *Bifidobacteria* has shown an anti-obesogenic effect; while the combination of this strain with prebiotic galacto-oligosaccharides may improve the function of the intestinal barrier in obese adults, it does not show synergism during simultaneous supplementation (Walter et al., 2018). Moreover, some studies have shown that while the separate administration of a probiotic and a prebiotic may have a beneficial effect on obesity, their joint administration as a synbiotic may not have such an effect in humans. The reason for this is, among other things, the need to use high doses of the prebiotic (Vallianou et al., 2020). On the other hand, some studies have shown that the use of a selected probiotic with proven anti-obesogenic properties in the synbiotic preparation, such as *Lactobacillus gasseri*, and galactomannan and inulin fibers as a prebiotic, can lead to a synergistic effect of these ingredients (Draper et al., 2017). Some researchers hypothesize that the anti-obesogenic effect of synbiotics may result from their impact on the gut-brain axis and an increased feeling of satiety. This effect is based, inter alia, on the production of short-chain fatty acids, which have the ability to regulate the activity of the gut-brain axis and influence food intake, by probiotic bacteria contained in synbiotics (Mischke et al., 2018).

Enteroendocrine cells (EECs) are highly specialized cells scattered throughout the gastrointestinal tract. They produce hormones by which they modulate gut function. These cells play the role of sensors of gut microbiota and their metabolites. EECs and gastrointestinal microbiota cooperate in the regulation of metabolism of fat, proteins, and glucose. Microbiota activates EECs and influences secretion and motility in the gastrointestinal tract. For example: prebiotics increase GLP1 (peptide promoting satiety) and PYY (peptide presenting anorexigenic properties) secretion and decrease ghrelin (a hormone responsible for appetite induction) secretion, thus influencing satiety and the development of excess body mass (Woźniak et al., 2021).

To date, human studies on the effects of synbiotics on body weight, BMI, and adipose tissue mass in obese patients have shown contradictory results. Nevertheless, some studies have shown a decrease in levels of leptin, total cholesterol, low-density lipoprotein (LDL), and triglycerides in the blood as a result of synbiotic supplementation. This inconsistency in results is probably caused by differences in the composition of the synbiotic preparations used (Vallianou et al., 2020). Therefore, the use of synbiotics and probiotics themselves in the treatment and prevention of obesity requires further research.

CONCLUSION

Dietary supplements with proven effects that support the reduction of excess body weight include capsaicin, bitter orange, white bean seeds, green coffee, berberine, and single and multi-strain probiotics. Some of these supplements have additional health benefits. Bitter orange has antioxidant and anti-ulcer properties. Berberine improves lipid metabolism and reduces blood glucose levels. Capsaicin has found application in the treatment of neurodegenerative diseases. Supplements that do not significantly reduce body weight are chitosan and vitamin D. Chitosan can lower blood pressure, while vitamin D improves the sensitivity of tissues to insulin.

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