PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 74 (2020), No. 2 (725), pp. 58–64.

DOI: 10.2478/prolas-2020-0009

Review

MICROBIAL COMMUNITY OF KEFIR AND ITS IMPACT ON THE GASTROINTESTINAL MICROBIOME IN HEALTH AND DISEASE

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Kefir is a fermented dairy product, created by fermentation of milk by bacteria and yeasts. Kefir is the most common traditional non-sweetened fermented dairy beverage in the Baltic countries. Whole kefir and specific fractions and individual organisms isolated from kefir provide a multitude of health benefits, including regulation of composition of the gut microbiome. This review aims to summarise the available data about influence of kefir consumption on the gut microbiome in healthy individuals and to highlight the effects that kefir consumption as well as separated fractions of kefir can have in disease states via modulation of the host microbiome.

Key words: *kefir, lactobacillus, microbiome, probiotics, dysbiosis.*

INTRODUCTION

The human gastrointestinal tract (GIT) microbiome is an ecological community of microorganisms — bacteria, archaea, fungi, viruses and protists (Hillman *et al.*, 2017). The dominant bacterial microorganisms of the normal human microbiome are firmicutes (30–52%), bacteroidetes (9–42%), actinobacteria (1–13%), and other microorganisms (~2%) such as streptococci, lactobacilli and enterobacteria. Previous studies have shown that diet has a significant impact on the GIT microbiome and health status of the host. Even a short-term specific diet has shown to have a strong influence on the microbial diversity of individuals from different populations (David *et al.*, 2014; Matijašić *et al.*, 2014; Shen *et al.*, 2014; Rajoka *et al.*, 2017; Klimenko, 2018). The gut microbiome is essential in maintaining health of the host, since it is responsible for vitamin synthesis, energy supply, immune cell maturation, and defense against infectious pathogens (Sekirov *et al.*, 2010). There are many factors affecting the composition and diversity of the gut microbiome, including intrinsic factors, diseases, medication, harmful habits, dietary factors (Zhernakova *et al.*, 2016) as well as geographical location (Nakamoto and Schnabl, 2016). Effects of specific local diets on the gut microbiome have been previously described (Del Chierico *et al.*, 2014; Lopez-Legarrea *et al.*, 2014), but there is lack of data about the impact of a typical Baltic countries' diet on the gut microbiome. Data from the European Food Safety Authority's (EFSA) Comprehensive European Food Consumption Database show that dietary patterns in the Baltic region differ from those in Western Europe. Higher intake of traditional sour milk products in the Baltic region has been noted and might have a positive effect on gut microbiome composition and diversity (Zhernakova *et al.*, 2016).

The most common traditional non-sweetened fermented milk product in Baltic countries is kefir. Whole kefir, as well as specific fractions and individual organisms isolated from kefir, provide a multitude of health benefits, including regulation of composition of the gut microbiome (Bourrie *et al.*, 2016). Fermentation starter cultures in kefir production are yeasts and bacteria. Up to 120 strains of lactobacilli can be isolated from kefir grains (Marth and Steele, 2001). Reported clinical effects attributed to consumption of lactobacilli include immune enhancement and prevention of intestinal disorders, since most probiotic strains are believed to have an ability to colonise the intestinal tract, thereby positively affecting the microbiome and perhaps excluding colonisation of pathogens (Batt and Tortorello, 2014, at p. 411).

Since the diet and microbial communities in the gut play key roles in human wellbeing, it is essential to understand the interaction between these three counterparts. As kefir is a key part of the diet in Baltic countries, this review aims to gather the available data about influence of kefir consumption on the gut microbiome in healthy individuals and highlight the effects that kefir consumption can have in disease states via modulation of the host microbiome.

TRADITIONAL USE AND CONSUMPTION OF FERMENTED MILK PRODUCTS

Kefir is one of the most popular and widely consumed fermented milk beverages in Latvia. Others include yogurt, buttermilk, soured milk and ryazhenka. Traditionally kefir and other fermented milk beverages are consumed together with hot dishes or as a snack between meals; seasoning, fruit or jam can be added to enrich taste of the beverage and it can be used as a base for the traditional cold beetroot soup. Latvian food consumption data in the EFSA Comprehensive European Food Consumption Database was collected from 1080 adults and 300 elderly subjects. Food consumption data accessible in the Database show that the mean amount of kefir consumed by an adult in Latvia is 40 g/day, by elderly — 46 g/day. The mean intake of kefir is similar in Estonia — 32 g/day by adults and 50 g/day by elderly. Kefir consumption differs outside the Baltic region — 0.23 g/day by adults in Netherlands, 0.5 g/day in Belgium, 0.6 g/day in Austria, 1.4 g/day — in Germany, 2.8 g/day in Czech Republic, and 3.3 g/day — in Slovenia. In Latvia, kefir is consumed by 29.2% adult subjects and 34.3% elderly subjects, both consuming 135 g/day. Consumption of other fermented dairy products is significantly lower. The second most consumed fermented dairy product after kefir is yogurt, including both plain and flavoured yogurts, reaching mean consumption of 20 g/day on the population level.

KEFIR

The nutritional composition of kefir is variable due to differences in milk composition, microbiological composition of the kefir grains used, time and temperature of fermentation and conditions of storage (Rosa *et al.*, 2017). Kefir is considered nutritionally valuable because of its rich chemical content, which includes protein, fats, carbohydrates, sugars, minerals and vitamins. Based on the information available in food composition databases, 100 grams of plain, cow milk kefir contain approximately 50–70 kilocalories, 3.4–4.2 grams of protein, 1.5–4.2 grams of fats, and 4.1–4.6 grams of carbohydrates consisting of milk sugar — lactose (Anonymous, 2019a; 2019b; Finelli, 2020). Common minerals in kefir include calcium, magnesium, potassium, and sodium which contribute to utilisation of carbohydrates, fats and proteins for cell growth, maintenance, and energy. Kefir also contains small amounts of microelements — iron, zinc, and copper, which have a role in cellular metabolism and blood production (Bakircioglu *et al.*, 2018).

The nutritional value of kefir is further enhanced by the fermentation process, which results in secondary bioactive ingredients. The starter culture that is used in kefir production significantly affects its viscosity and chemical composition (de Oliveira Leite *et al.*, 2013). The microbial community of kefir includes a complex mixture of lactic acid bacteria (*Leuconostoc*, *Lactobacillus*, *Streptococcus*, *Lactococcus*, *Enterobacter*, *Acinetobacter*, *Enterococcus*, and *Pseudomonas* spp.), acetic acid bacteria and yeasts (*Kluyveromyces*, *Candida*, *Saccharomyces*, *Rhodotorula,* and *Zygosaccharomyces*) (de Oliveira Leite *et al.*, 2013; Cais-sokolin`ska *et al.*, 2016). Studies based on sequencing of 16S ribosomal RNA genes present in kefir grains and milk have established that kefir grains typically have one (*Lactobacillus*) or two (*Lactobacillus* and *Acetobacter*) dominant bacterial genera. The most common species of *Lactobacillus* are *L. kefiranofaciens*, *L. kefiri*, and *L. parakefiri* (Hamet *et al.*, 2013; Marsh *et al.*, 2013; Korsak *et al.*, 2015).

Yeasts play a vital role in establishing an environment that allows the growth of kefir bacteria and the yeasts also produce several metabolites such as peptides, amino acids, vitamins, ethanol and CO_2 that contribute to the flavour and aroma of kefir (Irigoyen *et al.*, 2005; Ozcan *et al.*, 2019).

Whole kefir, as well as specific fractions and individual organisms isolated from kefir, have been demonstrated to have multiple health benefits when consumed. These include antiobesity, anti-hepatic steatosis, antioxidative, antiallergenic, antitumour, anti-inflammatory, cholesterol-lowering, constipation-alleviating, and antimicrobial properties. Kefir has shown significant and modulatory effects on the host gut microbiome, as the microbial communities confer gastrointestinal resistance properties, the microbes can easily colonize the new environment and they participate in a wide range of microbial interactions (Bourrie *et al.*, 2016; Kim *et al.*, 2019).

IMPACT ON MICROBIOME IN HEALTHY INDIVIDUALS

One of the main ways how food products containing probiotics like kefir can promote beneficial health effects is altering the gut microbiome. This can be achieved through introduction of new species or strains into the gastrointestinal tract or by promoting the growth of beneficial microbes that are already present. In multiple studies, consumption of kefir in an animal model has been associated with an increase in the abundance of bacteria that are considered beneficial, such as *Lactobacillus* and *Bifidobacterium*, while decreasing abundance of harmful microbial species like *Clostridium perfringens* (Liu *et al.*, 2006; Hamet *et al.*, 2016). However, an important limitation of studies concerning kefir is that each batch of kefir may consist of different microorganisms. This may explain some of the heterogeneous findings.

Studies on mice whose diet was supplemented with *L. kefiranofaciens* isolated from kefir suggest that *L. kefiranofaciens* can successfully adhere to and colonise the mouse gut (Xing *et al*., 2018), alleviate constipation by the improvement and regulation of the gut microbiome (Jeong *et al*., 2017) and reduce symptoms of depression (Sun *et al*., 2019).

Little data exists about the ability of specific probiotics to modify the gut microbiome composition of healthy human subjects. A randomised trial in twenty subjects whose diets were supplemented with *L. kefiri* showed that *L. kefiri* was recovered in the feces of all volunteers after one month of probiotic administration. After one month of probiotic oral intake, reduced abundance of *Bilophila*, *Butyricimonas*, *Flavonifractor*, *Oscillibacter*, and *Prevotella* was observed. After the end of probiotic intake *Bacteroides*, *Barnesiella*, *Butyricimonas*, *Clostridium*, *Haemophilus*, *Oscillibacter*, *Salmonella*, *Streptococcus*, *Subdoligranulum*, and *Veillonella* were significantly less abundant compared to baseline samples. It was concluded that *L. kefiri* showed a strong ability to modulate the gut microbiome composition, leading to a significant reduction of several bacterial genera directly involved in the onset of pro-inflammatory response and gastrointestinal diseases (Toscano *et al*., 2017). In this case, probiotic consumption led to a significantly reduced abundance of Firmicutes and Bacteroidetes, which are the two major phyla characterising the gut microbiome, and Proteobacteria, which are involved in the maintenance of a balanced gut microbial community. However, increased prevalence of Proteobacteria is often associated to a high risk of developing intestinal dysbiosis and gastrointestinal diseases. Reduced presence of this bacterial phylum shows a potential protective role of *L. kefiri* in intestinal health. (Shin *et al*., 2015)

Evidence shows that potential health benefits of probiotic products are strain and host dependent, leading to the need for more studies focused on specific strains, health targets, and human populations. A randomised, single-blind, and placebo-controlled study was aimed to evaluate the potential benefits of several probiotic strains isolated from kefir on gastrointestinal parameters in fifty-six healthy adults. The subjects consumed AB-kefir (containing *Bifidobacterium longum*, *Lactobacillus acidophilus*, *L. fermentum*, *L. helveticus*, *L. paracasei*, *L. rhamnosus*, and *Streptococcus thermophiles*) daily for three weeks. Reduced symptoms of abdominal pain, bloating and appetite were observed in male subjects compared to the control group. The abundance of bifidobacteria was increased in male subjects and was maintained after stopping AB-kefir consumption. After three weeks, gastrointestinal abundance of total anaerobes and total bacteria increased in female subjects compared to the control group. The results indicated that AB-kefir could potentially improve gastrointestinal function in adults (Wang *et al*., 2019).

A non-randomised trial in 20 people with functional constipation showed that 500 ml of kefir a day for four weeks significantly increased stool frequency, improved bowel satisfaction score and reduced gut transit time compared to the baseline (Turan *et al*., 2014).

IMPACT ON THE MICROBIOME IN DISEASE

Microbiome dysbiosis is a state when the gut microbiome is composed of a disproportion of resident commensal community species relative to the community found in a healthy individuals' intestines. Dysbiosis includes loss of the beneficial microbiome, increased abundance of potentially harmful microorganisms and low microbial diversity (Petersen and Round, 2014). A major cause of changes in the gut microbiome is antibiotic use but these disruptions are also linked to underlying diseases such as asthma (Abrahamsson *et al*., 2013), inflammatory bowel disease (Noverr and Huffnagle, 2004; Frank *et al*., 2007), diabetes (Karlsson *et al*., 2013) and liver diseases (Poeta *et al*., 2017).

The microbiome plays an important role in the host's immune system. Inflammatory bowel disease (IBD) is characterised by an imbalanced microbiome and loss of homeostasis (Nishida *et al*., 2018). IBD patients tend to have decreased bacterial diversity and complexity of the gut microbial ecosystem, unusual gastrointestinal tract microbes and lower amounts of Bacteroides and Firmicutes in their microbiome compared to healthy individuals (Frank *et al*., 2007). In paediatric and adult populations, IBD patients showed increased abundance of *Enterococcus* and reduced proportions of *Bifidobacterium*, *Adlercreutzia*, Veillonellaceae, *Faecalibacterium*, *Coprococcus*, *Roseburia*, and *Ruminococcus* (Kowalksa-Duplaga *et al*., 2019) in their faecal samples.

Any changes in gut microbiome play a role in the hosts immune system, as microbes take part in regulatory functions of the immune system by providing balance between pro- and anti-inflammatory states in the host's body (Noverr and Huffnagle, 2004; Arpaia *et al*., 2013). Experiments with animal models showed that administration of human commensal microbes *Bacteroides fragilis* and strains of Clostridia in germ-free mice protects the animals from colitis by activating their regulatory T-lymphocytes (Atarashi *et al*., 2013). Gut commensal organisms have anti-inflammatory features. *Lactobacillus acidophilus* and strains of *Bifidobacterium* are linked to increased T-reg lymphocyte effects. *Lactobacillus paracasei* and *L. casei* can both target inflammatory cytokines by reducing their activity and reduce inflammation. Targeting the microbiome in inflammatory diseases may be beneficial and improve clinical outcomes (von Schillde *et al*., 2012; Petersen and Round, 2014). Studies showed that IBD patients have significantly decreased abundance of microbes that produce anti-inflammatory metabolites. These microbes include *Coprococcus*, *Faecalibacterium*, *Roseburia*, *Ruminococcus*, *Anaerostipes*, *Blautia*, *Lachnospira*, and *Sutterella* (Quévrain *et al*., 2016; Gevers *et al*., 2014; Maukonen *et al*., 2015; Kinga Kowalksa-Duplaga *et al*., 2019)

Administration of specific microbes during IBD flare-ups can have promising effects. *Faecalibacterium prausnitzii* markedly reduced inflammation in colon by downregulating inflammatory cytokine production (Sokol *et al*., 2008). Other studies showed that administration of *Lactobacillus kefiri* decreased inflammatory markers like C-reactive protein, erythrocyte sedimentation rate, increased hemoglobin and reduced bloating symptoms in patients with IBD (Yilmaz *et al*., 2019). Consumption of 800 ml of kefir a day for four weeks has been shown to significantly increase total abundance of *Lactobacillus* in stool compared to control (no kefir) in patients with Crohn's disease (Yilmaz *et al*., 2019). Isolated *L. kefiri* strains from kefir downregulate expression of proinflammatory mediators and induce production of anti-inflammatory molecules in the gut immune system. This finding shows the potential for use of *L. kefiri* maintaining remission in IBD cases (Carasi *et al*., 2015).

Non-alcoholic fatty liver disease (NAFLD), also called hepatic steatosis, is characterised by excessive accumulation of fat in liver tissue with absence of secondary causes of steatosis. The most commonly known causes of liver steatosis are significant alcohol consumption, medication and hereditary disorders. NAFLD is a progressive disease that may progress to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Major causes of NAFLD are obesity, dyslipidemia, insulin resistance and metabolic syndrome (Aguilera-Méndez, 2019). The main driver for disease progression is unknown. The gut-liver axis and multiple "hit" theory have been used to explain liver injury. The first "hit" of the theory is lipid accumulation in liver in obese individuals together with insulin resistance. The second "hit" consists of liver injury. The factor that induces liver injury is the gut microbiome, its metabolic activity, intestinal permeability and insulin resistance. Liver cell inflammation is altered by activating toll-like receptors in hepatocytes (Poeta *et al*., 2017). Activation of toll-like receptors 4 (Tlr4) on hepatocytes is associated with obesity, inflammation and insulin resistance (Jia *et al*., 2014). The Farnesoid X receptor and a nuclear transcriptional factor are co-existing important components of activating and maintaining inflammation in hepatocytes. All the receptors can be induced by diet, and bile acids that have been modified by gut microbiome. Further injury, Tlr4 inducement and low-grade inflammation accounts for the progress of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis (NASH) (Poeta *et al*., 2017; Jia *et al*., 2014; Moschen *et al*., 2013).

NAFLD is characterised by increased intercellular permeability in intestines that allows dislocation of endotoxins and metabolites via bloodstream to liver causing inflammation (Miele *et al*., 2009). In obese NAFLD patients enhanced permeability is correlated with more rapid progression of disease, which is related to microbial dysbiosis and dislocation of toxins from intestines to liver through the bloodstream, causing inflammation and liver cell injury that leads to fat deposition in liver tissue (Sharma and Tripathy, 2019; Miele *et al*., 2009). Obese patients have bacterial overgrowth in small intestines known as SIBO. Prevalence of bacterial overgrowth and dysbiosis in NAFLD patients is higher and associated with development of more severe hepatic steatosis (Sabaté *et al*., 2008). In comparison to healthy control groups, NAFLD patients have higher abundance of Bacteroides, Firmicutes, Fusobacteria, Prevotellaceae, *Megasphaera*, *Ruminococcus torques*, and *Eubacterium biforme*. However, when NAFLD progresses and fibrosis develops, even higher prevalence of *Acidaminococcus*, *Prevotella*, and Proteobacteria are detected while no changes in Bacteroides are observed. Fusobacterium is associated with activation of inflammatory signals and is a recognised pathogen for acute and chronic periodontitis. It is believed that Fusobacterium species in the gut microbiome may play a role in activating inflammation in liver cells (Rau *et al*., 2018). Bacteroides are associated with NASH development and abundance of *Ruminoccosus* is related to development of fibrosis (Boursier *et al*., 2016). Patients with NASH have faecal dysbiosis and interventions aimed at this are associated with improvement of hepatic steatosis (Wong *et al*., 2013). Analysis of the gut microbiome in suspected people may be useful to suggest disease severity and prognosis (Boursier *et al*., 2016).

Interactions within a NAFLD patient's microbiome with probiotic therapy can improve patient metrics for liver aminotransferases, total-cholesterol, improve insulin resistance and reduce inflammatory marker TNF-α (Ma *et al*., 2013; Poeta *et al*., 2017). In a double-blind randomised clinical trial, acute treatment for patients with NAFLD with a mixture of 500 million of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* per day improved levels of liver aminotransferases (Aller *et al*., 2011). Also, experimental evidence with animals showed that administration of *Lactobacillus rhamnosus* GG had protective effects mice in which a high-fructose diet induced NAFLD. Positive effects were observed by increase of protein concentration in the tight junction of intestines, which leads to reduced translocation of endotoxins via bloodstream to liver and improved concentration of alanine-aminotransferases (Ritze *et al*., 2014). The major part of NAFLD patients are obese and have a high risk of developing type 2 diabetes, cardiovascular diseases and kidney complications (Byrne *et al*., 2015). A study on the effects of *Lactobacillus kefiranofaciens* demonstrated significant blood pressure reduction and reduction of serum cholesterol and glucose levels in mice (Maeda *et al*., 2008), thus potentially reducing the risk of diabetes and cardiovascular disease for NAFLD patients.

CONCLUSIONS

In this review we have covered examples of the positive health effects of kefir and kefir-related bacteria in various settings. There are both potentially protective effects in healthy individuals as well as beneficial effects in some disease states. Some mechanisms of interaction of members of the kefir microbiota with the human body were also summarised. The wide range of potential health promoting effects of kefir could lead to a further expansion on the popularity of both traditional fermented kefir and products that are manufactured with fractions of kefir or kefir-related microorganisms. In order to fully exploit the beneficial characteristics of kefir, a more in-depth understanding of the function of kefir-derived microbiota is critical. Especially, understanding the interactions of such microorganisms with human physiology and constituents of both normal and disbyotic gut microbiome could result in development of more efficient therapeutic and preventive tools for various health issues. Thus, even though considerable research has already been done in these fields, there is still more to learn if we are to fully exploit and understand the benefits of this fermented traditional product.

ACKNOWLEDGMENTS

This paper has been developed within the research project which is funded by the Latvian Council of Science, "Gut microbiome composition and diversity among health and lifestyle induced dietary regimen", project No. lzp-2018/ 2-0266.

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Received 24 February 2020
Accepted in the final form 29 February 2020

KEFĪRA MIKROBIOLOĢISKAIS SASTĀVS UN TĀ IETEKME UZ ZARNU TRAKTA MIKROBIOMU VESELĪBAS UN SASLIMŠANU GADĪJUMĀ

Kefīrs ir raudzēts piena produkts, kas tiek iegūts, baktērijām un raugiem fermentējot pienu. Kefīrs ir visvairāk patērētais tradicionālais, nesaldinātais, raudzētais piena produkts Baltijas valstīs. Kefīrs un atsevišķi no tā izdalīti mikroorganismi labvēlīgi ietekmē cilvēka veselību, tostarp regulējot zarnu mikrobioma sastāvu. Šī literatūras pārskata mērķis ir apkopot pieejamos datus par kefīra lietošanas ietekmi uz veselu indivīdu zarnu mikrobiomu un izcelt kefīra un tā frakciju lietošanas labvēlīgo ietekmi dažādu saslimšanu gadījumos, mainot saimniekorganisma zarnu mikrobiomu.