Gut microbiota and its importance in the development of obesity and insulin resistance

Tarmmikrobiotan och dess betydelse för utvecklingen av fetma och insulinresistens

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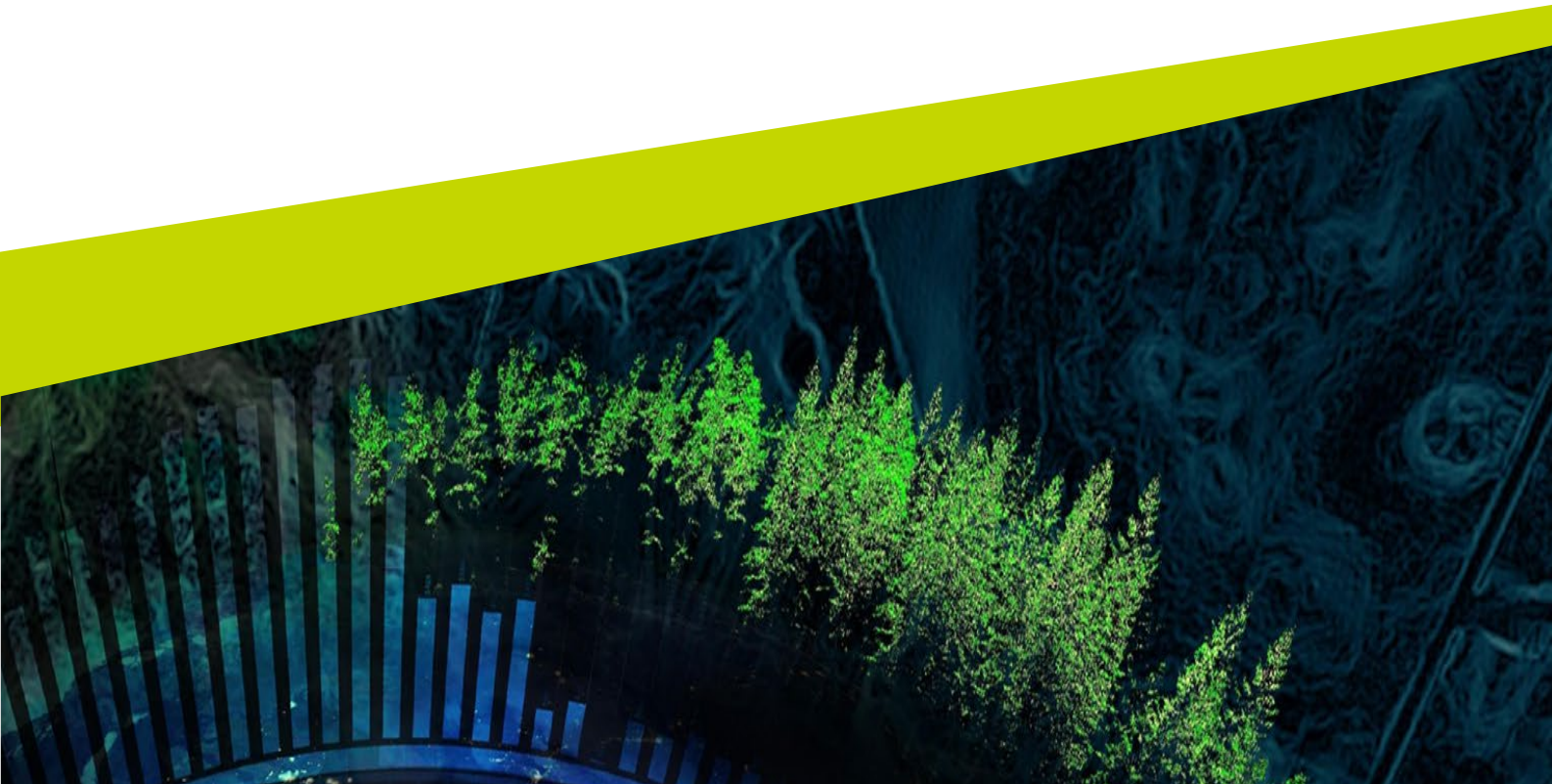

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Abstract

Obesity and insulin resistance are significant predisposing causes of co-existing diseases such as type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular and neurodegenerative disorders, and several types of cancer. Global obesity prevalence continues to accelerate and now affects a high number of people. Research has reported that lean and obese rodents and humans may exhibit variations in gut flora composition. Evidence from diverse sources indicates a significant association between gut microbiota and obesity/insulin resistance during the last years. Diet-related obesity promotes insulin resistance through mechanisms independent and dependent on the gut microbiota. Polyphenols, ketones, short-chain fatty acids and fibres can act on the gut microbiota, promoting beneficial bacteria and inhibiting the growth of pathogenic bacteria. However, some elements promote the development of undesirable bacteria in the gut, such as highly processed foods with extended shelf-life ingredients, excessive fructose consumption, and processed trans fatty acids. The gut microbiota is an important target for treating and preventing inflammation and metabolic disorders in human. This literature review examines several factors explaining the relationship between gut flora, and metabolic disorders such as insulin resistance and obesity. The influence of food on the modulation of bacterial composition in the gut and its consequences in the context of chronic diseases are also described.

Keywords: gut microbiota, obesity, insulin resistance

Table of contents

1. Introduction

The epidemics of obesity and metabolic disorders attacking the entire western world is challenging to explain. Environmental, genetic and epigenetic factors that affect metabolism do not explain the extent of these disorders either. In recent years, the attention of scientists concerned with metabolic conditions has been directed towards the microflora of the digestive tract. Currently, there is no doubt that intestinal bacteria play a crucial role in the pathogenesis of metabolic disorders (Ostrowska, 2013; Kumar Singh et al., 2019). However, a practical application of this knowledge in patients is still awaited. A change in diet and the use of pre-and probiotics leads to modulation of the intestinal microflora, which has a beneficial effect on metabolism. Experimental studies with intestinal microbiota transplants in mice and humans indicate that a specific intestinal microbiota composition may be a cause and not just a consequence of obesity and metabolic diseases, suggesting the possibility of modulating the intestinal microbiota in the prevention and treatment of obesity-related metabolic disorders. Furthermore, dietary intervention studies suggest that modulation of the gut microbiota may improve metabolic risk markers in humans and act as a possible weight loss promotion mechanism (Muscogiuri et al., 2019; Ostrowska, 2013).

Humans have several hundred species of bacteria in the gut, and the microbiome's composition varies significantly between individuals. Bacterial colonisation begins in utero and the gut microbiota composition changes throughout life. Still, the primary shifts, both in number and diversity, occur during breastfeeding and at the beginning of the introduction of solid foods (Rodríguez et al., 2015). The number, type and functions of microorganisms vary throughout the gastrointestinal tract. Still, most are found in the large intestine, where they are involved in fermenting undigested food components, especially carbohydrates and fibre, and have other important functions (Conlon & Bird, 2014). The leading roles of gut microbiota in humans are shown in Figure 1. In addition to protection against enteropathogens and absorption of nutrients from the diet, gut microbiota produces several bioactive compounds, some of which are beneficial to health, such as vitamins and certain short-chain fatty acids (SCFAs), and some of which are harmful, such as certain metabolites of amino acid degradation. Moreover, host defence mechanisms, particularly the mucosal barrier, are essential to protect tissues from the harmful effects of certain bacteria (Rowland et al., 2017; Conlon & Bird, 2014).

1.1. Aim

The purpose of this literature review was to define the gut microbiota, look at its role and relationship with obesity and diabetes and how it can be influenced; present differences in gut microbiota composition that may contribute to weight imbalance as well as impaired metabolism and the development of insulin resistance. The possibilities of nutritional modulation of the gut microbiota in the prevention and treatment of metabolic disorders are discussed.

1.2. Methods

Information used in this literature review was collected from scientific articles, publications, books, dissertations available at SLU's library and scientific databases such as Scopus, Web of Science, Science Direct, Cell Press Journal and PubMed.

2. Description of the microflora

The intestinal microbiota is a group of microorganisms (microbiome): bacteria, archaea, fungi, viruses forming a complex ecosystem in the gastrointestinal tract (Moszak et al., 2020). The human gastrointestinal tract contains:

- an enormous number of microorganisms,
- depending on the section (small intestine, large intestine, rectum).

The microbiota inhabiting the large intestine shows the greatest activity, abundance, and diversity. It is estimated that there are 500 to 1000 species belonging to 45 genera and 17 families of microorganisms, which account for 80% of dry faecal matter (Qin, 2017). Due to the nature of the environment in which they live, these bacteria are absolutely anaerobic or relatively anaerobic, and the metabolic transformations involving these bacteria are fermentative processes. The relationship between host and microbiota is not based exclusively on commensalism but is beneficial symbiosis. Microorganisms perform many useful functions: fermentation of certain nutrients, stimulation of the immune system to fight pathogenic microorganisms (Gołąb & Bil, 2007), regulation of intestinal development, production of vitamins like biotin and vitamin K, and production of hormones (Lozupone, 2012).

Bacteria are characterised by short generation times, rapid mutation rates, and the ability to exchange genes, allowing the human host to adapt rapidly to new environmental conditions, such as unfamiliar toxins or new food sources (Denamur & Matic, 2006). The gut microbiota develops soon after birth, and host genotype, mode of delivery, and early nutrition influence which bacteria become the first inhabitants (Lozupone, 2012). The early microbiota composition in infants born vaginally resembles the vaginal microbiota of their mothers, with a dominance of Lactobacillus and Prevotella species. In contrast, in infants born by cesarean section, the early microbiota is similar to the maternal skin microbiota, with a contribution of Staphylococcus species (Dominguez-Bello et al., 2010).

The composition of an individual's gut microbiota is usually described as stable (Faith et al., 2013); however, the abundance of bacterial species and microbial diversity change depending on the organism's physiological state during adulthood. This is evidenced by altered gut microbiota during pregnancy (Koren et al., 2012), inflammatory bowel disease (Qin, 2017), obesity (Turnbaugh et al., 2008), type 2 diabetes (Qin et al., 2012), atherosclerosis (Karlsson et al., 2012), and non-alcoholic fatty liver disease (Raman et al., 2013). The configuration of the microbiota depends on many factors. Still, the most dominant groups of gut microbes are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia, with the two classes Firmicutes and Bacteroidetes accounting for 90% of the intestinal microbiota. Figure 1. illustrates the main groups of good and bad bacteria that inhabit the intestines. According to the factors that have the greatest influence on intestinal microbiota composition, the most important are genetic factors, diet, geographical region, sanitary conditions, and medication (Rinninella et al., 2019).

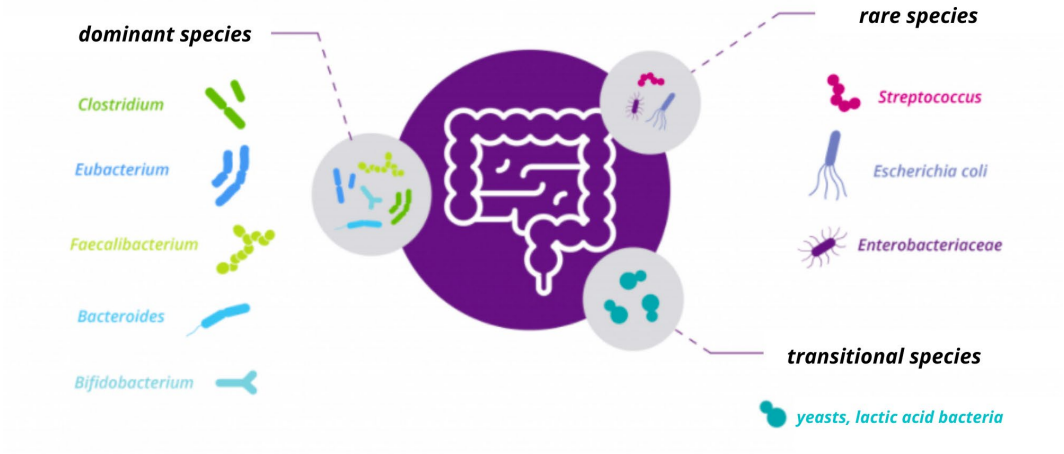

Figure 1. Composition of the gut microbiota; distinguishing dominant, rare and transient species. (Gut microbiota, 2021).

2.1. The role of intestinal microbiota

The gut microbiota provides the necessary capacity to ferment indigestible substrates such as dietary fibre and endogenous intestinal mucus. It supports digestion by helping the intestinal cells absorb nutrients (sugars, amino acids, vitamins and others) and ferment small pieces of food. The products of the fermentation process are gas and numerous metabolites, including short-chain fatty acids - the real "fuel" for the cells of the large intestine (Wong et al., 2006). The main SCFAs produced are acetate, propionate, and butyrate.

Butyrate is a major source of energy for human colonocytes (intestinal epithelial cells). It can induce apoptosis of colorectal cancer cells and activate intestinal gluconeogenesis, exerting beneficial effects on glucose and energy homeostasis (De Vadder et al., 2014). Propionate is carried to the liver, where it also regulates gluconeogenesis and satiety signals by interacting with intestinal fatty acid receptors (De Vadder et al., 2014). Acetate, the most abundant SCFA and a metabolite required for other bacteria's growth, reach peripheral tissues where it is implicated in cholesterol metabolism and lipogenesis and may play a role in central appetite regulation (Frost et al., 2014). Randomised controlled trials have shown that more significant production of SCFAs correlates with less diet-induced obesity and reduced insulin resistance (Lin et al., 2012). Butyrate and propionate, but not acetate, control gut hormones and decrease appetite and food intake in mice (Lin et al., 2012). Enzymes of the gut microbiome contribute to bile acid metabolism by producing non-conjugated and secondary bile acids that act as signalling molecules and as regulators of metabolism, affecting critical host pathways (Long et al., 2017).

The gut microbiota improves energy intake from the diet, modulates plasma lipopolysaccharide levels, which can initiate chronic low-grade inflammation progressing to obesity and type 2 diabetes, and moderates some host genes and proteins that regulate energy stores and fuel expenditure (Blaut, 2014; Tsukumo et al., 2009). These functions play an important role in the development of obesity

and metabolic disorders and further health consequences. However, there are still many questions surrounding the gut microbiota that need to be answered.

2.1.1. Effects of short-chain fatty acids on the activation of intestinal gluconeogenesis

Intestinal gluconeogenesis is a process by which glucose produced in the small intestine is released into the portal vein. This has a protective effect against diabetes and obesity by positively regulating glucose homeostasis and hepatic glucose production (Vily-Petit et al., 2020).

According to the study (De Vadder et al., 2016), succinate acts as a substrate for intestinal gluconeogenesis and leads to inhibition of hepatic glucose release and improved glucose and energy metabolism. Increased hepatic glucose release is thought to be a causal factor in insulin resistance and type 2 diabetes, while its suppression prevents obesity and diabetes (Abdul-Wahed et al.,2014). Researchers confirm that microbiota functions can influence host metabolism. This is a promising mechanism that could be targeted to treat and/or prevent impaired glucose metabolism, through innovative dietary and/or probiotic treatments for metabolic diseases such as obesity and diabetes.

3. Gut microflora and metabolic disorders

Obesity is characterised by abnormal and excessive accumulation of body fat that poses a health risk, including the host's genetic background, reduced physical activity and overconsumption of food (World Health Organization, 2009). Whereas insulin resistance is a condition of dysfunctional carbohydrate metabolism, in which peripheral cells are not sensitive to insulin, despite its normal or increased concentration. The production of increasing amounts of this hormone (above the actual demand of the organism) may lead to unpleasant health complications. Excessive and permanent work of the pancreas leads to its weakening. In the first step, high insulin might reduce glucagon; in later stages, insulin cannot reduce glucagon. As a result, glucagon production triggers gluconeogenesis, which causes a problem with glucose levels. Consequently, the accumulation of fat tissue results in overweight or even obesity. Insulin resistance is not a separate disease entity but is included in a group of closely related disorders called metabolic syndrome (Hatting et al., 2017).

Insulin resistance and obesity are combined with the appearance of chronic inflammation of low intensity in various tissues - that is, generalised inflammation throughout the body. The development of chronic inflammation in tissues causes them to cease to properly perform the function associated with adequate insulin sensitivity (de Luca & Olefsky, 2007).

The gut microbiota has been identified as an extra contributor to fat storage, weight gain, and insulin resistance (Cardinelli et al., 2014). Since the intestinal microbiota is involved in energy homeostasis, obtaining energy from food through fermentation processes and the formation of short-chain fatty acids (Jumpertz et al., 2011; Turnbaugh et al., 2006) also increases vascularisation of the villi, which leads to better uptake of dietary nutrients (Backhed et al., 2004). Moreover, the microbiota modulates the release of fasting-induced fatty factor, an inhibitor of lipoprotein lipase activity, which results in later storage of triglycerides in adipose tissue and liver (Backhed et al., 2004).

In obesity and type two diabetes, changes in the composition of the intestinal microflora are observed (Kootte et al., 2011). These changes consist of an increase in the number of Firmicutes and a decrease in the number of Bacteroidetes. These observations were mainly made in experimental studies and have not been unambiguously confirmed in humans (Duncan et al., 2008). Therefore, it cannot be said that the Firmicutes/Bacteroidetes ratio can be considered a marker of obesity or

metabolic disorders. Most studies of overweight and obese people find dysbiosis characterised by lower gut diversity (Shah et al., 2015).

A study on mice has given an amazing insight into how gut bacteria contribute to our body weight. The study found that when bacteria from the gut of obese mice were placed in the gut of lean mice, the lean mice became overfed and developed insulin resistance. When bacteria from the gut of lean mice were placed in the gut of obese mice, the mice became leaner (Vijay-Kumar et al., 2010). Like mice, both obese and lean individuals have very different gut bacteria. Although it is not yet known whether it is the gut bacteria that causes obesity or whether obesity causes bad gut bacteria, there is evidence that the wrong type of bacteria in the gut causes insulin resistance and inflammation (de Bandt et al., 2011).

3.1. Bacterium present in healthy individuals with adequate body weight

According to a recent study (le Roy et al., 2021), the newly identified bacterium Dysosmobacter welbionis J115T was detected in 62.7%-69.8% of the healthy population. They investigated the amount and frequency of Dysosmobacter (a novel butyrate-producing bacterium) in both the general population and individuals with metabolic syndrome and the effect of this bacterium on host metabolism, using mice with obesity diet-related diabetes. These results suggest that this bacterium directly and positively affects host metabolism and is a strong candidate for developing useful bacteria targeting obesity and related metabolic diseases.

Factors influencing the development of the intestinal microflora

The formation of the intestinal microbiota is determined by many factors, both genetic and environmental: the individual's genetic characteristics, the way the child was born, the type of nutrition and feeding, the medication is taken, stress, infections, smoking, type of physical activity, surgery, fasting from food. (Quigley, 2017; Cenit et al., 2017; Conlon & Bird, 2014; Fraumene et al., 2017).

Diet is one of the main factors influencing microbiota alterations (Quigley, 2017). The general features of the diet, i.e., Caloric intake, timing, nutrient diversity, vitamin and fibre intake, macronutrient percentage, affect the microbiota composition and can change it reasonably short (Quigley, 2017). Furthermore, it is interesting to note that Chrono nutrition- a science that investigates the phenomenon of biological rhythms (Arola-Arnal et al., 2019)- has become remarkably crucial as a modulator of the microbiota because disturbance of circadian rhythms can enhance the possibility of diseases (Manoogian & Panda, 2017). The microbiome is known to be affected not only by what is eaten but also by the time food is consumed (Kaczmarek et al., 2017). The time of food consumption has been found to be capable of restoring circadian rhythms influencing bacterial populations and their roles (Voigt et al., 2016). In particular, time-restricted feeding, a dietary pattern in which food intake is kept limited to a time window that can vary between 8 and 12 hours (Mattson et al., 2017; Longo & Panda, 2016), is able to restore the cyclic nature of the microbiota (Kaczmarek et al., 2017). Consequently, the restoration of circadian rhythms, including the rhythm of the microbiota, may also maximise each individual's physiology and lower the potential risk of disease (Manoogian & Panda, 2017).

Microorganisms residing in the human gut are certainly major contributors to host metabolism and, consequently, are considered possible clinical targets (Cani, 2018). Therefore, prebiotics, probiotics, and faecal microbiota transplantation as new possibilities to promote and sustain a healthy microbiota and consequently healthy homeostasis have emerged:

- Probiotics: it refers to "the administration of live microorganisms in adequate quantities that are able to provide health benefits to the host" (Hill et al., 2014). Probiotics support a healthy intestinal bacterial balance and have been associated with a wide range of health benefits. There are advantages for weight loss, digestive health, immune function, and more (Chapman et al., 2011; Angelakis et al., 2013).

- Prebiotics: substances present or incorporated into food to stimulate the development of normal intestinal flora, thereby improving health (Hutkins et al., 2016). A prebiotic may be a natural component of the diet, e.g. starch, dietary fibre, or food additives (nutritional supplements) of a health-promoting natural - healthy food for the colon (Wilson & Whelan, 2017).

Unlike probiotics, prebiotics do not contain any microorganisms but only stimulants (What Are Prebiotics? 2019). Prebiotics are undigested - resistant to the action of digestive enzymes in the gastrointestinal tract (Wilson & Whelan, 2017) - food components that have a beneficial effect on the host by selectively stimulating the growth or activity of one type or a limited number of bacteria in the colon and thereby improving host health (Lamsal, 2012).

- Faecal microbiota transplantation: has been recognised as a potentially beneficial medical treatment that can be used, for example, to treat insulin resistance in obese patients (Gianchecchi & Fierabracci, 2019).

Experimental studies used for the trophic function of microflora are conducted on germ-free mice, which are free of all detectable microorganisms and parasites.Transplantation of microflora from obese mice into the gut of microbial-free mice results in an increase in their body weight (Turnbaugh et al., 2006).

4. Factors influencing the development of favourable gut bacteria

4.1. Fibre

Dietary fibres are indigestible carbohydrates found in food. While most carbohydrates are broken down into simple sugars in the stomach or small intestine, dietary fibre passes into the large intestine undigested. Essentially, fibre supports gut health, helps control blood sugar levels, gives a feeling of satiety and supports the growth of beneficial gut bacteria. It is divided into two categories according to its solubility in water:

- Soluble fibre: dissolves in water and can be metabolised by "good" bacteria in the intestines.
- Insoluble fibre: does not dissolve in water.

4.1.1. Soluble Fibre

The intestines transform into a gel-like substance that slows stomach emptying, allowing vitamins and minerals to remain in the body longer and become better absorbed (Wanders et al., 2011). Soluble fibre also prevents spikes in blood sugar and insulin levels after eating a meal (Jenkins et al., 2000). It also maintains the feeling of satiety for a more extended period, probably by modulating the hunger hormone ghrelin (St-Pierre et al., 2009). Thanks to the reduced desire for food, the body does not crave various snacks or high-calorie foods, significantly preventing weight gain. Table 1. shows examples of soluble fibre present in foods.

Glucomannan

What sets glucomannan apart is that it is much more viscous than any other fibre. Glucomannan forms a gel in the gut that delays the gastric and intestinal emptying process enough to increase nutrient absorption significantly. It quiets hunger hormones and ferments as a prebiotic to promote good gut bacteria (Chearskul et al., 2009; H. L. Chen et al., 2006). Research shows that it also helps with weight control, supposedly by stimulating feelings of satiety - when feeling full and satisfied after a meal (Sood et al., 2008; Keithley, 2005).

4.1.2. Insoluble fibre

It appears to have an even more significant anti-inflammatory effect than soluble fibre. Like the previous type of fibre, it reduces ghrelin secretion (St-Pierre et al., 2009). As a result, by consuming large amounts of insoluble fibre, the feeling of hunger is remarkably reduced.

The consumption of insoluble fibre can also enhance fat burning directly. A long-term animal study compared two diets carried out for 45 weeks (Isken et al., 2010). These diets mimicked the standard Western diet - rich in refined sugar and lots of low-quality fat. The exception was that one group's diet contained soluble fibre, while the other diet was rich in insoluble fibre.

The mice that consumed soluble fibre had increased diversity of gut bacteria but were also obese and pre-diabetic until the end of the year. The mice that ate insoluble fibre showed almost no weight gain and performed significantly better fat metabolism. The best sources of insoluble fibre are shown in Table 1.

Table 1. The best sources of soluble and insoluble fibre (Apel, 2021).

Soluble	Insoluble
Brussels sprouts	Amaranth
Avocados	Blackberries
Beans	Unpeeled apples
Broccoli	Collard greens
Turnips	Green beans
Figs	Celery
Nectarines	Leeks
Apricots	Cabbage
Pears	Cauliflower
Oats and barley	Nuts
Carrots	Spring onions
Sweet potatoes	

4.1.3. Prebiotic Fibers and Resistant Starches

Prebiotic fibre and resistant starch, occurring predominantly in the foods shown in Table 2. nourish beneficial gut bacteria, providing fuel to colonise the digestive tract (Bird, 2000).

In recent years, more and more studies have demonstrated the benefits of resistant starch and its impact on health-enhancing processes:

- 30-70% of resistant starch from the diet becomes fermented in the large intestine through bacteria colonising the colon, thus performing a prebiotic function;
- it affects lipid metabolism: by absorbing bile acids, it lowers the level of cholesterol (LDL fraction), reduces the level of triglycerides in the blood;
- lowers blood glucose levels and regulates the insulin needed for its metabolism, giving a feeling of satiation.

Prebiotic fibre supports weight management by nourishing beneficial gut bacteria (A. Parnell & A. Reimer, 2012; Macfarlane et al., 2006). Prebiotics are found in less common foods, so it may take more creativity in cooking to incorporate them into the regular diet.

Table 2. Good sources of resistant starches and prebiotic fibre (Apel, 2021).

Resistant starches	Prebiotic Fibre
Raw green bananas	Raw dandelion greens
Raw plantain flour	Raw garlic
Raw potato starch	Leeks
	Raw jicama
	Jerusalem artichoke
	Chicory root

4.1.4. Complex carbohydrates in rye bread

Rye bread is produced from a mixture of rye flour and grains, depending on the type of bread. It is thicker, darker and has a stronger taste than the usual white and wheat bread. Rye bread is high in fibre and has a rich nutritional profile (Table 3.). The exact composition of such bread depends on the amount of rye flour used. The darker rye bread contains more rye flour than the lighter varieties.

Table 3. The nutritional content of 1 slice of rye bread 32 grams (FoodData Central, 2018)

Calories	83
Protein	2.7 grams
Carbohydrates	15.5 grams
Fat	1.1 grams
Fibre	1.9 grams
Selenium	18% of the Daily Value (DV)
Thiamine	11.6% of the DV
Manganese	11.5% of the DV
Riboflavin	8.2% of the DV
Niacin	7.6% of the DV
Vitamin B6	7.5% of the DV
Copper	6.6% of the DV
Iron	5% of the DV
Folate	8.8% of the DV

In addition, rye bread provides trim levels of zinc, pantothenic acid, phosphorus, magnesium, calcium and other trace elements. Relative to ordinary bread, such as white or whole-grain bread, rye bread has higher fibre content and provides more micronutrients, especially B vitamins (FoodData Central, 2018; FoodData Central, 2019; FoodData Central, Bread, Wheat, 2019).

According to the study (Östman et al., 2019), where glucose kinetics were examined, it was confirmed that the consumption of wholemeal rye bread leads to lower postprandial plasma insulin concentrations than the consumption of wheat bread, but usually does not differ much in terms of glycaemic profile.

In summary, rye bread is rich in soluble fibre, which helps slow down digestion and absorption of carbohydrates through the digestive tract. This leads to a more gradual rise in blood sugar levels enabling weight control also since this type of bread is low in calories. Controlling blood sugar levels is very important for everyone, especially those struggling with type 2 diabetes and who cannot have sufficient insulin production. Moreover, rye bread also contains phenolic compounds such as ferulic acid and caffeic acid, which can also slow sugar and insulin release into the bloodstream (Maćkowiak et al., 2016).

4.2. Ketones as a factor in reducing inflammatory cells produced in the gut

A study (Ang et al., 2020) published in the peer-reviewed scientific journal Cell addresses this issue and shows that ketones have an autonomous effect on gut bacteria in the body that may help reduce inflammation.

For two months, 17 patients who were overweight lived in a metabolic department where all meals were prepared for them. They ate either a diet consisting of 50% carbohydrate, 15% protein, and 34% fat for four weeks or a ketogenic diet consisting of 5% carbohydrate, 15% protein and 80% fat. After the first four weeks, the participants switched to the second diet. The researchers found that the different diet regimes caused meaningful changes in the gut microbiome. There was no difference in the total bacterial load, but specific species changed remarkably. Of these, Bifidobacteria showed the biggest decrease on the ketogenic diet. This is very exciting because the scientists were also able to show that in mice, Bifidobacteria produce Th17 cells, immune cells that take a role in inflammation and autoimmune reactions. Through decreasing the amount of Bifidobacteria, the ketogenic diet may lower the amount of Th17 cells. Although this does not prove that the result is a beneficial drop in inflammation, it is definitely information that would support further targeted research. The scientists also studied different variants of high-fat diets in mice and found very different results for high-fat diets, ketogenic and non-ketogenic. They not only had different results on gut microbiota, but they had completely contrasting outcomes. This highlights, even more, the weakness of any study claiming that a high-fat diet has a specific impact on gut bacteria if it doesn't also control carbohydrates - and if it doesn't take into consideration whether or not ketones are present (Ang et al., 2020).
The writers even showed that ketone esters could trigger similar changes, suggesting that at least part of the outcome derives from the ketone bodies themselves, and part may result from carbohydrate restriction.
However, while the science of how the foods we eat influence our microbiome is just developing, studies like this one illustrate the importance of being specific about the details of an intervention diet. They also demonstrate that measuring a physiological result beyond changes in bacteria gives much more potentially relevant information.

The Effects of Ketogenic Diet on Intestinal Microbiota

The gut microbiota has a significant impact on health and disease, with nutrition being a major factor affecting its bacterial composition and general heterogeneity (Clemente et al., 2012). The ketogenic diet not only has become a common diet to help cure epilepsy, type 2 diabetes, obesity, neurodegenerative issues, and other disorders (Dashti, 2004). This eating pattern is described as a diet high in fat (>60% energy), very low in carbohydrate (<10% energy), and adequate in protein (Urbain et al., 2017). The primary variation of the keto diet was composed of 80% of daily energy intake from fat, 15% protein, and 5% carbohydrate (Paoli et al., 2015). The modification has since been made to lower the total daily % fat and raise the daily % protein and/or carbohydrate, and the total caloric intake has not been reduced (Paoli et al., 2015). Consuming a very low carbohydrate diet shifts the body from glucose to fat as the primary fuel source (Urbain et al., 2017; Paoli et al., 2015). Lipid metabolism produces water-soluble ketone bodies, known as ketogenesis (Urbain et al., 2017).

Animal studies:

The digestive tracts of humans and mice are made up of structurally and anatomically alike organs, which is why mice are commonly used for the investigation of gut microbiota (Nguyen et al., 2015). Even though they have significant anatomical, physiological, and genetic features in common, the researchers indicate key differences that may be shaped by various diets, nutritional behaviours, physical shape, body size, and metabolic demands (Nguyen et al., 2015). A 16-week study (Ma et al., 2018) analyzed the effects of ketogenic feeding on gut microbiome composition and possible benefits to neurovascular function in young and healthy mice (Ma et al., 2018). They determined that such a diet increased the beneficial gut microbiota, A. muciniphila, and Lactobacillus bacteria, which are capable of producing short-chain fatty acids that help protect the intestinal lining (Ma et al., 2018). The ketogenic diet reduced the number of potentially pro-inflammatory bacterial species, Desulfvibrio and Turibacter (Swidsinski et al., 2017). However, such a diet reduced the overall diversity of the microbiota, likely because of the low carbohydrate consumption, which reduces the polysaccharides in the gut that many microbes are fed on (Swidsinski et al., 2017).

4.3. Butyrate

Nutritional recommendations suggest large amounts of fibre in our diet (Smiley, 2017). Dietary fibre is broken down into short-chain fatty acids such as butyrate (butyric acid), propionate, and acetate (Prasad & Bondy, 2019).

Butyrate is also produced in small amounts in mammalian (mainly attributed to ruminants, also related to the gut microbiota activities) cells due to fat breakdown and glucose metabolism. Thus, butyrate can undoubtedly be found in animal fats and dairy products (Pouteau et al., 2003). Figure 2 shows examples of some animal-based dietary sources of butyrate (Pouteau et al., 2003).

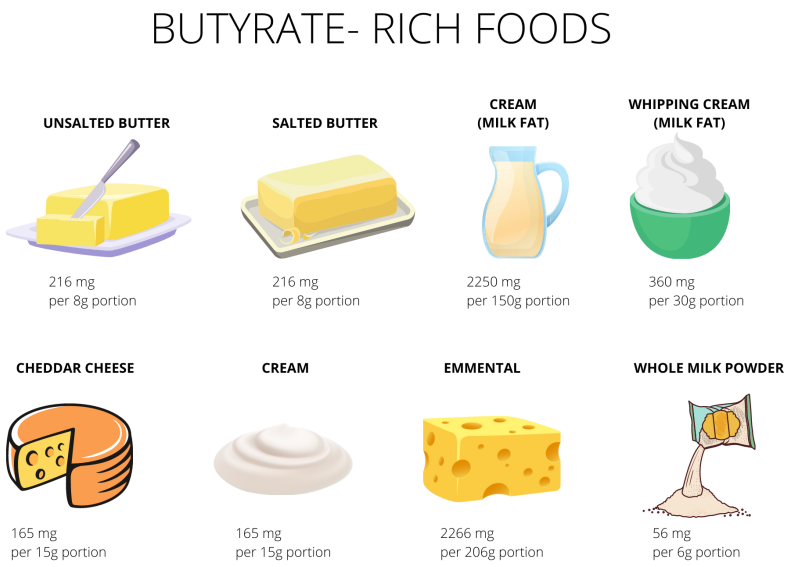

Figure 2. Butyrate- Rich Foods. Serving Size Varies (Cho, 2020).

The role and benefits of butyrate in the context of obesity and insulin resistance:

- Controls blood sugar, hunger and lowers cholesterol (Puddu et al., 2014; Chen et al., 2018). Once absorbed into the blood, butyric acid can be beneficial in maintaining proper blood pressure (Figure 3).
- Butyrate has been shown to decrease inflammation even in the brain and stop toxins from penetrating the intestinal lining (Säemann et al., 2000).
- A 2014 study found that consuming butyrate was associated with increased amounts of healthy bacteria in the gut. It was once thought that butyrate produced by fermentation in the lower intestine was the same as butyrate from the diet. Still, this study shows that consuming short-chain fatty acids from butter may affect gut health in a different way. This may mean that it is not enough to either produce butyrate or eat it. Perhaps doing both is the most convenient option (Vidrine et al., 2013).

A 2012 study demonstrated that lowering the amount of fibre (an initial switch to short-chain fatty acids) did help participants who suffered from long-term constipation. The study ran for six months, and after two weeks without fibre, participants were allowed to increase the amount of fibre as necessary. Following two weeks without fibre, the participants felt so relieved that they maintained zero fibre intake throughout the six months. Among the high-fibre, low-fibre, and no-fibre groups, participants with zero fibre had the most frequent bowel movements (Ho, 2012).

Although it is too early to say that the body definitely needs or does not need fibre, it is worth pointing out those plant foods that make short-chain fatty acids are generally considered optimal health foods. However, it is sometimes forgotten to consider blood glucose jumps, anti-nutrients, GMOs, pesticides, allergens, and other components that the foods might cause (Cho, 2020).

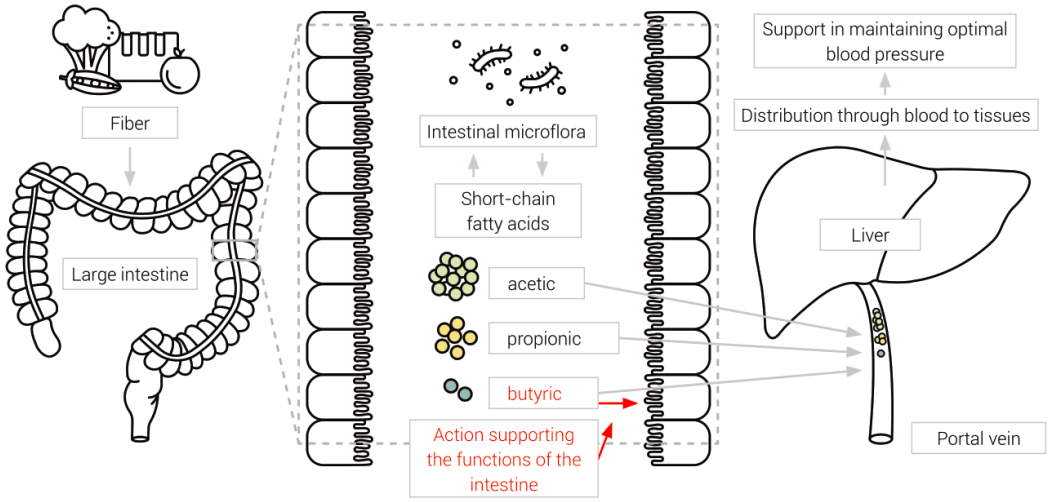

Figure 3. The health-promoting role of butyric acid. Together with other short-chain fatty acids, butyric acid has a nourishing effect on intestinal epithelial cells, helping to support barrier function, intestinal barrier function and immune system function. Once absorbed into the blood, butyric acid may help maintain normal blood pressure (Marques et al., 2017).

4.4. Polyphenols

Polyphenols are anti-nutrients, but they are also secondary metabolites found in abundance in many foods attributed to positive health effects. Dark chocolate, flaxseed, cocoa powder and many fruits and vegetables are rich in polyphenolic compounds. Some of their health benefits include weight management and lowering blood pressure. However, studies have shown that high intakes of polyphenols may contribute to causing kidney damage, cancer development and altered thyroid hormone production. In addition, they have the potential to impair nutrient digestion (Mennen et al., 2005).

Most polyphenols pass through the small intestine without absorption, thus coming into contact with the intestinal microbiota that inhabits the large intestine (Scalbert & Williamson, 2000). As a result, this has led to the development of a bidirectional two-way reaction between polyphenolic compounds and the gut microbiota. The first is that polyphenols are biotransformed to their metabolites by the gut microbiota, resulting in increased bioavailability of polyphenols. Secondly, polyphenolic compounds affect the intestinal microbiota composition, mainly by inhibiting pathogenic bacteria and stimulating beneficial bacteria (Figure 4.). They may act as a prebiotic and enrich beneficial bacteria (Lee et al., 2006) . Therefore, interactions between dietary polyphenols and the intestinal microbiota may affect host health (Ozdal et al., 2016).

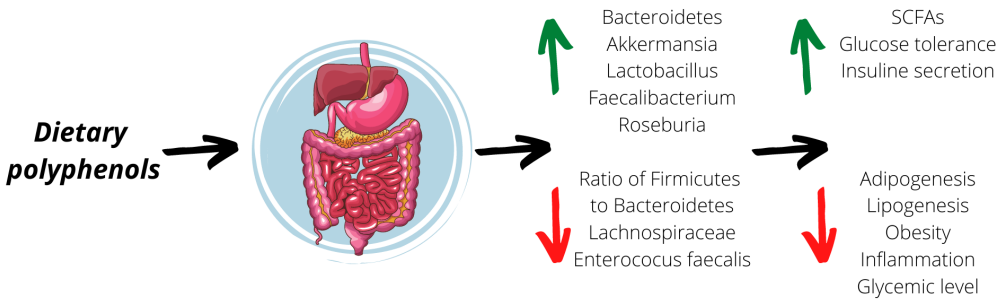

Figure 4. Effects of polyphenols on the composition of the gut microflora and potential outcomes related to metabolic health. (Kasprzak-Drozd et al., 2021).

Fasting- Inducible Adipose Factor

The body has a precisely tuned mechanism regulating the burning and storage of fat (Gut Microbiota and Obesity - Microbewiki, 2016). In fact, the liver produces a protein called fasting inducible adipose factor (FIAF). FIAF blocks enzymes called lipoprotein lipase that instruct the body to store fat. Essentially, as a result, this means that once FIAF is high, the body burns extra fat, and the liver generates the appropriate amount of FIAF to suit the body's demands. However, an issue is that the bacteria in the gut also produce FIAF, although they modify it for their own goals. It is thought that gut bacteria actually inhibit the formation of FIAF when following a high-fat, high-sugar diet, thus causing the body to store fat instead of burning it. It cannot be said that all gut bacteria are harmful - they can be beneficial as long as they are present in the right place. However, too many of them or the wrong types can lead to obesity. If gut bacteria are deprived of starch or sugar, they become starved. These starved bacteria produce FIAF, and thus fat burning occurs. Once the gut bacteria are fed sugar or starch, they stop producing FIAF, and the body starts storing fat (Backhed et al., 2004).

Coffee as a contributor to the activity of beneficial intestinal bacteria

Coffee polyphenols also act as a prebiotic for Bacteroidetes, a group of bacteria more commonly found in lean people (Magne et al., 2020; Kumar Singh et al., 2019). Medium-chain triglycerides, especially the shortest of the medium-chain fats, create intense pressure on the colon bacterial population. When they are taken during fasting, the body actively interferes with gut bacteria in their attempts to store extra fat. It could be possible that the body temporarily suppresses the gut bacteria by consuming coffee with fat and then supplies food for the “skinny people" bacteria to proliferate. For example, it was found that coffee was associated with reduced body weight, obesity, liver triglycerides and energy intake (Cowan et al., 2014) . The coffee resulted in a more beneficial body composition and therefore improved the critical ratio of Firmicutes to Bacteroidetes. In addition, coffee boosted circulating short-chain fatty acids, which also favours the gut. Changing the milk in the coffee to butter might be good in multiple different ways. One of the antioxidant polyphenols in coffee is helpful to the body's efficiency, called chlorogenic acid. Once putting milk protein casein into the coffee by adding milk, semi-half, cream, or most fake creamer, the polyphenols become 3.4 times much less bioavailable (Duarte & Farah, 2011). This means that swapping milk or cream for butter gives 3.4 times more antioxidants from the coffee.

Nutrition based on foods rich in polyphenols

A new study (Peron et al., 2021) reconfirmed that consuming polyphenols in food impacts the intestinal microbiota composition. Polyphenol metabolites (biodegradable by the gut microbiota) may contribute to host health benefits by increasing the number of butyrate-producing bacteria (Mithul Aravind et al., 2021).

The MaPLE study was a randomised, controlled, crossover study involving adults aged 60 years and older living in a nursing home during an eight-week polyphenol-rich diet. Specifically, subjects consumed three servings/day of selected polyphenol-rich foods, including blueberries and their derivatives, orange juice, pomegranate juice, green tea, Renetta apple and apple purée, and dark chocolate, providing a total polyphenol intake of 1391 mg/day in the polyphenol diet vs 812 mg/day in the control diet.

The results of the MaPLE study showed that this type of nutrition reduces intestinal permeability in older adults by inducing changes in the intestinal microbiota and promoting the good bacteria responsible for the production of butyrate (the order Clostridiales and the genera Roseburia, Butyricicoccus and Faecalibacterium). Compared to the control diet, the polyphenol-rich diet increased serum metabolites associated with polyphenols and methylxanthine intake (Peron et al., 2021).

Generally, these results expose the complex correlations between polyphenol intake, intestinal permeability and gut microbiota composition in older adults. This fact may be necessary for determining personalised dietary interventions for older adults, regulating their body weight and blood sugar levels.

5. Factors influencing the development of negative microflora

5.1. Highly processed food

Highly-processed foods: this category contains colours, stabilisers, flavourings, sweeteners, preservatives and the entire artificial arsenal of the modern food industry. These foods contain ingredients extracted from food, such as lactose, casein, gluten, maltodextrin or glucose-fructose syrup. They undergo processes such as carbonation, hardening, weight and volume increase, the addition of anti-caking agents or emulsifiers. All these elements are added to food due to the requirements of modern trade to provide the cheapest possible products, convenient for everyday use, practically ready to eat, and extend shelf-life. The authors that classify the degrees of processed foods recommend limiting highly processed products in the diet. Studies show an association between manufactured foods and metabolic diseases.

5.1.1. Processed food promotes inflammation.

According to a study (Zinöcker & Lindseth, 2018), researchers report evidence linking highly processed foods to gut microbes associated with obesity and metabolic disease. While not all the mechanisms are yet known (and many studies have been conducted in mice), one likely link is inflammation. Gut bacteria are sensitive to what is consumed, and their diversity changes depending on the available nutrients and chemicals produced by the surrounding bacteria. Ingredients in heavily

processed foods, such as artificial sweeteners and emulsifiers, may stimulate gut bacteria to create a more favourable pro-inflammatory environment (Suez et al., 2014; Chassaing et al., 2015).

5.1.2. Processed foods are missing metabolism-regulating fibre.

Processed foods do not provide the nutritional value that natural foods guarantee (Institute of Medicine et al., 2013). One of the key nutrients directly linked to both the gut microbiome and insulin is fibre. As I described above, fibre plays a crucial role in determining what microbiota develops in the gut (Zinöcker & Lindseth, 2018). Typically, the low fibre content of ultra-processed foods may favour a less diverse microbiome. Moreover, dietary fibre is not hydrolysed or broken down by digestive enzymes. Rather, gut microbes ferment dietary fibre, making metabolites such as SCFAs- acetate, propionate and butyrate (Müller, 2019; Myhrstad et al., 2020). These end up in the liver, some of which are used for energy production, and a small amount circulates in the body's blood and tissues. Research shows that these SCFAs help control metabolism and improve insulin resistance (Myhrstad et al., 2020).

5.1.3. Nutrients in Processed Foods are Acellular

The nutrients in wholesome foods are mostly contained in cells. The digestive system has to release these nutrients into the body before the organism can use them. In contrast, the energy contained in ultra-processed foods is either mainly cell-free or not present in cells. Acellular nutrients are more accessible, so gut microbes can take them up before they are absorbed in the small intestine (Zinöcker & Lindseth, 2018). This principle is most easily seen in whole grain products. When whole grains are ground into flour, the result is a mixture of cellular and cell-free nutrients. But as these grains are further milled, more and more cellular nutrients are released, as is the case with white flour. This is also applicable to the oils and starches extracted from the seeds - most of these nutrients are acellular.

Cell-free nutrients have less diversity and therefore do not benefit from the same gut microbes as whole foods. Research in mice has shown that this can alter the structure of the microbiome in the colon (Turnbaugh, Bäckhed, et al., 2008).

The researchers fed the mice a Western-like diet rich in simple sugars, starches and fats. As a result, they observed a significant reduction in the microbiome's diversity and a rise of sugar-metabolising bacteria in the distal part of the colon, where they are not normally found. This could cause a knock-on phenomenon of molecules released by the bacteria entering the bloodstream or the intestinal wall - developments associated with type 2 diabetes (Cani et al., 2008).

5.2. Trans-fatty acids

In research from de Brito Medeiros et al. (2021), they examined the hypothesis that naturally and industrially-produced trans-fatty acids may have different effects on metabolic parameters and on the gut microbiota of rats. The Wistar rats were split into three groups depending on diet: control group, with soybean oil and normal fat; hydrogenated vegetable fat (industrial); and ruminant fat (natural). After 53 days of treatment, serum levels of biochemical markers, fatty acid composition of liver, heart and adipose tissue, histological and oxidative parameters of the liver, and gut microbiota composition were evaluated. The gut microbiome was significantly different between groups. Overall, results show that ruminant fat reverses the fatty liver normally caused by a high-fat diet, potentially related to modifying the gut microbiota and its anti-inflammatory capacity (de Brito Medeiros et al., 2021).

5.3. Fructose

Fructose is the main component of fruit. The liver converts fructose into glucose or triglycerides, which are then stored as fat. Fructose can also be harmful to the body because it feeds the harmful bacteria in the gut. When it enters the gut, pathogenic bacteria readily consume it and multiply.

Fructose has also been associated with inflammation in a variety of ways. A study published in 2021 in Nature Communications looked at the effects of fructose on the mouse and human immune cells. Researchers found that fructose changes cellular metabolic pathways to promote inflammation, harming cells and tissues (Jones et al., 2021).

A mice study (Todoric et al., 2020) looked at what happens when fructose metabolism reduces the proteins that maintain the intestinal barrier, a mucus-covered layer of cells that stops toxins from escaping the gut. This weakened intestinal barrier leads to endotoxin leakage, which causes inflammation, including in the liver. This triggers a process that contributes to fat accumulation in the liver (Todoric et al., 2020).

Changes in the microbiome

Excess fructose can alter the gut microbiome. One small study from 2020 (Beisner et al., 2020) compared the microbiome of women consecutively following a low fructose diet, a diet rich in fruit and a diet with high fructose corn syrup. This allowed the results of the diets to be compared in the same participant (as the gut microbiome can vary from person to person). They found that a diet with high fructose corn syrup reduced levels of healthy bacteria, while eating the same amount of fructose in fruit led to more positive changes, probably due to the fibre content of the fruit and vegetables (Beisner et al., 2020).

Effects on natural honey consumption in diabetic patients

The most numerous group of compounds in honey are carbohydrates. The largest amounts are found in monosaccharides, such as glucose (~34%) and fructose (~39%). Other carbohydrates, including sucrose, maltose (7.3%) and melezitose, can be found in smaller amounts in honey. This study investigated the effect of natural honey on body weight and some biochemical blood markers of individuals with diabetes. This research suggests that 8-week consumption of honey can beneficially affect body weight and blood lipid levels in diabetes patients (Bahrami et al., 2009).

It cannot be clearly stated that fructose affects the development of negative intestinal microflora. According to the research above (Bahrami et al., 2009), it was indicated that honey consumption positively impacts metabolic problems, yet honey is mainly fructose. However, other components of honey are worth considering (potassium, chlorine, phosphorus, magnesium, calcium, iron, manganese, cobalt, or vitamins - A, B1, B2, B6, B12, C, folic acid, pantothenic acid and biotin), which may have caused these changes through positive influence on intestinal microbiota. Therefore, further studies should be conducted.

6. Discussion and conclusion

The daily diet and quality of food have a significant impact on the functioning of the whole body. It is known that obesity promotes the development of harmful intestinal flora, causing dysbiosis and the other way around. Gut bacteria can support and repair the organism or create an environment for the development of various diseases. It is the type of bacteria that can determine the reversal of negative metabolic processes.

Although reports on gut microbiota composition in obese individuals are not consistent, diminished microbiota diversity appears to be a recurring phenomenon. It is claimed that these changes may be related to altered short-chain fatty acids composition, energy homeostasis and inflammation. Nevertheless, the causal relationship between gut microbiota composition and energy homeostasis is complex, with variables such as genes, age, environment and diet significantly affecting gut microbiota functionality.

The gut microbiota affects many areas of human health, from innate immunity to appetite and energy metabolism. Targeting the gut microbiome with a proper diet rich in various nutrients, prebiotics, probiotics, short-chain fatty acids, and bioactive components is beneficial to human health. It can potentially reduce obesity and decrease the risk of type 2 diabetes. Food preservatives, trans fats from highly processed foods, and excess simple sugars can negatively impact the gut microbiota and contribute to metabolic diseases, including abnormal body weight and inflammation. The gut microbiota needs to be considered an essential aspect of nutrition. Our community should align education and public health messages of origin based on a healthy digestive system.

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