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Review

Mechanisms of Action of Kefir in Chronic Cardiovascular and Metabolic Diseases

Fabio S Pimenta[a] Maria Luaces-Regueira[b] Alyne MM Ton[a]
Bianca P Campagnaro[a] Manuel Campos-Toimil[b] Thiago MC Pereira[a,c]
Elisardo C Vasquez[a]

[a]Laboratory of Translational Physiology and Pharmacology, Pharmaceutical Sciences Graduate Program, Vila Velha University (UVV), Vila Velha, Brazil, [b]Pharmacology of Chronic Diseases (CDPHARMA), Molecular Medicine and Chronic Diseases Research Centre (CIMUS), University of Santiago de Compostela, Santiago de Compostela, Spain, [c]Federal Institute of Education, Science and Technology (IFES), Vila Velha, Brazil

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Microbiota • Endothelial dysfunction • Baroreflex • Insulin resistance • Hypertension • Dyslipidemia • Atherosclerosis

Abstract
The gut microbiota maintains a complex mutual interaction with different organs of the host. Whereas in normal conditions this natural community of trillions of microorganisms greatly contributes to the human health, gut dysbiosis is related with onset or worsening of diverse chronic systemic diseases. Thus, the reestablishment of gut microbiota homeostasis with consumption of prebiotics and probiotics may be a relevant strategy to prevent or attenuate several cardiovascular and metabolic complications. Among these functional foods, the synbiotic kefir, which is a fermented milk composed of a mixture of bacteria and yeasts, is currently the most used and has attracted the attention of health care professionals. The present review is focused on reports describing the feasibility of kefir consumption to provide benefits in cardiometabolic diseases, including hypertension, vascular endothelial dysfunction, dyslipidemia and insulin resistance. Interestingly, recent studies show that mechanisms of actions of kefir in cardiometabolic diseases include recruitment of endothelial progenitor cells, improvement of the balance vagal/sympathetic nervous system, diminution of excessive generation of reactive oxygen species, angiotensin converting enzyme inhibition, anti-inflammatory cytokines profile and alteration of the intestinal microbiota. These findings provide a better understanding about the mechanisms of the beneficial actions of kefir and motivate further investigations to determine whether the use of this synbiotic could also be translated into clinical improvements in cardiometabolic diseases.

Elisardo C Vasquez, PhD

Laboratory of Translational Physiology and Pharmacology, PPGCF, Vila Velha University
Espírito Santo (Brazil)
E-Mail evasquez@terra.com.br

Introduction

While infectious diseases were the most important health issue in the world until the beginning of the 20th century [1, 2], cardiovascular and metabolic diseases gradually became the largest contributors to global morbidity and mortality, and these problems are expected to continue for at least several more decades [3]. Recent research has indicated that there is a reciprocal interaction between gut microbiota and the function of different organs of the host. The occurrence of gut dysbiosis contributes to the onset or worsening of systemic abnormalities, including cardiovascular and metabolic diseases [4, 5]. This current scenario has resulted in growing interest in the use of probiotic nutraceuticals, which are known to maintain gut homeostasis and to prevent or reverse gut dysbiosis [6-8].

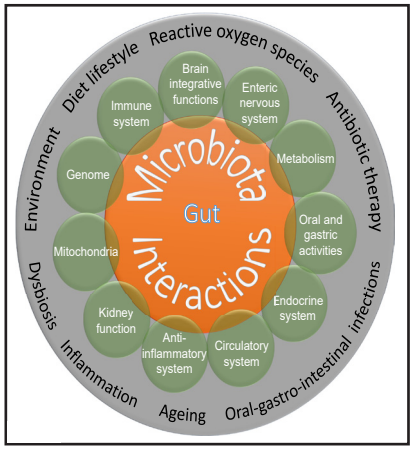

Fig. 1. Functional gut microbiota interactions and examples of disturbances leading to dysbiosis.

Gut microbiota refers to a wide community of non-pathogenic microorganisms, which co-habit with enterocytes symbiotically [4-6], providing a variety of effects on benefits to the host by creating barriers against pathogenic microorganisms by killing them, colonizing available niches, and consuming and producing nutrients besides protecting the intestinal mucosa through cellular and/or humoral mechanisms [5-7]. Evaluation of host-microbiota dynamics also suggests that the normal gut microbiota interacts with integrative brain areas of the host via components of the autonomic nervous system (enteric, afferent and efferent pathways) and with target systemic organs via circulatory and endocrine systems [8-13].

As illustrated in Fig. 1, several factors can lead to disturbance of gut microbiota (dysbiosis), including acute and chronic infections of the gastrointestinal tract, antibiotic therapy, systemic diseases, aging, diet, and lifestyle [14-17]. Here, we briefly review experimental and clinical data regarding the beneficial effects of a dairy functional food on cardiac dysautonomia, endothelial dysfunction, arterial hypertension dyslipidemia and insulin resistance, which are characteristics of cardiometabolic diseases.

Functional Foods and Kefir

Functional foods are those that provide benefits beyond basic nutrition when consumed along with the regular diet and nutraceuticals are extracts containing biologically active food components supplied in forms other than foods [17, 18]. As a consequence of the cumulative knowledge on benefits of functional food, a growing number of investigations have been conducted to attempt to understand the mechanisms of the beneficial actions of different food components [19-22]. Therefore, we are facing a fascinating moment of significant discoveries related to the reciprocal interactions between functional foods (and nutraceuticals) and the gut microbiota [17, 18].

Although people commonly still consider bacteria to be disease-causing, the Nobel Laureate Elie Metchnikoff theorized the benefits of lactic acid bacteria in as early as 1910. Currently, it is well-known that a healthy diet supplemented with functional food has health-promoting effects on gut dysbiosis, improving the immune system and function of the body organs [4, 23].

Probiotics and synbiotics are already being consumed as food supplements, which are known to improve gut homeostasis [24], are safe to use and produced at low costs [8, 25]. Probiotics are biomodulators composed of live bacteria and other microorganisms that when administered in adequate amounts, are important tools expected to prevent or alleviate gut

microbiota disturbances and confer a health benefit to the host [24-28]. Commonly used live microorganisms in probiotic products are mostly *Lactobacillus, Lactococus*, *Streptococcus*, *Enterococcus*, strains of gram-positive bacteria and certain yeast strains (*Saccharomyces*) [6, 25, 28].

There is a growing body of evidence [28-30] that the mechanisms underlying the effects of probiotics on the host gut include (a) production of antimicrobial substances (e.g., bacteriocins, microcins, defensins, free fatty acids and hydrogen peroxide), (b) competition for adhesion to the epithelium and for nutrients, (c) immunomodulatory actions and (d) inhibition of bacterial toxin production. All of these mechanisms are currently characterized and explored as important tools to alleviate the progression of gut microbiota disturbances and dysfunction of organs in the body. In parallel, it is known that the beneficial effects of probiotics can be augmented by adding non-digestible food components, such as certain oligosaccharides (e.g., inulin, oligofructose, lactulose), which are prebiotics with enormous potential for modifying gut microbiota [8, 31, 32]. Interesting, prebiotics improve the survival of probiotic microorganisms in the gastrointestinal tract with limited effect on other microorganisms [33]. Although both "synbiotic' and "symbiotic" terms have been used to describe this combination, we call "synbiotic" the synergistic blends of both prebiotics and probiotics, which are used or administered with the purpose of benefiting the health on the host. Conversely, we use the term "symbiotic" to describe different living microorganisms that live together, each obteining specific benefits from the other (symbiosis) in the gut microbiota.

The discovery that fermented milk products have positive health effects occurred several centuries ago. Kefir originated from the Northern area of the Caucasus Mountains [9, 34], and its use has spread worldwide because it is passed hand-to-hand [33, 34]. Kefir grains are constituted by a complex microbial community containing species of lactic and acetic acid bacteria and yeasts, and they are used to obtain a fermented milk named kefir [9, 34, 35]. Recent microbiological analysis of kefir grains being consumed in our region (Grand Vitoria, Brazil) [36, 37] showed a microflora formed by beneficial bacteria (e.g., *Lactobacillus kefiranofaciens, Bifidobacterium*) and yeasts (e.g., *Candida kefir*) which have been shown to preserve gut eubiosis and correct dysbiosis by adhering to gastrointestinal mucus [31, 38]. These beneficial microbes then protect against the invasion of pathogenic microbes [7, 39, 40] and against the cytotoxic effects of pathogenic microbial toxins [41].

Insights from Kefir Effects in Cardiovascular Diseases

Although kefir has long been consumed worldwide based on the belief that it has beneficial effects, studies have only recently evaluated the magnitude of its protective effects in cardiovascular diseases. The first goal of our group was to determine the time course and concentration of kefir to reach a significant valuable benefit on high blood pressure (BP). Those studies were performed in spontaneously hypertensive rat (SHR) [36].

Antihypertensive effects of kefir

Different researchers have shown hypotensive effects of milk fermented with kefir grains and its derivate microorganism or biogenic compounds in experimental models of arterial hypertension [42-44]. In agreement, our laboratory reported that the probiotic kefir must be administered for at least 30 days to achieve a significant reduction of hypertensive levels [36, 45, 46]. Interestingly, this hypotensive effect of kefir was accompanied by a significant reduction in tachycardia and left ventricular hypertrophy, which are characteristics of the SHR model [36, 45, 46]. Hypotensive effects have also been observed when the milk administered was fermented by *Lactobacillus fermentum* [47], *Lactobacillus coryniformis* plus *Lactobacillus gasseri* [47], *Lactobacillus helveticus* [48], *Lactobacillus paracasei* [49] and *Lactococcus lactis* [50].

It is becoming clear that an important mechanism by which kefir causes a reduction of BP is through the inhibition of the excessive generation of reactive oxygen species (ROS) (e.g., O_2^-, $ONOO^-$ and H_2O_2) [36]. Elevated oxidative stress also contributes to the appearance and maintenance of other cardiovascular abnormalities, such as vascular inflammation, disturbed blood flow or abnormal shear stress, endothelial dysfunction, and arterial wall remodeling [51-54]. Kefir and kefir-derived bioactive products lower BP by acting as an enhancer of baroreflex sensitivity and an inhibitor of angiotensin-converting enzyme (ACE) [43, 54, 55]. Thus, kefir leads to neural and biochemical changes that contribute to decreases in BP by preventing or reversing gut dysbiosis and/or by other systemic mechanisms, as described in more detailed below.

Kefir and autonomic neural control of cardiovascular function

Our group has evaluated the effects of kefir on the abnormal autonomic control of BP and cardiac function in the SHR model. First, we investigated the basal cardiac parasympathetic (vagal) and sympathetic tone related with the control of chronotropism [56, 57]. Those data showed a decreased vagal tone and an increased sympathetic tone in the SHR, which were partially restored after the treatment with kefir for 60 days [46]. The magnitude of the kefir effect on the autonomic control of the heart was similar to that obtained by other interventions [54, 58-60]. The challenge is now to design new studies aiming to determine if the origin of the abnormality is located at central areas or peripheral nerves/receptors.

It is well-established that the baroreflex is impaired in cardiovascular and metabolic diseases, as demonstrated in the SHR model of hypertension [36, 45, 46]. Those authors, using a traditional method (see detailed description in reference [59]), evaluated the baroreflex control of arterial pressure in conscious SHR animals treated for 60 days with kefir, and the results demonstrated that kefir improved the baroreflex function [46]. Based on the pharmacological approaches used, the authors concluded that the kefir improved the baroreflex by restoring the balance between parasympathetic and sympathetic activity to the heart [46], which is in agreement with the results observed through spectral analysis of the arterial BP and heart rate (HR) [61]. However, an open question derived from the above studies is the following: by which mechanisms can probiotics and synbiotics affect brain areas? Although additional studies are required to answer this question, relevant studies suggest interactions between gut endocrine cells and vagal afferents through gut chemosensing mechanisms [5, 10]. Interestingly, in 2011, Bravo et al. demonstrated that vagotomy in mice mitigated this bidirectional communication between the central and the enteric nervous system [62]. In parallel, many researchers have demonstrated that bacteria from gut microbiota can synthesize and respond to hormones and neurotransmitters, such as acetylcholine, gamma-amino butyrate acid (GABA), serotonin and catecholamines [63]. Therefore, we speculate that the improvement in the baroreflex function and the arterial BP and HR variability in hypertensive animals could occur because kefir restores the normal gut microbiota [38] and consequently restores the production of neuroactive compounds in the intestinal lumen and subsequent effects on the bidirectional interaction gut-brain [5, 63].

Effects of kefir on endothelial dysfunction

In normal conditions, the endothelium maintains a balance between relaxation and contraction, but this equilibrium can be disrupted in chronic cardiovascular diseases (e.g., oxidative stress, arterial hypertension and atherosclerosis) and metabolic diseases (e.g., diabetes mellitus) [36, 64]. Physiologically, endothelial dysfunction can be easily identified via nitric oxide (NO)-dependent mechanisms when the vessel exhibits an impaired response to the gold-standard vasodilator acetylcholine and/or an exacerbated response to α1-vasoconstrictor agonists. Oxidative stress is a common cause of endothelial dysfunction because it can compromise NO availability and, consequently, its functionality. Hence, pharmacological and non-pharmacological (e.g., functional food therapy) therapies are relevant strategies to reduce oxidative stress.

After the findings from Rashid et al. (2014) that probiotics prevented endothelial dysfunction of mesenteric artery rings in rats with common bile duct ligation [65], our group evaluated the effects of the probiotc kefir on the endothelial dysfunction in SHR [36]. The time-course of the treatment showed that at least eight weeks of treatment with kefir were required to observe a markedly beneficial effect on the endothelial dysfunction in this model of arterial hypertension [36]. The authors have demonstrated that the impaired vasodilation of aortic rings in response to acetylcholine was significantly improved by chronic treatment with kefir [36]. Additionally, kefir was able to relax the remaining contraction, which is observed when the test of vascular responsiveness to acetylcholine is repeated under conditions of pre-incubation with the NO synthase blocker L-NAME [36]. Other authors have shown that the treatment of SHR or obese animals with isolated *Lactobacillus fermentum* or *Lactobacillus coryniformis* was able to reverse the impaired aortic relaxations [66, 67], probably by the same mechanism of the synbiotic kefir (improving the balance $\cdot O_2^-$/NO).

The same group of investigators has shown that kefir was also able to attenuate endothelial dysfunction in large vessels from SHR by decreasing intravascular production of $\cdot O_2^-$, $ONOO^-$ H_2O_2 and restoring intravascular NO bioavailability [36, 45]. In agreement, the pre-incubation of aortic rings with the inhibitor of NADPH oxidase apocynin improved the vasodilation in the SHR but not in the control group and/or in SHR kefir-treated animals [36, 67], which is clear evidence that kefir treatment could be a useful nutraceutical adjuvant for increasing NO bioavailability and decreasing ROS production. Moreover, probiotics can decrease the levels of toll-like receptor-4 (TLR4)-induced ROS and NADPH oxidase activity in that animal model of hypertension [66]. Thus, cumulative data show that kefir treatment is an effective approach for treating impaired endothelial vasodilation observed in cardiovascular diseases and involving different pathway mechanisms. Increase in contractile force to α1-adrenoceptor agonists is also a hallmark of chronic cardiovascular and metabolic diseases [67, 68]. However, the effectiveness of kefir to prevent or reverse exacerbated vasoconstrictions observed in cardiovascular diseases is still an open issue.

Our research group has focused on the hypothesis that endothelial dysfunction is also linked with physical damage of the vessel layer. This possibility is corroborated by findings showing repair of the disorganization of the media layer of aorta vessels from SHR administered with milk fermented by *Lactobacillus paracasei* and *Lactobacillus plantarum* [11, 12]. Recently, our research group demonstrated through scanning microscopy analysis that kefir was able to attenuate the injury observed on the vascular endothelial surface in SHR rats [36]. These observations suggest that although the main mechanism by which kefir improves endothelial dysfunction that accompanies the arterial hypertension is through its antioxidant effect, it also may include the recruitment of endothelial progenitor cells, as discussed below.

Although most publications have reported antioxidative properties of kefir [11, 17, 36, 43, 45], the molecular pathways that contribute to this process remain open to further investigation. One reason this is a continuous challenge is because kefir grains contain several single chemical substances, making it difficult to magnify the relative contribution of each single molecule or micoorganism. Recently, some authors revealed that some probiotic strains present in kefir synthesize antioxidant enzymes (peroxidase, superoxide dismutase, glutathione reductase, feruloyl esterase and pseudo-catalase enzymes) and non-enzymatic substances with radical-scavenging capacities to counteract ROS [69-71]. In parallel, our group showed that the soluble non-bacterial fraction diminishes the production of pro-oxidant angiotensin II through the inhibition of ACE activity [54].

Anti-atherosclerotic and Anti-inflammatory Effects

Complications of atherosclerosis constitute a major cause of morbidity and mortality worldwide; therefore, it is important to explore multiple options, including probiotics, for the prevention and treatment of this complex disease. The advantage for the use of probiotics is that they contain live bacteria that normally do not reside in the human gastrointestinal tract and are quickly eliminated in the feces [72, 73]. There are studies showing that the daily consumption of kefir and kefir-derived products can result in significant hypocholesterolemic [74-76] and immunomodulatory [77-79] effects, as discussed below.

The hypocholesterolemic effect exhibited by kefir could be attributed to the microorganisms and derived biogenic compounds of this symbiotic living in the gut microbiota [72, 73 ,79-81]. One of the effects of the synbiotic kefir on the gastrointestinal tract seems to involve the endogenous cholesterol metabolism pathway, ensuring its assimilation and metabolization by microorganisms, inhibiting cholesterol absorption in the small intestine [82-88]. Moreover, there are data suggesting that kefir may oppose hypercholesterolemia by 1) inhibition of the enzyme HMG-CoA reductase, which is a key enzyme of cholesterol synthesis [11, 86] and 2) the deconjugation of bile salts, increasing the demand for cholesterol for "de novo" synthesis [80, 86, 88]. In fact, a specific yeast strain into the kefir presents high levels of bile salt hydrolase activity [89], which deconjugates bile acids and increases its excretion in the feces [78, 79, 90], helping to lower cholesterol. Formulation of kefir, or biogenic compounds, plus digestive enzymes administered in hypercholesterolemic mice augments HDL and decreases LDL [76], and exhibit anti-inflammatory and immunomodulatory activities [84, 85, 91, 92], corroborating the concept that probiotics and synbiotics, including kefir, are promising for treatment of dyslipidemias.

Kefir consumption results in transient changes in the levels of cytokines [92-94], TNFα and INFγ, in both *in vivo* [83, 84] and in *in vitro* experiments [93]. Several studies with whole kefir, kefir fractions, or organisms isolated from kefir demonstrated that anti-inflammatory cytokines promote a Th2 response while simultaneously inhibiting the pro-inflammatory Th1 response [39, 78, 92-95]. Interestingly, it was recently found that a protein derived from *Lactobacillus plantarum*, has a significant anti-inflammatory effect through regulating the gut barrier, microbiota and inflammatory cytokines [96].Therefore, kefir and derived isolated microorganisms can increase anti-inflammatory cytokines and decrease pro-inflammatory responses, justifying its anti-atherosclerotic potential.

The first demonstration of the anti-atherogenic properties of kefir was recently published by our research group, showing that chronic administration of the soluble non-bacterial fraction of kefir was also able to attenuate the lipid deposition in atherosclerotic mice (~100%) independently of hypercholesterolemia, which was justified by the alteration of cytokines profile [97]. These data corroborate previous findings of Uchida et al. [98], who reported a reduction of atherosclerosis in hypercholesterolemic rabbits using *Lactobacillus kefiranofaciens*. Thus, while treatment against atherosclerosis has been conventionally focused on hypercholesterolemia, kefir represents a valuable alternative to delay the progression of the disease by immunomodulatory effects, opening new perspectives of treatment.

Benefits of Kefir on Metabolic Syndrome: Focusing on Insulin Resistance

It is well-known that the urbanization and modern sedentary lifestyle are closely related to the increase of metabolic syndrome (MS) [99-101]. MS is characterized by a series of interlinked physiological and biochemical factors (insulin resistance, hyperglycemia, visceral adiposity, dyslipidemia, hepatic steatosis, hypertension, endothelial dysfunction, and chronic inflammation) that contribute to the increase of cardiovascular risk (2-fold), type 2 diabetes mellitus (5-fold) and all-cause mortality (1.5-fold) [99-102]. The worldwide prevalence of MS ranges from 10% to 84%, depending on the region, population and other associated

factors [103-105]. Obesity and insulin resistance seem to be the major predisposing factors to comorbidities, such as type 2 diabetes, cardiovascular and neurodegenerative diseases.

Although conventionally lifestyle changes and pharmacotherapy are the main strategies to control MS progression, these actions result only in partial success [33, 34]. In the last decade, it has been shown that a healthy gut microbiome helps to control obesity and insulin resistance [106-110]. The intestinal microbiome differs in lean and obese subjects and insulin-resistant patients developed an improvement in the metabolic profile after transplantation with 'healthy gut microbiota' from lean donors [108, 111]. Liou et al. [112] demonstrated that the transference of the gut microbiota from gastric bypass-treated mice to non-operated germ-free mice led to a decrease in weight and fat mass, in agreement with the suggestion that an alteration in the gut microbiota contributes to reduce MS after bariatric surgery [109]. Physiologically, it is known that the intestinal microbiome can modulate carbohydrate and lipid metabolism, hepatic glycogen and fatty storage, gut motility and appetite [109, 111], suggesting that the microbiota is an important adjuvant for MS treatment. These observations were confirmed in experimental fatty liver models. Kefir was capable of reducing activity of the lipogenesis pathway (fatty acid synthase and acetyl-CoA carboxylase) and increasing fatty acid oxidation by protein overexpression of phosphorylated AMP-activated protein kinase, hepatic carnitine palmitoyltransferase-1 and peroxisome proliferator-activated receptor-α in the liver, extending its applicability to hepatic steatosis, which is strongly associated with MS [113, 114]. Thus, the use of probiotics and synbiotics, mainly kefir, is a promising alternative for the prevention and treatment of MS and related disorders [89, 113, 114].

In 2002, Teruya et al. [115] reported that kefir could activate the insulin signaling pathway (possibly by activation of PI 3-kinase or other upstream molecules), culminating in the enhancement of glucose influx in skeletal muscle cells. Ten years later, an *in vivo* study performed by Hadisaputro et al [94]. revealed that kefir supplementation reduces glycemia and improves the balance between pro- and anti-inflammatory cytokines (IL1, IL6, TNF/IL-10 ratio) in an experimental model of type 1 diabetes [94]. These results were recently confirmed in an experimental model of MS [116]. In agreement with this study's results, Punaro et al. [117] also demonstrated antioxidative and renoprotective effects after kefir supplementation using STZ-diabetic rats. Ostadrahimi et al. [118] showed that kefir reduces glycemia and HbA1c in type 2 diabetes patients, suggesting that this symbiotic therapy may be an interesting adjuvant in the treatment of diabetes. Other authors have shown that kefir was able to reduce ROS intracellular levels in insulin-responsive muscle cells [117] and in STZ-induced diabetes mellitus in rats [118]. In addition, proteinuria and azotemia observed in rats with type I diabetes mellitus were reduced by treatment with kefir, an effect apparently related to its antioxidant capacity [115]. Despite the above reports, there is a need for additional

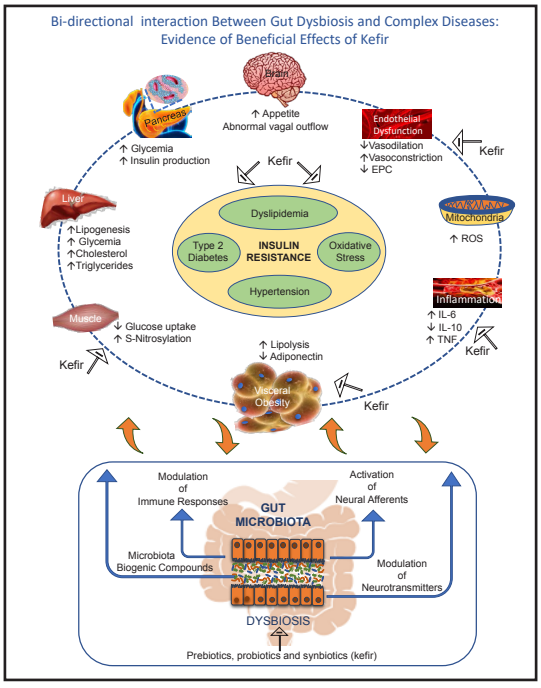

Fig. 2. Schematic illustration of the bidirectional interaction of the gut microbiota and several organs and showing beneficial effects of kefir treatment in some chronic metabolic diseases related with insulin resistance. Minus signal arrow head indicates evidence of protective effect of kefir. Abbreviations: EPC: endothelial progenitor cell, IL: interleukin, ROS: reactive oxygen species, TNF: tumor necrosis factor.

clinical and experimental studies, including other models of arterial hypertension related with the enzymatic conversion of angiotensin I to II [119], a mechanism by which kefir may reduce high BP [54]. Fig. 2 summarizes the potential beneficial effects of kefir on different targets, highlighting the bidirectional interaction between gut microbiota and complex diseases, such as dyslipidemia, type 2 diabetes and arterial hypertension.

Finally, all of these beneficial effects of kefir on the glycemic profile deserve another point of view. It is known that gut microbiota can modulate the microbial composition of the gastrointestinal tract and the state of hunger or satiety. Interestingly, this hypothesis was recently confirmed in zebrafish, one of the most widely used animal models for developmental research [120]. After eight days of consuming probiotic *Lactobacillus rhamnosus* (widely present in kefir), these animals showed up-regulation and down-regulation of anorexigenic and orexigenic genes, respectively, suggesting that probiotics may regulate genes involved in glucose metabolism and appetite control [120]. Therefore, the beneficial effects of kefir in MS may be related not only to the bioavailability of its active components but also to an alteration of the intestinal microbiota.

Conclusions and Perspectives

There are several lines of evidence suggesting a bidirectional interaction between gut microbiota and the cardiovascular and metabolic diseases, influencing each other through microbiome-derived biogenic compounds, the central nervous system, the immune system, metabolic pathways, and the circulatory system. In this review, we have discussed the mechanisms of interactions between gut microbiota and cardiovascular and metabolic diseases, which include the autonomic control or the cardiac and vascular function, dyslipidemias and insulin resistance, and we suggested some mechanisms by which the synbiotic kefir appears to ameliorate those abnormalities. However, additional studies are required to verify if milk fermented by kefir grains from different origins and production processes could have similar beneficial effects. It is also expected that in the near future, analysis of the gut microbiome could be used routinely to determine the adequate prescription of synbiotic agents to patients suffering from cardiovascular and metabolic diseases.

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Disclosure Statement

The authors declare that they have no competing interests.

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