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# Kefir as a therapeutic agent in clinical research: a scoping review

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## Abstract

Increasing research has been conducted on the role of probiotics in disease treatment. Kefir, a safe, low-cost probiotic fermented milk drink, has been investigated in many *in vitro* and animal studies, although parameters for human therapeutic dose or treatment time have not yet been determined. Here we perform a scoping review of clinical studies that have used kefir as a therapeutic agent, compiling the results for perspectives to support and direct further research. This review was based on Joanna Briggs Institute guidelines, including studies on the effects of kefir-fermented milk in humans. Using the term KEFIR, the main international databases were searched for studies published in English, Spanish or Portuguese until 9 March 2022. A total of 5835 articles were identified in the four databases, with forty-four eligible for analysis. The research areas were classified as metabolic syndrome and type 2 diabetes, gastrointestinal health/disorders, maternal/child health and paediatrics, dentistry, oncology, women's and geriatric health, and dermatology. The many study limitations hampered generalisation of the results. The small sample sizes, methodological variation and differences in kefir types, dosage and treatment duration prevented clear conclusions about its benefits for specific diseases. We suggest using a standard therapeutic dose of traditionally prepared kefir in millilitres according to body weight, making routine consumption more feasible. The studies showed that kefir is safe for people without serious illnesses.

**Key words:** **Kefir: Probiotics: Gut microbiota: Therapeutic uses**

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## Introduction

The idea that gut health and microbiota balance directly affect the homeostasis of human organ systems is gaining increasing acceptance. Accordingly, foods are being researched as therapeutic agents in search of benefits that help maintain the body in a healthy state. The human gut is home to trillions of microbes, and their impact on human health has been extensively studied[1]. In addition to being an important digestive organ, the intestine is the largest immune organ in the human body[2]. Numerous studies on the influence of intestinal microbiota have shown the importance of diet for wellbeing. Interactions between intestinal microorganisms and a series of health problems have been described[3–6].

Gut microbiota refers to the microbes that reside in the human gastrointestinal tract[7]. It contributes to the integrity of the intestinal epithelial barrier by maintaining cell junctions and promoting damage repair, as well as by helping protect the host against pathogenic microorganisms, neutralising the effects of toxins and/or drugs and providing essential metabolites/vitamins[8,9]. It also improves nutrient bioavailability and modulates the intestinal epithelium's absorption capacity[10]. Research on gut microbiota is ongoing in a number of fields, including dermatology[11], endocrinology[12,13], dentistry[14,15] and oncology[16,17].

While the inherited genome is essentially stable over the host's lifetime, the microbiome is immensely diverse[18,19], dynamic[20], and responsive to external stimuli, which increases its potential as a target for therapeutic intervention. The composition of the microbiota is influenced by host genotype, environment and diet[10].

Intestinal dysbiosis refers to changes in the quantitative and qualitative composition of our commensal microbes, which can alter host microbial interaction and contribute to an inflammatory disease state, which is associated with the development of many non-communicable diseases[21]. One current strategy for treating dysbiosis is the use of probiotics in an effort to recover microbial diversity and disturbed gut microbiota.

Probiotics refers to microorganisms that, when administered in adequate amounts, confer health benefits to the host[22–25]. A probiotic must be able to survive under gastrointestinal conditions (acidic pH, enzymes, bile salts, etc.), have the ability to adhere to the intestinal mucosa, antagonise pathogens and stimulate the immune system[22,25]. Among their different mechanisms of action, the following stand out: colonisation and normalisation of disturbed intestinal microbial communities in children and adults, competitive exclusion of pathogens and production of bacteriocins, modulation of faecal enzyme activities associated with bile salt metabolism, inactivation of

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carcinogens and other xenobiotics, production of short-chain and branched-chain fatty acids (which have broad effects in the gut and peripheral tissue by interacting with short-chain fatty acid receptors, which modulate tissue sensitivity to insulin), cell adhesion and mucin production, immune system modulation and interaction with the brain–gut axis by regulating endocrine and neurological function[22,26]. Prebiotics, foods that contain non-digestible fibre, stimulate the growth and activity of beneficial microorganisms[27], and include human milk oligosaccharides, inulin, fructooligosaccharides and galactooligosaccharides[28].

Kefir is fermented milk produced by the action of bacteria and yeast that symbiotically associate in kefir grains[29]. This slightly effervescent and foamy beverage originates from the action of the natural microbiota present in these grains[30], which consists of an inert matrix of polysaccharides and proteins[31]. This matrix is densely populated by species of lactic acid bacteria, acetic acid bacteria and yeast[32].

The large number of microorganisms in kefir and their microbial interactions as well as the bioactive compounds that result from microbial metabolism and the benefits associated with this beverage make kefir a natural probiotic. The microbial composition of kefir can vary, being influenced by region of origin, duration of use, substrate and management techniques[33]. However, kefir grains generally contain relatively stable and specific microbiota, always including a predominance of certain *Lactobacillus* species.[29,34].

Numerous *in vitro* and animal studies have demonstrated the beneficial action of milk fermented by kefir grains and its nutraceutical potential, which includes anti-inflammatory[35–37], antioxidant[38,39], anticancer[39,40], antimicrobial[41–43], antidiabetic[44], antihypertensive[45–48] and anti-hypercholesterolaemic properties[49,50]. These effects can be attributed to probiotic microorganisms and the wide diversity of bioactive compounds produced during the fermentation process[39,51]. However, clinical research on these benefits is still in its infancy, complicated by the heterogeneity of dosages and forms of administration, making it difficult, for example, to compile results through meta-analysis. Thus, the present scoping review aimed to assess clinical studies that have tested kefir as a therapeutic agent for diseases or health conditions, identifying therapeutic patterns and adverse effects. From this analysis, the data were organised to point out strategies and present perspectives for future research.

## Methodology

This is a scoping review of human studies on the effects of milk fermented by kefir grains as a therapeutic agent for diseases of organic systems or to improve patient health conditions. This review was structured according to Joanna Briggs Institute guidelines[52]. Scoping reviews are useful when studies in a topic are heterogeneous, as they map and summarise existing evidence and identify possible knowledge gaps to direct future research[52]. A search was performed in the main international databases: PubMed, Web of Science, Embase and Scopus, using the term KEFIR. The inclusion criteria were prospective clinical studies, with kefir as the object of the study, published in English, Spanish or Portuguese until 9 March 2022. Duplicated studies and those using water kefir were excluded, since it was not the focus of this review. The inclusion and exclusion criteria were identified by reading the abstracts and, occasionally, if there were any doubts, by reading the full article. Study eligibility was determined by two independent researchers, and a third arbitrated in cases of disagreement. The search results were managed using EndNote.

The titles and abstracts of all articles were evaluated for potential relevance according to the inclusion and exclusion criteria. Data from the selected clinical studies were extracted and summarised regarding the objective, materials and methods (design, dose and intervention time), sample/population, comparison parameters between groups, adverse effects and clinical outcome. The selection process for relevant studies is shown in Fig. 1.

## Results

The term kefir resulted in a wide range of studies in the selected databases. The vast majority, however, concerned laboratory research on strains of microorganisms in kefir or were *in vitro* or animal studies testing its disease-fighting properties or its ability to maintain a healthy state. A total of 5835 articles were identified in the four databases, and forty-four were eligible for analysis after applying the inclusion and exclusion criteria and removing duplicates. The selection process for relevant studies is shown in Fig. 1.

Clinical studies published in English (but not Portuguese or Spanish) on kefir as a therapeutic agent can be found beginning in 2002, and this number has shown a growing trend, reaching eight in 2021, as shown in Fig. 2. Turkey, Iran, and the United States have produced the most clinical studies, followed by Brazil and Taiwan, as illustrated in Fig. 3. Most studies are single-centre clinical trials, with some crossover trials, one case series and one case report, all prospective studies. The mean sample size was 45·9 (standard deviation 28·7) participants.

The mean intervention time could not be calculated, since it was presented in days, weeks, months, medication cycles, continuous use or single dose, or was not daily, as in O'Brien *et al.*[53], in which it was administered twice a week for 15 weeks. The study population also varied, although none of the subjects had serious diseases or severe comorbidities, which we considered exclusion criteria.

Table 1[54–96] presents the population, sample size, therapeutic dosage, kefir preparation type, intervention time and main findings of each study. Two pairs of publications (Ostadrahimi *et al.*[68] and Alihosseini *et al.*[72]; Fathi *et al.*[70] and Fathi *et al.*[71]) used the same population to investigate different outcomes.

The largest number of clinical studies with kefir was for the prevention or treatment of metabolic and gastrointestinal diseases, and their results were usually positive. Other fields of knowledge in which kefir was tested included maternal/child health and paediatrics, dentistry, oncology, women's and geriatric health, and dermatology (Table 2).

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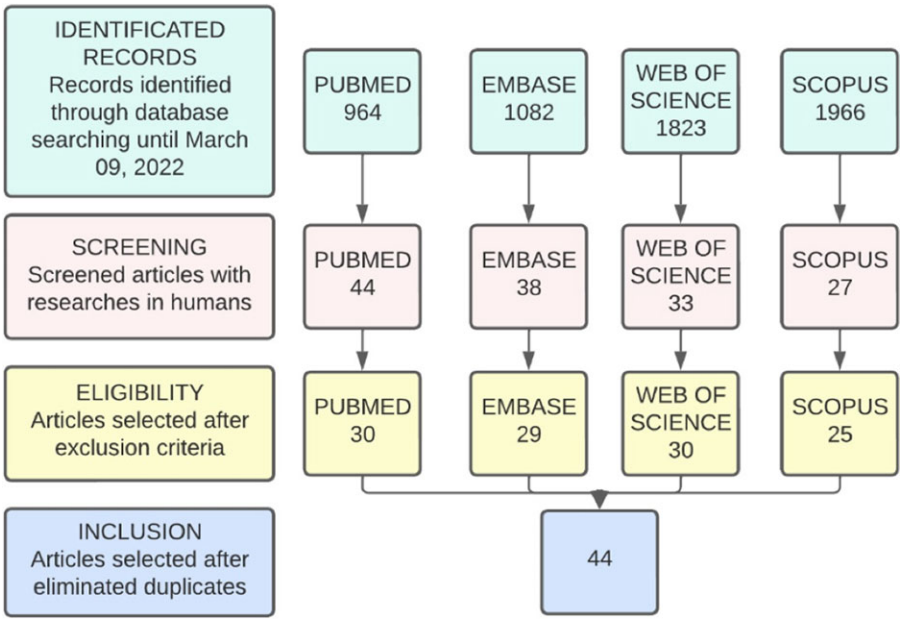


**Fig. 1.** Flowchart of article inclusion.

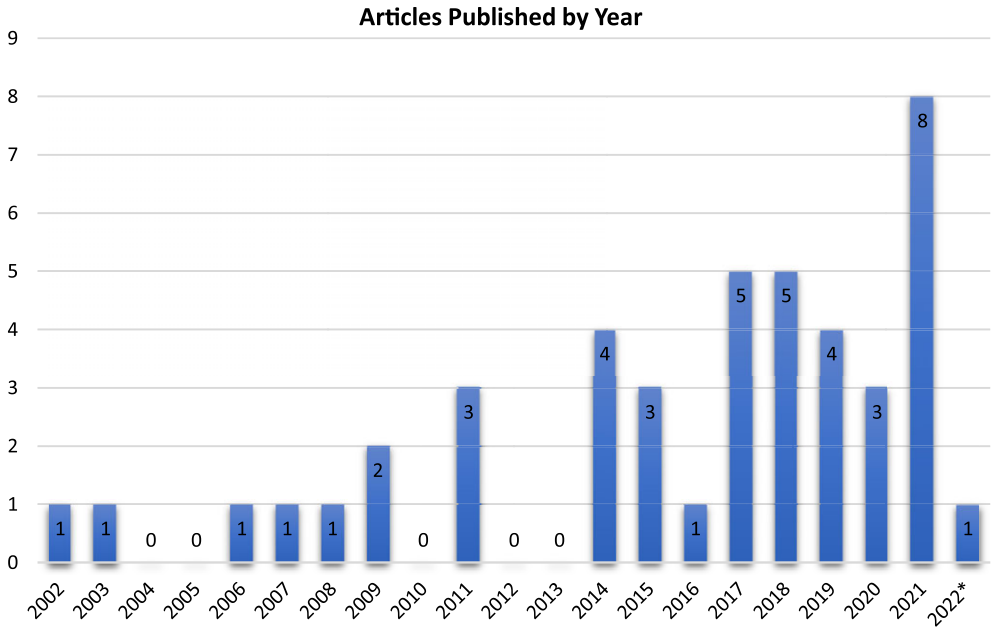


**Fig. 2.** Year of publication of English-language studies on kefir as a therapeutic agent. *Until 9 March 2022.

## Discussion

The discussion of the results will be presented according to the field in which kefir was studied in humans as a therapeutic agent.

### *Metabolic syndrome and type 2 diabetes*

Metabolic syndrome is considered a pro-thrombotic and pro-inflammatory state characterised by a set of clinical findings that include central and abdominal obesity, systemic hypertension, insulin resistance and atherogenic dyslipidaemia, including elevated inflammatory cytokine activity[97,98]. Therapeutic options involve dietary control, regular exercise and pharmacological treatment for dyslipidaemia, hypertension and hyperglycaemia[98].

Gut microbes influence host metabolic balance by modulating energy absorption, intestinal motility, appetite, glucose and lipid metabolism, and hepatic fat storage[99]. Dysbiosis favours the translocation of bacterial fragments and can lead to systemic inflammation and insulin resistance[99,100]. Administration of pre- and probiotics can reduce low-grade inflammation and improve intestinal barrier integrity, aiding metabolic balance. Zonulin, a family of proteins associated with the permeability of the

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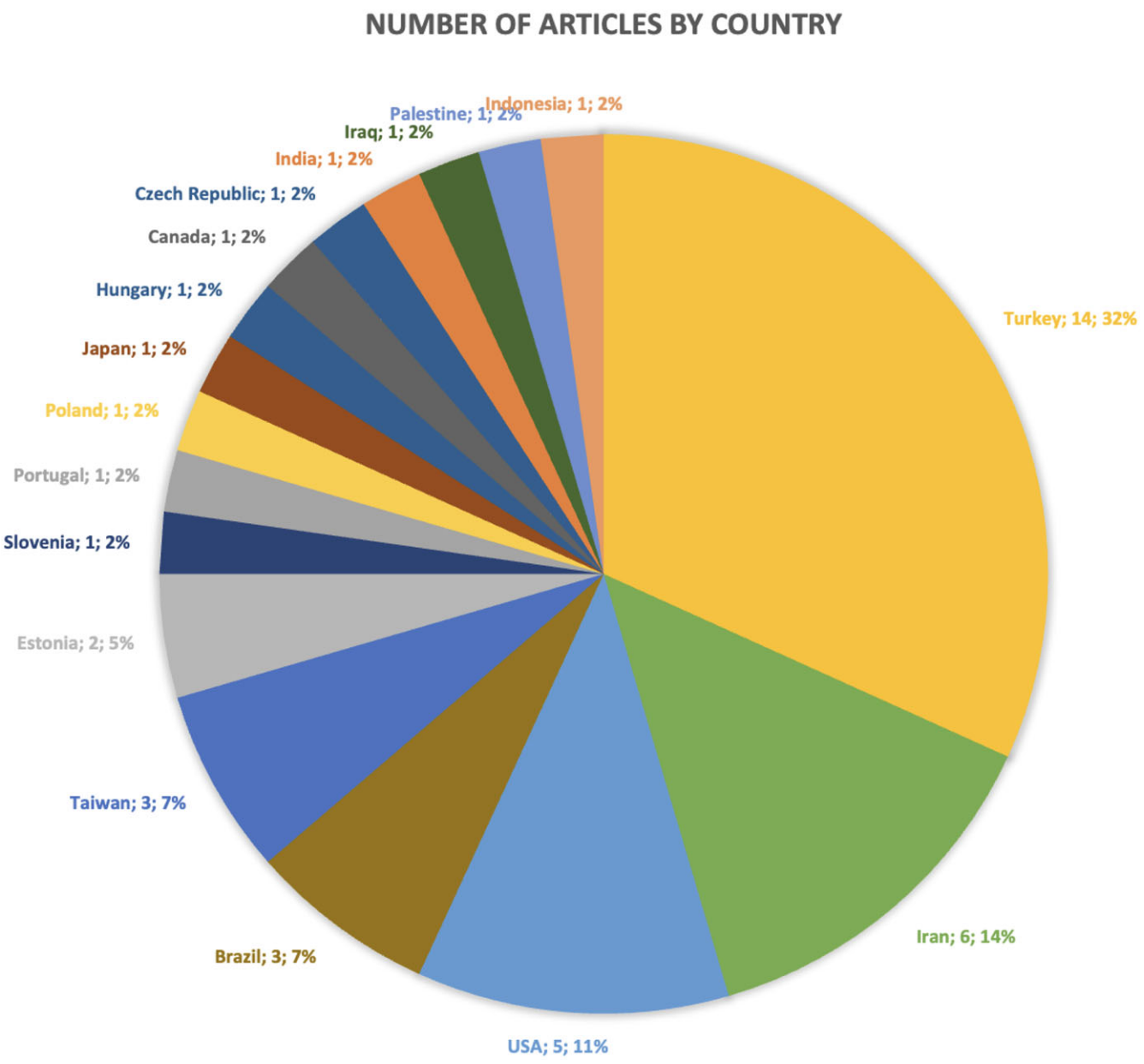


**Fig. 3.** Number of articles according to country of origin (absolute number, percentage).

intestinal barrier[101], is a physiological modulator of the tight intercellular junctions of the intestinal epithelium, and the loss of barrier function secondary to its up-regulation can lead to an uncontrolled influx of food and microbial antigens. Pražnikar *et al.*[85] studied the effects of supplementing asymptomatic overweight adults with milk or kefir for 3 weeks, finding that kefir supplementation led to lower serum zonulin levels than milk.

Bellikci-Koyu *et al.*[82] and Da Silva Ghizi *et al.*[95] tested the effects of regular kefir consumption in people with metabolic syndrome. The intervention period in both studies was 12 weeks and they used similar dosages, although the kefir preparation methods differed. The bioactive peptide profile of milk kefir is completely different from that of raw milk, including 236 unique peptides produced during the fermentation process, many with antihypertensive (angiotensin-converting enzyme inhibitors), antimicrobial, immunomodulatory, antioxidant and antithrombotic properties[46]. Bellikci-Koyu *et al.*[82] found no significant differences between milk and kefir groups, while Da Silva Ghizi *et al.*[95] considered the origin of their fermented beverage key to their more expressive findings than Bellikci-Koyu *et al.*[82]. Da Silva Ghizi *et al.* used milk inoculated with kefir grains, which contains more than thirty live bacteria species and twelve yeast and fungi species in a complex symbiotic system, a culture that synthesises several bioactive compounds during the fermentation process, such as organic acids, bioactive peptides, bacteriocins and exopolysaccharides[39,46,51]. Industrial kefir production, which usually involves commercial starter

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**Table 1.** Overview of included studies

| Reference | Population | n | Kefir type and dosage in intervention group | Intervention time | Outcome observed (Yes/No) | Main findings |
|---|---|---|---|---|---|---|
| St-Onge *et al.*[54] | Healthy mildly hypercholesterolemic men aged 27–61 years whose body mass index ranged from 26 to 38 kg/m$^2$. | 13 | Kefir (i.p.) 500 ml/d | 28 d | No | Neither kefir nor milk supplementation decreased total cholesterol, HDL-cholesterol, LDL-cholesterol or triacylglycerol concentrations. |
| Hertzler and Clancy[55] | Healthy adults with lactose maldigestion. | 15 | Flavoured kefir (i.p.) 519 g and plain kefir (i.p.) 508 g | Single dose | Yes | Plain kefir improved lactose digestion just as well as plain yogurt. |
| Figler *et al.* [56] | Healthy adults aged 18–59 years | 120 | Biofir® kefir (i.p.) 500 ml | 28 d | Yes | All microbes increased 4·3-fold in the traditional Russian kefir group (controls) and 6·8-fold in the probiotic Biofir® group. |
| Forejt *et al.*[57] | Women aged 18–55 with miscellaneous digestive problems (constipation, flatulence, heaviness) | 50 | Kefir (i.p.) 200 ml 1×/d after evening meal | 14 d | Yes | 93·5 % of the participants reported improved alimentary function after 14 d of kefir consumption |
| Topuz *et al.*[58] | Patients newly diagnosed with stage II, III or IV colorectal cancer with a baseline ECOG of 0, 1 or 2 | 37 | Oral lavage with kefir (i.p.), swallowing 250 ml 2×/d after meals on the first 5 d of each chemotherapy cycle | 6 cycles of chemotherapy | No | Kefir had no effect on serum pro-inflammatory cytokines levels or a protective effect on mucositis due to 5-FU-based chemotherapy compared with controls. |
| Can *et al.*[59] | Patients aged >18 years with stage II, III or IV colorectal cancer, a baseline ECOG of 0, 1 or 2, and standard treatment with 5-FU or oral fluoropyrimidine | 37 | Kefir (i.p.) 250 ml 2×/d for 1 week during chemotherapy treatment. | 6 cycles of chemotherapy | No | No QOL difference between the experimental and control groups. Experimental group had increased complaints but decreased sleep disturbances. |
| Merenstein *et al.*[60] | Healthy children aged 1–5 years enrolled from primary care offices after being prescribed antibiotics for upper respiratory infections. | 125 | Kefir (i.p.) 150 ml 1×/d during antibiotic use for upper respiratory infections | 10 d | No | No differences in diarrhoea rates between groups (active 18%, placebo 21·9%). No differences in secondary outcomes. |
| Bekar *et al.*[61] | Patients with dyspepsia and *H. pylori* infection | 82 | Kefir (i.p.) 250 ml 2×/d + triple therapy* | 14 d | Yes | Adding kefir to triple therapy* increased *H. pylori* eradication rates and decreased triple therapy-related adverse effects. |
| Kullisaar *et al.*[62] | Healthy adults aged 40–65 years with mean a BMI of 30 ± 5 kg/m$^2$ | 73 | Kefir (i.p.) 200 ml 1×/d | 14 d | Yes/No | Three different OxS-related parameters of LDL (BDC-LDL, oxLDL and Beta 2-GPI-oxLDL) decreased significantly in the group with probiotic *L. fermentum* ME-3). The concentrations of oxLDL and BDC-LDL did not change in the group without probiotic additive. |
| Mądry *et al.*[63] | Clinically symptomatic, healthy young adults aged 20–25 years with LI | 15 | Kefir (u.t.) 400 ml (lactose content 18·4 g) | Single dose | Yes | Kefir and yogurt tolerance was significantly better than milk in young adults with LI. |
| Bakken [64] | Adults with *Clostridium difficile* infection and risk factors for recurrence who chose not to undergo FMT | 25 | Kefir (i.p.) 5 oz (~150 ml) with each meal (at least 3×/d) + medical treatment for diarrhoea | Continuous | Yes | STAW and kefir can be as effective as FMT at resolving recurrent *C. difficile* infection. |
| Ghasempour *et al.*[65] | Healthy volunteers aged 22–32 years with good oral hygiene | 22 | Kefir (h.p.) 100 ml gargled and swallowed 1×/d, with no brushing, eating or drinking for 1 h | 14 d | Yes | Kefir and sodium fluoride mouth rinse were equally effective in reducing the count of salivary mutans streptococci. |
| Turan *et al.*[66] | Adults aged 27–78 years who met the diagnostic criteria for functional constipation according to Rome II criteria. | 20 | Kefir (i.p.) 250 ml 2×/d | 28 d | Yes | Kefir increased defecation frequency and led to significant improvement in stool consistency, as well as a significant decrease in laxative use, improved bowel satisfaction scores and shortened colonic transit times. |
| Judiono *et al.*[67] | Patients with T2DM whose last blood glucose level was <200 mg/dL, HbA1c equivalent 6–8 with no complications or illnesses | 108 | Kefir (h.p.) 200 ml/d | 30 d | Yes | Clear kefir reduced blood glucose (HbA1c, FBG, PBG) and increased C-peptide levels. |

**Table 1.** (*Continued*)

| Reference | Population | n | Kefir type and dosage in intervention group | Intervention time | Outcome observed (Yes/No) | Main findings |
|---|---|---|---|---|---|---|
| O'Brien *et al.*[53] | Healthy adults aged 18–35 years | 67 | Kefir (h.p.) and a fruit base, 16 ounces (454 g) ≤30 min after each training session 2×/week | 105 d | Yes | No significant increase in CRP level in the exercise + kefir group compared with the exercise + control group, indicating attenuated exercise- induced inflammation after training. |
| Ostadrahimi *et al.*[68] | Diabetic patients with fasting blood glucose ≥125 mg/dl, aged 35–65 years, no insulin therapy and illness duration <20 years | 60 | Kefir (i.p.) 600 ml 2×/d (at lunch and supper) | 56 d | Yes | FBG and HbA1C decreased more with kefir than conventional fermented milk. |
| Tu *et al.*[69] | Patients with osteoporosis (screened for inclusion and exclusion criteria) | 40 | 1600 mg freeze-dried kefir-fermented milk (h.p.) per day + 1500 mg $CaCO_3$ supplement | 6 months | Yes | Kefir was associated with short-term changes in bone turnover markers and greater 6-month increases in hip BMD among osteoporotic patients. Kefir therapy increases BMD whether or not bone turnover is suppressed. |
| Fathi *et al.*[70] | Healthy overweight or obese pre-menopausal women aged 25–45 years with BMI 25·0–34·9 kg/m$^2$ and regular menstruation cycles | 58 | Kefir (ip) 250 ml 4×/d + weight maintenance diet | 56 d | Yes | The kefir and milk groups had significantly greater reductions in weight, BMI and WC compared with controls after 8 weeks. |
| Fathi *et al.*[71] | Same as Fathi (70) | 58 | Same as Fathi (70) | Same as Fathi (70) | Yes | Over 8 weeks, kefir caused a significant yet similar improvement in serum lipid profile to low-fat milk in a dairy-rich diet in otherwise healthy overweight or obese premenopausal women. |
| Alihosseini *et al.*[72] | Same as Ostadrahimi (68) | 60 | Same as Ostadrahimi (68) | Same as Ostadrahimi (68) | Yes | HOMA- IR significantly decreased in the probiotic fermented milk group after the intervention. Mean serum insulin did not reduce significantly, the mean homocysteine level decreased significantly in the probiotic fermented milk and conventional fermented milk groups. |
| Gölünük *et al.*[73] | Sedentary men aged 18–25 years with no chronic diseases. | 36 | Kefir (i.p.) 300 ml 1×/d 30 min before exercise (1 h aerobic session) | 15 d | Yes | Significant change in ALT and TOS values in the kefir group, but not in other blood parameters ($p > 0{\cdot}05$) |
| Diken *et al.*[74] | Healthy men aged 25–55 years, smokers (30 cigarettes/d for ≥5 years) and non-smokers | 30 | Kefir (u.t.) 200 ml at lunch | 42 d | Yes/No | Kefir did not affect most parameters, including FBG, but significantly increased lymphocytes, and decreased neutrophils and eosinophiles in non-smokers. |
| De Araujo *et al.*[75] | Infants aged 6–24 months with recurrent wheezing and who had not yet begun maintenance treatment with a steroid inhaler | 58 | 1 g sachet lyophilised probiotic mixture (kefir i.p.) dissolved in a spoonful of juice or milk, preferably consumed during the first meal of the day | 56 d | Yes/No | No significant reduction in clinical parameters of wheezing but a significant increase in regulatory T-cell-mediated IL-10 and Th 1-mediated standard IL-12 in cell cultures. |
| Alp and Baka[76] | Healthy adolescents aged 12–17 years who applied for orthodontic treatment | 45 | Kefir (i.p.) 100 ml 2×/d | 42 d | Yes | Daily kefir consumption and probiotic toothpaste decreased salivary microbial colonization in orthodontic patients. |
| Maki *et al.*[77] | Hospitalised patients with physical or mental disabilities | 42 | Powdered milk and lyophilised kefir- fermented milk (i.p.) 2 g 3×/d | 84 d | Yes | Kefir significantly reduced constipation compared to baseline. Including kefir in the diet can greatly enhance the QoL and health of disabled individuals with constipation. |
| Abd-Alwahab and Al-Dulaimi[78] | Adults aged 40–50 years (no other characteristics described) | 75 | Kefir (h.p.) 200 ml/d prepared in two concentrations (5% and 7·5%). | 21 d | Yes | Kefir caused a significant decrease in serum cholesterol, triacylglycerol, LDL-C and VLDL-C and a significant increase in HDL-C compared with controls. |

**Table 1.** (*Continued*)

| Reference | Population | n | Kefir type and dosage in intervention group | Intervention time | Outcome observed (Yes/No) | Main findings |
|---|---|---|---|---|---|---|
| Gezginc and Maranci[79] | Healthy adults aged 19–25 years who did not consume drugs, alcohol or tobacco | 23 | 200 ml kefir (u.t.) 3×/week + 200 ml yogurt/d | 90 d | Yes | No significant difference in total cholesterol levels but a significant decrease in LDL-cholesterol and MDA values, and a significant increase in apelin-13 and leptin levels. |
| Sepp *et al.*[80] | Healthy adults aged 35–65 years | 71 | Kefir (i.p.) 200 ml/d | 56 d | Yes/No | The antioxidative probiotic *L. fermentum* ME-3 can lower the risk of diseases linked to low richness and diversity of gut microbiota and high polyamine level. |
| Özcan *et al.*[81] | Menopausal women aged 45–65 years with sleep disorder complaints for ≥1 year | 68 | Kefir (i.p.) 250 ml 2×/d (morning and evening) | 30 d | Yes | Kefir had positive effects on sleep disturbances, depression and QoL in menopausal women. |
| Bellikci-Koyu *et al.*[82] | MetS patients without severe comorbidities aged 18–65 years | 22 | Kefir (i.p.) 180 ml/d | 84 d | Yes | Kefir led to improvements in glycaemic status, inflammation-related indicators, and blood pressure, but none stayed significant compared with unfermented milk. |
| Yılmaz *et al.*[83] | Patients with IBD | 45 | Kefir (u.t.) 400 ml/d (2× 200 ml) | 28 d | Yes | Regular kefir usage improved symptoms and QoL in the short term in patients with Crohn's disease and had a positive effect on the biochemical parameters, such as Hgb, ESR and CRP. |
| Bashiti and Zabut[84] | Men recently diagnosed with diabetes aged 3–65 years | 42 | Kefir (h.p.) 250 ml 1×/d + metformin | 70 d | Yes | Kefir can reduce fasting blood sugar, HbA1c and phosphorous, while increasing calcium in adult males with diabetes. |
| Pražnikar *et al.*[85] | Healthy white overweight adults aged 30–60 years | 28 | Kefir (i.p.) 300 ml/d | 21 d | Yes | Kefir improved serum zonulin levels and had positive effects compared with milk. Similar improvement in lipid profiles and serum glucose levels as milk in asymptomatic overweight adults. |
| Ton *et al.*[86] | Patients with Alzheimer's disease without clinical comorbidities who took the maximum dose of acetylcholinesterase inhibitor (donepezil, 10 mg/d) | 13 | Kefir (h.p.) 2 ml/kg/d blended with organic strawberries | 90 d | Yes | Symbiotic supplementation for 90 d in older patients with Alzheimer's disease had favourable effects on cognitive dysfunction, systemic inflammation, systemic oxidative stress and blood cell damage. |
| Wang *et al.*[87] | Healthy adults aged 20–40 years | 54 | Lyophilised kefir (i.p.) 1 sachet (2 g)/d | 21 d | Yes | AB-kefir had beneficial effects against abdominal symptoms such as pain, bloating and appetite and positive modulatory effects on gut microbiota profiles. |
| Lee *et al.*[88] | Healthy men aged 20–30 years | 16 | SYNKEFIR™ lyophilised kefir (i.p.), 20 g/d | 28 d | Yes | Supplementation with SYNKEFIR™ significantly improved exercise performance, reduced lactic acid production after exercise, accelerated recovery and caused no adverse reactions. |
| Reddy *et al.*[89] | Healthy children aged 8–12 years | 80 | Kefir (h.p.) 100 ml/d | 30 d | Yes | Probiotic products efficiently reduce mean colony-forming units of *S. mutans* compared with controls. |
| Alves *et al.*[90] | Healthy and atopic volunteers aged 18–64 years | 19 | Kefir (h.p.) 100 ml/1×/d | 56 d | Yes | Significant improvement in all skin outcomes suggests that atopic individuals may benefit from kefir, especially for skin hydration. |
| Kurt *et al.*[91] | Mothers who had just given birth | 11 | Kefir (h.p.) 500 ml/d | 30 d | Yes | Mothers who regularly consumed kefir tended to have more carbohydrates in their milk than controls. Kefir may affect the carbohydrate profile in mother's milk, including galactooligosaccharides. These structures with prebiotic properties may support infant intestinal microbiota. |

**Table 1.** (*Continued*)

| Reference | Population | n | Kefir type and dosage in intervention group | Intervention time | Outcome observed (Yes/No) | Main findings |
|---|---|---|---|---|---|---|
| Hosainzadegn and Hosainzadegan[92] | Woman (aged 58 years) with uncontrolled diabetes mellitus for 15 years | 1 | Kefir (h.p.) 500 ml/d | 3 months | Yes | Patient weight decreased from 88 to 84 kg, and HbA1c decreased from 7·9 to 7·1. |
| Smoak *et al.*[93] | Adults aged ≥40 years who had undergone chemotherapy and/or radiation therapy in the past 2 years and were currently enrolled in an exercise programme | 24 | Kefir (i.p.) 8 oz (~240 ml) 3×/week (after each exercise session) | 84 d | Yes | Kefir appears to be a well-tolerated post-exercise supplement that can improve lean body mass, depression, fatigue, gastric distress and a biomarker of gut dysbiosis in cancer survivors engaged in regular exercise. |
| Caferoglu and Aytekin Sahin[94] | Healthy women aged 21–24 years | 22 | Kefir (u.t.) 200 ml 1× | Single dose | Yes | Adding kefir to a high-GI meal may prevent increased appetite and food intake, resulting in postprandial response similarly to a low-GI meal. |
| Da Silva Ghizi[95] | Sedentary adults aged >18 years with MetS | 48 | Kefir (h.p.) 1·6 ml/kg for men or 1·9 ml/kg for women 1×/d, 5 d/week | 84 d | Yes | Kefir reduced cardiovascular risk (Framingham scores) and oxidised LDL (a marker of atherosclerosis) in people with metabolic syndrome, as well as blood pressure, triacylglycerol levels and FBG. Higher HDL-c levels were also detected in women after treatment. |
| Tunay and Taş[96] | Healthy mothers aged 27–38 years who had just given birth | 30 | Kefir (i.p.) 250 ml 2×/d (morning and evening) | 30 d | Yes | When added to the maternal diet, the bacteria in kefir are transmitted to the infant. |

*n*, sample number; i.p., industrial preparation; h.p., home preparation; u.t., unspecified type; AD, Alzheimer's disease; ALT, alanine aminotransferase; BDC-LDL, baseline diene conjugates of low-density lipoprotein; Beta2-GPI-oxLDL, oxLDL-β2 glycoprotein I; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; FMT, faecal microbiota transplantation; GI, glycaemic index; HbA1c, glycated haemoglobin; Hgb, haemoglobin; HOMA-IR, insulin resistance Homeostasis Model Assessment; IBD, inflammatory bowel disease; LI, lactose intolerance; MDA, malondialdehyde; MetS, metabolic syndrome; oxLDL, oxidised low-density lipoprotein; OxS, oxidative stress; PBG, postprandial blood glucose levels; QoL, quality of life; STAW, staggered and tapered antibiotic withdrawal; T2DM, type 2 diabetes mellitus; TOS, total oxidant status; WC, waist circumference. Triple therapy* consists of lansoprazole (30 mg), amoxicillin (1000 mg) and clarithromycin (500 mg).

**Table 2.** Areas of clinical research on kefir

| Area of research | Conditions | n | Reference |
|---|---|---|---|
| MetS and T2DM | Insulin resistance/T2DM | 15 | St-Onge *et al.*[54], Kullisaar *et al.*[62], Judiono *et al.*[67], Ostradahimi *et al.*[68], Fathi *et al.*[70], Fathi *et al.*[71], Alihosseini *et al.*[72], Diken *et al.*[74], Abd-Alwahab and Al-Dulaimi[78], Gezginc and Maranci[79], Bellikci-Koyu *et al.*[82], Bashiti and Zabut[84], Pražnikar *et al.*[85], Hosainzadegn and Hosainzadegan[92], Da Silva Ghizi *et al.*[95] |
| | Dyslipidaemia | | |
| | Systemic hypertension | | |
| | Obesity | | |
| MetS prevention | Nutrition and exercise | 4 | O'Brien *et al.*[53], Caferoglu and Aytekin Sahin[94], Gölünük *et al.*[73], Lee *et al.*[88] |
| Gastroenterology | Lactose intolerance | 2 | Hertzler and Clancy[55], Madry *et al.*[63] |
| | Microbiota profile and gastrointestinal symptoms | 4 | Figler *et al.*[56], Sepp *et al.*[80], Forejt *et al.*[57], Wang *et al.*[87] |
| | *Clostridium difficile* | 1 | Bakken[64] |
| | Constipation | 2 | Maki *et al.*[77], Turan *et al.*[66] |
| | *H. pylori* | 1 | Bekar *et al.*[61] |
| | IBD | 1 | Yilmaz *et al.*[83] |
| Maternal/child health and paediatrics | Breastfeeding | 2 | Kurt *et al.*[91], Tunay and Taş[96] |
| | ATB-associated diarrhoea | 1 | Merenstein *et al.*[60] |
| | Recurrent wheezing | 1 | De Araujo *et al.*[75] |
| Odontology | Salivary count of *S. mutans* | 3 | Reddy *et al.*[89], Alp and Baka[76], Ghasempour *et al.*[65] |
| Oncology | Adverse effects of QT | 2 | Topuz *et al.*[58], Can *et al.*[59] |
| | Cancer rehabilitation | 1 | Smoak *et al.*[93] |
| Women's and elderly health | Menopause symptoms | 1 | Özcan *et al.*[81] |
| | Osteoporosis | 1 | Tu *et al.*[69] |
| | Alzheimer's disease | 1 | Ton *et al.*[86] |
| Dermatology | Atopic dermatitis | 1 | Alves *et al.*[90] |

ATB, antibiotic; IBD, inflammatory bowel disease; MetS, metabolic syndrome; QT, chemotherapy; T2DM, type 2 diabetes mellitus.

cultures, allows standardisation of this process, although it results in loss of cell viability. Commercial kefir contains a smaller number and variety of microorganisms, especially yeasts[46,102]. Moreover, in fermented food production (including kefir), the backslopping technique is used to increase production by up to fifty times, maintaining the physico-chemical characteristics and nutritional values, but decreasing the microbiological diversity and producing some consistency deficiencies[31]. In a randomised, double-blind, placebo-controlled clinical study, Da Silva Ghizi *et al.*[95] found significant improvement in several clinical parameters in the kefir group compared with controls (who received homemade curd prepared with the same type of milk as the kefir group), including blood pressure, lipid profile blood, fasting glucose and oxidised LDL, which led to lower cardiovascular risk according to Framingham scores. Abd-Alwahab and Al-Dulaimi[78] administered grain-fermented kefir drink to volunteers, finding significant improvement in the lipid profile, although their control group received water instead of milk, which prevents direct comparison of the results.

One hypothesis about kefir's mechanism of action on serum cholesterol levels is the deconjugation of bile acids by *Lactobacillus* spp., while yeasts increase bile acid discharge, which in turn increases cholesterol expenditure during production[78,103]. In addition, colonic microbiota can metabolise dietary and endogenous cholesterol, reducing it mainly to coprostanol (5β-colestan-3β-ol) and coprostanone, both through low intestinal absorption and elimination through faeces[104,105]. Higher intake of calcium, which is abundant (about 0·12/100 g) in kefir, can also positively affect the serum lipid profile[106–108]. St-Onge *et al.*[54], Fathi *et al.*[71], Pražnikar *et al.*[85], Ostadrahimi *et al.*[68], Gezginc and Maranci[79] and Bashiti and Zabut[84] investigated kefir's effects on the lipid profile, but found different results, probably a consequence of the studies' different methodologies.

The conflicting outcomes of these studies can be explained, at least in part, by the heterogeneity of their populations, especially the floor (baseline) effect (i.e. the lower the baseline level of an outcome, the less likely a treatment will result in a reduction in that outcome level), which was evident in studies such as that by Gezginc and Maranci[79], who tested the influence of kefir on the lipid profile of healthy young people.

Hosainzadegn and Hosainzadegan[92] reported a case of marked improvement in glycated hemoglobin (HbA1c) levels (from 7·9 to 7·1) and a 4 kg weight loss in a woman with type 2 diabetes after 3 months of using kefir prepared at home. Clinical studies by Judiono *et al.*[67], Ostradahimi *et al.*[68], Alihosseini *et al.*[72], Bellikci-Koyu *et al.*[82], Bashiti and Zabut[84] and Praznikar *et al.*[85] were included in a systematic review with meta-analysis[109] of randomised clinical trials that assessed the effects of kefir drink on glycaemic control. The authors found significant improvement in fasting glucose and insulin levels in participants who consumed kefir, but no significant difference in HbA1c levels. The results of this meta-analysis, however, can be questioned due to the heterogeneity of study populations, dosages, and intervention times.

Weight control and exercise are also involved in the prevention and treatment of metabolic syndrome. Studies by O'Brien *et al.*[53], Gölünük *et al.*[73] and Lee *et al.*[88] investigated the effects of kefir on post-exercise oxidative stress parameters. The samples of these studies were healthy young people, although the intervention time, kefir type, quantity and tested parameters differed greatly. Kefir improved total oxidant status

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levels (an indicator of oxidative stress)[73], did not change C-reactive protein levels (which increased in the control group)[53], improved exercise endurance, reduced lactic acid production after exercise, accelerated recovery[88] and did not significantly affect the other parameters.

Regarding weight loss, Fathi *et al.*[70] and Hosainzadegn and Hosainzadegan[92] found positive results with kefir, unlike other studies that measured anthropometric parameters such as weight, body mass index and waist circumference[53,88,95]. Caferoglu and Aytekin Sahin[94] investigated whether adding kefir to a low or high glycaemic index meal would affect participant appetite and food intake, finding that kefir can help limit appetite and energy intake for high glycaemic index meals but not low glycaemic index meals[94].

## Gastrointestinal health/disorders

The gastrointestinal tract and its microbiome provide unique metabolic functions to the host and are critical to maintaining health. The abundance of different species of microorganisms, their function and their interaction with organic systems have been the focus of numerous medical studies[110]. Metagenomics and analysis of twin data have shown that environmental factors, such as diet and domestic cohabitation, far outweigh heritable genetic contributions to gut microbiota composition and function[111].

Inflammatory bowel disease is characterised by chronic and relapsing inflammation of the gastrointestinal tract and includes 2 chronic idiopathic inflammatory diseases: Crohn's disease and ulcerative colitis[83,112,113]. These heterogeneous and complex immune disorders of the gastrointestinal tract share many common clinical features but differ in inflamed areas and are treated differently[110,113,114]. Considered a serious and debilitating condition that affects general health and quality of life, inflammatory bowel disease has been associated with intestinal dysbiosis, which decreases microbial biodiversity and slows or stops important functions of intestinal barrier integrity and immune system regulation, which results in inflammation and increased immune response[114]. In addition, mucolytic and pathogenic bacteria are also increased, which leads to degradation of the mucosal barrier and greater pathogen penetration into intestinal tissues[114,115].

Probiotics and faecal microbial transplantation, both aimed at reintroducing beneficial microbes into dysbiotic guts, are currently being used to treat inflammatory bowel disease[114,116]. Since kefir contains a diverse range of microorganisms, many of which have already been studied as probiotics[117], it has promise as an alternative treatment for intestinal dysbiosis. Wang[87] found that 21 d of freeze-dried (industrialised) kefir had positive effects on gastrointestinal symptoms, such as abdominal pain and bloating, and increased abundance of bifidobacteria. Forejt *et al.*[57] found significant improvement in gastrointestinal discomfort and lower *Enterococcus faecalis* after 2 weeks of kefir therapy in a sample of women. Figler *et al.*[56] investigated how consuming two types of kefir influenced the levels of primary probiotic *Streptococcus*, *Lactobacillus* and *Bifidobacterium* among the total number of microbes, finding that these populations increased in both groups after 4 weeks, with a more expressive increase in the intervention group (Biofir® kefir). In contrast, Sepp[80] found increased diversity of *Lactobacillus* spp. after 8 weeks only in the group who received kefir (industrialised) with added *L. fermentum* ME-3. The studies' samples, however, were healthy people with no diagnosed gastrointestinal disease, and different intervention times were used. In a sample of patients with Crohn's disease, Yilmaz *et al.*[83] found that regular kefir use can improve both symptoms and short-term quality of life and has a positive effect on biochemical parameters (such as haemoglobin, C-reactive protein and erythrocyte sedimentation rate).

Kefir has also been studied as an adjuvant treatment in two other gastrointestinal pathologies, *Helicobacter pylori* infection and recurrent *Clostridioides difficile* infection. Among patients who received kefir, Bekar *et al.*[61] found a lower prevalence of side effects, such as headache, nausea, diarrhoea and abdominal pain, in a group that received a triple therapy consisting of lansoprazole (30 mg), amoxicillin (1000 mg) and clarithromycin (500 mg). This may have important implications for increasing treatment adherence. In a case series of patients at risk of recurrent *Clostridioides difficile* infection, Bakken[64] used continuous kefir ingestion in association with a regimen of staggered and tapered antibiotic withdrawal, finding the same efficacy as faecal microbial transplantation.

Microorganisms present in kefir, such as *Lactococcus* spp., *Lactobacillus* spp. and some strains of *Kluyveromyces* spp. hydrolyse lactose to glucose and galactose[118]. During the fermentation process, milk proteins are also extensively hydrolysed, releasing functional peptides and improving digestibility[119]. Two studies tested kefir for digestibility in healthy adults with poor digestion[55] or lactose intolerance[63], both using a single intervention dose. They concluded that milk fermented with kefir, as well as yogurt, causes less severe discomfort than normal milk.

Turan *et al.*[66] and Maki *et al.*[77] studied the effects of kefir on chronic intestinal constipation, a highly prevalent condition for which diet is a possible treatment[97]. The first study enrolled patients who met Rome II criteria for chronic constipation, without metabolic or structural disorders that could be responsible for the disease; the second enrolled patients with some physical or mental disability who were admitted to a Japanese hospital. In addition to the different study populations, the type and amount of kefir used were completely different. Turan *et al.*[66] used a higher dose of kefir (250 ml twice per day) for 28 d, while Maki *et al.*[77] used lyophilised kefir at a much lower dose (about 1/8 of Turan *et al.*) for 84 d. Turan *et al.* found that kefir supplementation was associated with a statistically significant decrease in laxative use, increased defecation frequency, higher bowel satisfaction scores and shortened colonic transit times. Maki *et al.*[77] found that kefir worked better in patients with non-severe chronic constipation and suggested identifying individuals who could benefit from its use. Clinical trials with larger sample sizes and a control group are highly recommended to determine kefir's benefits in preventing and/or treating these gastrointestinal disorders.

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## Maternal/child health and paediatrics

Intestinal bacterial colonisation in the first years of life (generally the first three) has a major impact on the immune system, and the immunological influences of microbiota during this specific window can determine resistance or susceptibility to diseases, affecting the host's health throughout life[120–122]. Breast milk is a critical factor in the development and composition of intestinal microbiota in neonates. One possible origin of the bacteria in this fluid, many of which are potentially probiotic, is the maternal gastrointestinal tract via bacterial translocation through the lymphatic system[123]. Tunay *et al.*[96] tracked transmission of bacteria unique to kefir grains (*Lactobacillus kefiranofaciens*, *Lentiactobacillus kefiri*, *Lentiactobacillus parakefiri*) in breast milk and the faeces of newborns, finding that these microorganisms were transmitted to milk through maternal consumption of kefir, resulting in infant intestinal colonisation. Kurt *et al.* assessed the effects of milk kefir in nursing mothers in relation to the carbohydrate profile of their breast milk[91]. The authors detected a trend towards more carbohydrates, including galactooligosaccharides (structures with prebiotic properties), in the milk of mothers who consumed kefir. They also reported that neither the mothers nor their infants experienced abdominal discomfort from using kefir. While a good body of evidence about the effects of probiotics on paediatric populations already exists[124–126], studies about the benefits of kefir in children are still incipient.

Merenstein *et al.*[60] tested kefir's effects on prevention of antibiotic-associated diarrhoea, a disease with a high morbidity rate and low treatment adherence[127]. The sample consisted of children aged between 1 and 5 years who received antibiotics to treat upper airway infections. Although they found no difference in diarrhoea rates between the intervention and control groups, they did find different absolute numbers of diarrhoea incidents in children aged 3–5 years (14% in the control group versus 6% in the kefir group) and in boys (32% in the control group versus 24% in the kefir group, compared with a 2% difference among girls in these groups). The differences in absolute numbers of diarrhoea incidents in the older groups were quite expressive (57% higher in the placebo group), which suggests that a study with a larger sample in this population could help elucidate the promising role of kefir for preventing antibiotic-associated diarrhoea. The authors further reported that patient safety was excellent, as expected for a food.

De Araújo *et al.* studied the effects of lyophilised kefir on the clinical parameters of wheezing among infants aged 6–24 months and on cytokine expression via T-helper 1 and T-regulatory cells[75], finding no significant decrease in the clinical parameters of wheezing, only a trend towards lower recurrence (perhaps the sample was too small to demonstrate significance). However, they suggested that this probiotic mixture triggers immunomodulation due to the production of T-helper 1 and T-regulatory cell cytokines, including IL-10 and IL-12, since there they increased significantly in the intervention group. Intestinal bacteria contribute to proper development of the immune system in the first years of life, and the intestinal flora and its metabolites (such as short-chain fatty acids) actively participate in the proliferation and differentiation of B cells and T cells, inducing a protective antibody response[128].

## Dentistry

The human mouth harbours a complex microbiome whose imbalance can lead to dental caries and periodontal disease[129]. When metabolising carbohydrates, cariogenic microorganisms produce lactic, formic, acetic and propionic acids, which decrease the mouth's pH to below 5·5, resulting in demineralisation of enamel hydroxyapatite crystals and proteolytic breakdown of the hard tissue structure of the teeth. *Streptococcus mutans* is the most important bacterial species related to oral health[130]; it is more abundant in disease and is the main bacteria involved in early childhood caries[131]. Three included studies analysed the effects of kefir on the salivary count of *S. mutans*. Nevertheless, the results differed depending on the population, intervention time and dosage. The results showed that kefir was as effective as sodium fluoride for reducing salivary *S. mutans* counts in young adults[65]. Daily consumption of kefir and the use of probiotic toothpaste decreased salivary microbial colonisation in orthodontic patients[76]; probiotic products together with dental restorations effectively reduced *S. mutans* in children aged 8–12 years[89].

## Oncology

*In vitro* and animal studies have found positive results with probiotic dietary products like kefir in the prevention and treatment of various types of cancer[40,132,133]. Studies by Topuz *et al.*[58] and Can *et al.*[59] explored the use of kefir in very similar populations, using the same dose in almost identical intervention times, although their objectives differed. Topuz *et al.* measured serum levels of pro-inflammatory cytokines, the antimicrobial effects of kefir and the mucositis rate in patients with colorectal cancer receiving chemotherapy (5-fluorouracil or oral fluoropyrimidine), but found no statistically significant differences between the intervention and control groups. Can *et al.*[59] explored kefir's ability to prevent treatment-related gastrointestinal symptoms and its effects on the quality of life of cancer patients. They detected no differences in quality-of-life indices and reported more gastrointestinal complaints, but found better sleep quality in patients who used kefir. The amount of fermented milk used in the intervention may explain the increased complaints, since the ingestion of 250 ml of any liquid can be uncomfortable and increase symptoms such as nausea, vomiting and diarrhoea. Furthermore, the control group did not receive any type of similar liquid.

Smoak *et al.*[93] studied patients with cancer who had undergone chemotherapy or radiotherapy in the previous 2 years and were enrolled in an exercise programme at the University of Northern Colorado Cancer Rehabilitation Institute. The intervention group drank approximately 240 ml of kefir up to 30 min after the exercise sessions, which took place three times a week for 12 weeks. The control group performed the same exercises but received no placebo. The kefir group improved in lean body mass, depression symptoms, fatigue, gastric discomfort and a

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biomarker of intestinal dysbiosis, which suggests that including kefir as part of a post-exercise diet can have significant psychological and physical benefits for cancer survivors[93].

### Women's and geriatric health

Özcan *et al.*[81] studied perimenopause middle-aged women, in whom hormonal changes can lead to sleep and mood disturbances, sexual problems and, in the long term, decreased bone density[134,135]. The authors used the Women's Health Insomnia Rating Scale, the Menopause-Specific Quality of Life Questionnaire and the Beck Depression Inventory to determine whether kefir benefitted post-menopausal women suffering from sleep disorders. After 1 month of intervention there was significant improvement in the first two parameters but not in Beck Depression Inventory results, which showed a non-significant trend towards improvement. Despite the study's small sample size, the authors found kefir to be a non-pharmacological alternative for minimising some of the discomforts of the menopausal transition period.

Tu *et al.*[69] studied patients with osteoporosis, a disorder especially prevalent in postmenopausal women and older men, characterised by decreased bone mass and increased fracture risk[136]. Therapy for patients with osteoporosis includes non-pharmacological measures (exercise, adequate calcium intake, etc.), medications to increase bone density and improve bone strength, and strategies to reduce the risk of falling[136,137]. In their controlled, parallel, double-blind intervention study, Tu *et al.*[69] divided participants into an intervention group, which received 1600 mg of freeze-dried milk kefir plus $CaCO_3$ (1500 mg) daily, while the control group received the same amount of $CaCO_3$ plus placebo (1600 mg of freeze-dried unfermented raw milk) daily for 6 months. By 6 months, the intervention had promoted short-term changes in bone turnover markers and greater increases in hip bone mineral density.

In the field of neurodegenerative diseases, Ton *et al.*[86] conducted an uncontrolled clinical investigation to explore the antioxidant effects of milk fermented by kefir grains in patients with Alzheimer's disease. Alzheimer's disease causes progressive functional and cognitive decline in older adults and is the most common cause of dementia worldwide[138]. From a pathological point of view, it is characterised by extracellular deposition of β-amyloid peptides and intracellular accumulation of hyperphosphorylated and aggregated hyperphosphorylated tau (a protein abundant in neurons), forming neurofibrillary tangles[139]. The central mediators in the pathogenesis of Alzheimer's disease are oxidative stress and neuroinflammation[140–142]. Numerous studies have shown that gut microbiota play an important role in brain function[143–145]. The brain and microbiota communicate through a complex bidirectional connection known as the 'microbiota–gut–brain axis', which involves the immune system, neuroendocrine mechanisms, tryptophan metabolism, vagus nerve and enteric nervous system.[3,143,146]. Lipopolysaccharides (endotoxins) and bacterial amyloids synthesised by the gut microbiota can activate brain immune response and lead to neuroinflammation[143,144]. Neuroinflammatory cytokines may compromise β-amyloid clearance, leading to its accumulation in the brain[8,147]. Ton *et al.*[86] evaluated the benefits of kefir supplementation for 90 d at a dose of 2 ml/kg/d on cognitive function and biomarkers of oxidative stress, inflammation and cell damage in older adults with Alzheimer's disease. They found improvement in every test (memory, visual–spatial function and abstraction skills, executive and language functions, constructive skills and attentive function), a protective effect for mitochondria, and cytoprotective and anti-apoptotic action, whose effects slow neurodegeneration.

### Dermatology

The skin and gut appear to share a series of indirect bidirectional metabolic pathways known as the 'gut–skin axis'[90]. Patients with atopic dermatitis, a highly prevalent inflammatory skin disease worldwide, present with intestinal and cutaneous dysbiosis[120,148,149]. This condition of microbiome imbalance, along with skin barrier dysfunction, immune dysregulation and environmental risk factors, contributes to disease onset and the atopic march[11,150]. In their controlled crossover intervention study, Alves *et al.*[90] compared the effects of kefir ingestion (grain-fermented at home) on the skin of adults with and without atopic dermatitis. The primary outcomes were transepidermal water loss and stratum corneum hydration in all participants and the severity scoring of atopic dermatitis (SCORAD) index in patients with atopic dermatitis. Significant improvements were found in both groups, including a significant SCORAD index decrease in the atopic dermatitis group.

### Kefir production and dosage

Commercially produced kefir models may contain different species of *Lactobacillus* than those produced with the inoculation of the grains, which can make an important difference, because species exclusive to kefir grains such as *L. kefiranofaciens* and *L. kefiri* have already demonstrated beneficial health effects[151–154]. Furthermore, commercial kefir samples usually do not contain acetic acid bacteria, which are abundant in traditionally prepared kefir[155–157]. Another noteworthy difference between commercially and traditionally prepared kefir is the variety of yeasts, radically smaller in commercial models[156]. Bourrie *et al.*[158,159] demonstrated the impact of these microbial differences on kefir's ability to improve metabolic parameters in obese mice.

On the basis of these animal studies and on the analysed intervention studies, our suggestion is to use a therapeutic dose pattern in millilitres of traditionally prepared kefir (kefir grains inoculated in milk), due to its greater microbiological complexity and potential bioactive compounds.

The randomised, double-blind, placebo-controlled trial by Da Silva Ghizi *et al.*[95] was the only one to use individualised dose per kilogram (1·6 ml/kg for males and 1·9 ml/kg for females), calculated on the basis of studies by Reagan-Shaw *et al.*[160] and Rosa *et al.*[161]. This dose was close to the lowest standardised doses used in other studies that showed benefits. So, we suggest this individualised dose to be used in future studies avoiding underdose/overdose error. For example, a dose of

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1·6 ml/kg for a man weighing 90 kg would be 144 ml of kefir per day, making routine consumption much more viable. When such individualisation is not possible, doses of 100–200 ml/d are suggested.

These doses were determined by the perception that a minimum amount necessary is better tolerated by people and is more economically viable, increasing the probability of the consumption of this food to become a habit and its possible benefits to extend over time. Such doses would also make the methodology of future studies closer to the reality of the population. Very high amounts of kefir can hamper the viability of longer-term use due to palatability and maintenance costs, even when prepared at home. Daily doses of 500 or 600 ml, used in some studies, are not feasible long term for the general population, thus preventing any possible benefits.

## Conclusions

Despite a good body of evidence and interesting and promising findings in several areas of research, the included studies involved many limitations and their results cannot be generalised. The small sample sizes, methodological differences and varying kefir types, dosage and therapy times prevent us from drawing clear conclusions about its benefits for specific diseases. However, this review indicates fruitful paths for further research on kefir, facilitating the compilation of data and strengthening the results of future meta-analyses.

We suggest using a daily therapeutic dose pattern in millilitres of traditionally prepared kefir according to body weight (1·6 ml/kg for males and 1·9 ml/kg for females) or, alternatively, doses of 100–200 ml/d.

The studies included in this review found kefir to be a safe food for people without serious illnesses. However, further research is necessary before generalising this to people with severe disabilities or more advanced diseases. A healthy, balanced diet is fundamental for quality of life and the prevention of numerous diseases. Easy access to the initial culture (kefir grains), often available by donation, makes this healthy food a viable nutritional alternative for low-income populations, guaranteeing, at the very least, an optimal source of bioactive compounds and essential nutrients.

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## Conflict of interest

None.

## Authorship

M.K.B.: conception and design, analysis and interpretation, data collection, writing the article, critical revision of the article, final approval of the article, overall responsibility.

G.R.B.: analysis and interpretation, data collection, critical revision of the article, final approval of the article, overall responsibility.

R.R.B.: critical revision of the article, final approval of the article, overall responsibility.

All authors have read and approved the final version of the article.

## References

1. Walker RL, Vlamakis H, Lee JWJ, *et al.* (2021) Population study of the gut microbiome: associations with diet, lifestyle, and cardiometabolic disease. *Genome Med* **13**, 188.
2. Pu Q, Lin P, Gao P, *et al.* (2021) Gut microbiota regulate gut-lung axis inflammatory responses by mediating ILC2 compartmental migration. *J Immunol* **207**, 257–267.
3. Yue Q, Cai M, Xiao B, *et al.* (2022) The microbiota–gut–brain axis and epilepsy. *Cell Mol Neurobiol* **42**, 439–453.
4. Bonaz B, Bazin T & Pellissier S. (2018) The vagus nerve at the interface of the microbiota-gut-brain axis. *Front Neurosci* **12**, 49.
5. Anand S & Mande SS (2018) Diet, microbiota and gut–lung connection. *Front Microbiol* **9**, 2147.
6. Dabke K, Hendrick G & Devkota S. (2019) The gut microbiome and metabolic syndrome. *J Clin Invest* **129**, 4050–4057.
7. Strandwitz P (2018) Neurotransmitter modulation by the gut microbiota. *Brain Res* **1693**, 128–133.
8. Pereira TMC, Coco LZ, Ton AMM, *et al.* (2021) The emerging scenario of the gut–brain axis: the therapeutic actions of the new actor kefir against neurodegenerative diseases. *Antioxidants (Basel)* **10**, 1845.
9. Zheng H, Xu P, Jiang Q, *et al.* (2021) Depletion of acetate-producing bacteria from the gut microbiota facilitates cognitive impairment through the gut–brain neural mechanism in diabetic mice. *Microbiome* **9**, 145.
10. Iebba V, Totino V, Gagliardi A, *et al.* (2016) Eubiosis and dysbiosis: the two sides of the microbiota. *New Microbiol* **39**, 1–12.
11. Yu Y, Dunaway S, Champer J, *et al.* (2020) Changing our microbiome: probiotics in dermatology. *Br J Dermatol* **182**, 39–46.
12. Li R, Li Y, Li C, *et al.* (2020) Gut microbiota and endocrine disorder. *Adv Exp Med Biol* **1238**, 143–164.
13. Qi X, Yun C, Pang Y, *et al.* (2021) The impact of the gut microbiota on the reproductive and metabolic endocrine system. *Gut Microbes* **13**, 1–21.
14. Kitamoto S & Kamada N (2022) Periodontal connection with intestinal inflammation: microbiological and immunological mechanisms. *Periodontol 2000* **89**, 142–153.
15. de Oliveira AM, Lourenco TGB & Colombo APV (2022) Impact of systemic probiotics as adjuncts to subgingival instrumentation on the oral–gut microbiota associated with periodontitis: a randomized controlled clinical trial. *J Periodontol* **93**, 31–44.
16. Gori S, Inno A, Belluomini L, *et al.* (2019) Gut microbiota and cancer: How gut microbiota modulates activity, efficacy and toxicity of antitumoral therapy. *Crit Rev Oncol Hematol* **143**, 139–147.
17. Routy B, Gopalakrishnan V, Daillere R, *et al.* (2018) The gut microbiota influences anticancer immunosurveillance and general health. *Nat Rev Clin Oncol* **15**, 382–396.
18. Mosca A, Leclerc M & Hugot JP (2016) Gut microbiota diversity and human diseases: should we reintroduce key predators in our ecosystem? *Front Microbiol* **7**, 455.

https://doi.org/10.1017/S0954422423000070 Published online by Cambridge University Press

19. Pasolli E, Asnicar F, Manara S, *et al.* (2019) Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. *Cell* **176**, 649–662 e620.
20. Lloyd-Price J, Mahurkar A, Rahnavard G, *et al.* (2017) Strains, functions and dynamics in the expanded human microbiome project. *Nature* **550**, 61–66.
21. Byndloss MX & Baumler AJ (2018) The germ-organ theory of non-communicable diseases. *Nat Rev Microbiol* **16**, 103–110.
22. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, *et al.* (2019) Mechanisms of action of probiotics. *Adv Nutr* **10**, S49–S66.
23. Tamime AY (2002) Fermented milks: a historical food with modern applications-a review. *Eur J Clin Nutr* **56**(Suppl 4), S2–S15.
24. Brunser O (2017) Probiotics: innocuousness, prevention and risks. *Rev Chil Pediatr* **88**, 534–540.
25. Hill C, Guarner F, Reid G, *et al.* (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* **11**, 506–514.
26. Vieira AT, Fukumori C & Ferreira CM (2016) New insights into therapeutic strategies for gut microbiota modulation in inflammatory diseases. *Clin Transl Immunology* **5**, e87.
27. Ceapa C, Wopereis H, Rezaiki L, *et al.* (2013) Influence of fermented milk products, prebiotics and probiotics on microbiota composition and health. *Best Pract Res Clin Gastroenterol* **27**, 139–155.
28. Quigley EMM (2019) Prebiotics and probiotics in digestive health. *Clin Gastroenterol Hepatol* **17**, 333–344.
29. de Oliveira Leite AM, Miguel MA, Peixoto RS, *et al.* (2013) Microbiological, technological and therapeutic properties of kefir: a natural probiotic beverage. *Braz J Microbiol* **44**, 341–349.
30. Weschenfelder S, Wiest JM & Carvalho HHC (2013) Anti-*Escherichia coli* activity in traditional kefir and kefir whey. *Rev Inst Latic "Cândido Tostes"* **64**, 48–55.
31. Farag MA, Jomaa SA, El-Wahed AA, *et al.* (2020) The many faces of kefir fermented dairy products: quality characteristics, flavour chemistry, nutritional value, health benefits, and safety. *Nutrients* **12**, 346.
32. Leite AM, Miguel MA, Peixoto RS, *et al.* (2015) Probiotic potential of selected lactic acid bacteria strains isolated from Brazilian kefir grains. *J Dairy Sci* **98**, 3622–3632.
33. Weschenfelder S (2009) Characterization of traditional kefir on physicalchemical composition, sensorial characteristic and anti-*Escherichia coli* activity. Master's thesis, Universidade Federal do Rio Grande do Sul (UFRGS).
34. Stiemsma LT, Nakamura RE, Nguyen JG, *et al.* (2020) Does consumption of fermented foods modify the human gut microbiota? *J Nutr* **150**, 1680–1692.
35. Chen HL, Hung KF, Yen CC, *et al.* (2019) Kefir peptides alleviate particulate matter <4 μm ($PM_{4.0}$)-induced pulmonary inflammation by inhibiting the NF-κB pathway using luciferase transgenic mice. *Sci Rep* **9**, 11529.
36. Carasi P, Racedo SM, Jacquot C, *et al.* (2015) Impact of kefir derived *Lactobacillus kefiri* on the mucosal immune response and gut microbiota. *J Immunol Res* **2015**, 361604.
37. Seo MK, Park EJ, Ko SY, *et al.* (2018) Therapeutic effects of kefir grain *Lactobacillus*-derived extracellular vesicles in mice with 2,4,6-trinitrobenzene sulfonic acid-induced inflammatory bowel disease. *J Dairy Sci* **101**, 8662–8671.
38. Ghoneum M, Abdulmalek S & Pan D (2020) Reversal of age-associated oxidative stress in mice by PFT, a novel kefir product. *Int J Immunopathol Pharmacol* **34**, 2058738420950149.
39. Azizi NF, Kumar MR, Yeap SK, *et al.* (2021) Kefir and its biological activities. *Foods* **10**, 1210.
40. Sharifi M, Moridnia A, Mortazavi D, *et al.* (2017) Kefir: a powerful probiotics with anticancer properties. *Med Oncol* **34**, 183.
41. Al-Mohammadi AR, Ibrahim RA, Moustafa AH, *et al.* (2021) Chemical constitution and antimicrobial activity of kefir fermented beverage. *Molecules* **26**, 2635.
42. Rodrigues KL, Caputo LR, Carvalho JC, *et al.* (2005) Antimicrobial and healing activity of kefir and kefiran extract. *Int J Antimicrob Agents* **25**, 404–408.
43. Bolla PA, Carasi P, Bolla Mde L, *et al.* (2013) Protective effect of a mixture of kefir-isolated lactic acid bacteria and yeasts in a hamster model of *Clostridium difficile* infection. *Anaerobe* **21**, 28–33.
44. Hadisaputro S, Djokomoeljanto RR, Judiono, *et al.* (2012) The effects of oral plain kefir supplementation on proinflammatory cytokine properties of the hyperglycemia Wistar rats induced by streptozotocin. *Acta Med Indones* **44**, 100–104.
45. Brasil GA, Silva-Cutini MA, Moraes FSA, *et al.* (2018) The benefits of soluble non-bacterial fraction of kefir on blood pressure and cardiac hypertrophy in hypertensive rats are mediated by an increase in baroreflex sensitivity and decrease in angiotensin-converting enzyme activity. *Nutrition* **51–52**, 66–72.
46. Ebner J, Asci Arslan A, Fedorova M, *et al.* (2015) Peptide profiling of bovine kefir reveals 236 unique peptides released from caseins during its production by starter culture or kefir grains. *J Proteomics* **117**, 41–57.
47. Friques AG, Arpini CM, Kalil IC, *et al.* (2015) Chronic administration of the probiotic kefir improves the endothelial function in spontaneously hypertensive rats. *J Transl Med* **13**, 390.
48. Klippel BF, Duemke LB, Leal MA, *et al.* (2016) Effects of kefir on the cardiac autonomic tones and baroreflex sensitivity in spontaneously hypertensive rats. *Front Physiol* **7**, 211.
49. Liu JR, Wang SY, Chen MJ, *et al.* (2006) Hypocholesterolaemic effects of milk-kefir and soyamilk-kefir in cholesterol-fed hamsters. *Br J Nutr* **95**, 939–946.
50. Wang Y, Xu N, Xi A, *et al.* (2009) Effects of Lactobacillus plantarum MA2 isolated from Tibet kefir on lipid metabolism and intestinal microflora of rats fed on high-cholesterol diet. *Appl Microbiol Biotechnol* **84**, 341–347.
51. Rosa DD, Dias MMS, Grzeskowiak LM, *et al.* (2017) Milk kefir: nutritional, microbiological and health benefits. *Nutr Res Rev* **30**, 82–96.
52. JBI Manual for Evidence Synthesis (2020) Chapter 11: Scoping reviews. https://jbi-global-wiki.refined.site/space/MANUAL/4687342/Chapter+11%3A+Scoping+reviews (accessed October 2021).
53. O'Brien KV, Stewart LK, Forney LA, *et al.* (2015) The effects of postexercise consumption of a kefir beverage on performance and recovery during intensive endurance training. *J Dairy Sci* **98**, 7446–7449.
54. St-Onge MP, Farnworth ER, Savard T, *et al.* (2002) Kefir consumption does not alter plasma lipid levels or cholesterol fractional synthesis rates relative to milk in hyperlipidemic men: a randomized controlled trial [ISRCTN10820810]. *BMC Complement Altern Med* **2**, 1.
55. Hertzler SR & Clancy SM. (2003) Kefir improves lactose digestion and tolerance in adults with lactose maldigestion. *J Am Diet Assoc* **103**, 582–587.


https://doi.org/10.1017/S0954422423000070 Published online by Cambridge University Press

56. Figler M, Mozsik G, Schaffer B, *et al.* (2006) Effect of special Hungarian probiotic kefir on faecal microflora. *World J Gastroenterol* **12**, 1129–1132.
57. Forejt M, Šimůnek J, Brázdová Z, *et al.* (2007) The influence of regular consumption of kefir beverage on the incidence of *Enterococcus faecalis* in the human stool. *Scr Med (Brno)* **80**, 279–286.
58. Topuz E, Derin D, Can G, *et al.* (2008) Effect of oral administration of kefir on serum proinflammatory cytokines on 5-FU induced oral mucositis in patients with colorectal cancer. *Invest New Drugs* **26**, 567–572.
59. Can G, Topuz E, Derin D, *et al.* (2009) Effect of kefir on the quality of life of patients being treated for colorectal cancer. *Oncol Nurs Forum* **36**, E335–E342.
60. Merenstein DJ, Foster J & D'Amico F (2009) A randomized clinical trial measuring the influence of kefir on antibiotic-associated diarrhea: the measuring the influence of kefir (MILK) study. *Arch Pediatr Adolesc Med* **163**, 750–754.
61. Bekar O, Yilmaz Y & Gulten M (2011) Kefir improves the efficacy and tolerability of triple therapy in eradicating *Helicobacter pylori*. *J Med Food* **14**, 344–347.
62. Kullisaar T, Shepetova, J, Zilmer K, Songisepp E, Rehema A, Mikelsaar M & Zilmer M (2011) An antioxidant probiotic reduces postprandial lipemia and oxidative stress. *Cent Eur J Biol* **6**, 32–40.
63. Mądry E, Krasińska B, Woźniewicz M, *et al.* (2011) Tolerance of different dairy products in subjects with symptomatic lactose malabsorption due to adult type hypolactasia. *Prz Gastroenterol* **6**, 310–315.
64. Bakken JS (2014) Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent *Clostridium difficile* infection. *Clin Infect Dis* **59**, 858–861.
65. Ghasempour M, Sefdgar SA, Moghadamnia AA, *et al.* (2014) Comparative study of kefir yogurt-drink and sodium fluoride mouth rinse on salivary mutans streptococci. *J Contemp Dent Pract* **15**, 214–217.
66. Turan I, Dedeli O, Bor S, *et al.* (2014) Effects of a kefir supplement on symptoms, colonic transit, and bowel satisfaction score in patients with chronic constipation: a pilot study. *Turk J Gastroenterol* **25**, 650–656.
67. Judiono J, Hadisaputro S, Indranila KS, *et al.* (2014) Effects of clear kefir on biomolecular aspects of glycemic status of type 2 diabetes mellitus (T2DM) patients in Bandung, West Java [study on human blood glucose, c peptide and insulin]. *FFHD* **4**, 340–348.
68. Ostadrahimi A, Taghizadeh A, Mobasseri M, *et al.* (2015) Effect of probiotic fermented milk (kefir) on glycemic control and lipid profile in type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Iran J Public Health* **44**, 228–237.
69. Tu MY, Chen HL, Tung YT, *et al.* (2015) Short-term effects of kefir-fermented milk consumption on bone mineral density and bone metabolism in a randomized clinical trial of osteoporotic patients. *PLoS One* **10**, e0144231.
70. Fathi Y, Faghih S, Zibaeenezhad MJ, *et al.* (2016) Kefir drink leads to a similar weight loss, compared with milk, in a dairy-rich non-energy-restricted diet in overweight or obese premenopausal women: a randomized controlled trial. *Eur J Nutr* **55**, 295–304.
71. Fathi Y, Ghodrati N, Zibaeenezhad MJ, *et al.* (2017) Kefir drink causes a significant yet similar improvement in serum lipid profile, compared with low-fat milk, in a dairy-rich diet in overweight or obese premenopausal women: A randomized controlled trial. *J Clin Lipidol* **11**, 136–146.
72. Alihosseini N, Moahboob SA, Farrin N, *et al.* (2017) Effect of probiotic fermented milk (kefir) on serum level of insulin and homocysteine in type 2 diabetes patients. *Acta Endocrinol (Buchar)* **13**, 431–436.
73. Gölünük SB, Öztaşan N, Sözen H, *et al.* (2017) Effects of traditional fermented beverages on some blood parameters in aerobic exercises. *Biomed Res* **28**, 9475–9480.
74. Diken H, Oguz Z, Kaya H, *et al.* (2017) Effect of kefir consumption on erythrocyte osmotic fragility and some haemetological parameters in smokers and non-smokers. *Acta Physiol* **221**, 60.
75. De Araujo GV, De Lorena VMB, Montenegro SML, *et al.* (2017) Probiotics as an adjunct for the treatment of recurrent wheezing in infants and effects on expression of T-helper 1 and regulatory T cytokines. *J Funct Foods* **35**, 398–407.
76. Alp S & Baka ZM (2018) Effects of probiotics on salivary *Streptococcus mutans* and *Lactobacillus* levels in orthodontic patients. *Am J Orthod Dentofacial Orthop* **154**, 517–523.
77. Maki R, Matsukawa M, Matsuduka A, *et al.* (2018) Therapeutic effect of lyophilized, kefir-fermented milk on constipation among persons with mental and physical disabilities. *Jpn J Nurs Sci* **15**, 218–225.
78. Abd-Alwahab WI & Al-Dulaimi FK (2018) Effects of kefir as a probiotic on total lipid profile and activity of aspartate amino transferase and alanine amino transferase in serum of human. *Biochem Cell Arch* **18**, 411–414.
79. Gezginc Y & Maranci C (2018) Effect of fermented food consumption on biochemical parameters and adipokines levels. *Progr Nutr* **20**, 642–647.
80. Sepp E, Smidt I, Štšepetova J, *et al.* (2018) The effect of *Lactobacillus fermentum* ME-3 on the intestinal microbiota and urine polyamines content: a double-blind placebo-controlled pilot trial. *J Funct Foods* **48**, 430–438.
81. Ozcan H, Oskay U & Bodur AF (2019) Effects of kefir on quality of life and sleep disturbances in postmenopausal women. *Holist Nurs Pract* **33**, 207–213.
82. Bellikci-Koyu E, Sarer-Yurekli BP, Akyon Y, *et al.* (2019) Effects of regular kefir consumption on gut microbiota in patients with metabolic syndrome: a parallel-group, randomized, controlled study. *Nutrients* **11**, 2089.
83. Yilmaz I, Dolar ME & Ozpinar H (2019) Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: a randomized controlled trial. *Turk J Gastroenterol* **30**, 242–253.
84. Bashiti TA & Zabut BM (2019) Effect of probiotic fermented milk (Kefir) on some blood biochemical parameters among newly diagnosed type 2 diabetic adult males in Gaza governorate. *Curr Res Nutr Food Sci* **7**, 568–575.
85. Praznikar ZJ, Kenig S, Vardjan T, *et al.* (2020) Effects of kefir or milk supplementation on zonulin in overweight subjects. *J Dairy Sci* **103**, 3961–3970.
86. Ton AMM, Campagnaro BP, Alves GA, *et al.* (2020) Oxidative stress and dementia in Alzheimer's patients: effects of synbiotic supplementation. *Oxid Med Cell Longev* **2020**, 2638703.
87. Wang MC, Zaydi AI, Lin WH, *et al.* (2020) Putative probiotic strains isolated from kefir improve gastrointestinal health parameters in adults: a randomized, single-blind, placebo-controlled study. *Probiotics Antimicrob Proteins* **12**, 840–850.
88. Lee MC, Jhang WL, Lee CC, *et al.* (2021) The effect of kefir supplementation on improving human endurance exercise performance and antifatigue. *Metabolites* **11**.


https://doi.org/10.1017/S0954422423000070 Published online by Cambridge University Press

89. Reddy S, Madhu V, Punithavathy R *et al.* (2021) Comparative evaluation of efficacy of kefir milk probiotic curd and probiotic drink on streptococcus mutans in 8–12-year-old children: an *in vivo* study. *Int J Clin Pediatr Dent* **14**, 120–127.
90. Alves E, Gregorio J, Baby AR *et al.* (2021) Homemade kefir consumption improves skin condition-a study conducted in healthy and atopic volunteers. *Foods* **10**, 2794.
91. Kurt TT, Gökırmaklı Ç & Guzel-Seydim ZB (2021) Effects of kefir consumption on carbohydrate profile of mother's milk. *FFHD* **11**, 473–483.
92. Hosainzadegn H & Hosainzadegan M (2021) Traditional probiotic (kefir) effects on glycated hemoglobin A level and weight of an indexed diabetic patient. *Int J Prev Med* **12**, 139.
93. Smoak P, Harman N, Flores V, *et al.* (2021) Kefir is a viable exercise recovery beverage for cancer survivors enrolled in a structured exercise program. *Med Sci Sports Exerc* **53**, 2045–2053.
94. Caferoglu Z & Aytekin Sahin G (2021) The effects of kefir in mixed meals on appetite and food intake: a randomized cross-over trial. *Rev Nutr* **34**, e190174.
95. Da Silva Ghizi AC, De Almeida Silva M, De Andrade Moraes FS, *et al.* (2021) Kefir improves blood parameters and reduces cardiovascular risks in patients with metabolic syndrome. *PharmaNutrition* **16**, 100266.
96. Tunay RT & Taş TK (2022) Verticle transmission of unique bacterial strains from mother to infant via consuming natural kefir. *Int Dairy J* **126**, 105251.
97. Aziz I, Whitehead WE, Palsson OS, *et al.* (2020) An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. *Expert Rev Gastroenterol Hepatol* **14**, 39–46.
98. Samson SL & Garber AJ (2014) Metabolic syndrome. *Endocrinol Metab Clin North Am* **43**, 1–23.
99. Festi D, Schiumerini R, Eusebi LH, *et al.* (2014) Gut microbiota and metabolic syndrome. *World J Gastroenterol* **20**, 16079–16094.
100. Li HY, Zhou DD, Gan RY, *et al.* (2021) Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients* **13**, 3211
101. Fasano A (2020) All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Res* **9**, F1000 Faculty Rev-69.
102. Gonzalez-Orozco BD, Garcia-Cano I, Jimenez-Flores R, *et al.* (2022) Invited review: milk kefir microbiota—direct and indirect antimicrobial effects. *J Dairy Sci* **105**, 3703–3715.
103. Brashears MM, Gilliland SE & Buck LM (1998) Bile salt deconjugation and cholesterol removal from media by *Lactobacillus casei*. *J Dairy Sci* **81**, 2103–2110.
104. Lye HS, Rusul G & Liong MT (2010) Removal of cholesterol by lactobacilli via incorporation and conversion to coprostanol. *J Dairy Sci* **93**, 1383–1392.
105. Ooi LG & Liong MT (2010) Cholesterol-lowering effects of probiotics and prebiotics: a review of *in vivo* and *in vitro* findings. *Int J Mol Sci* **11**, 2499–2522.
106. Ditscheid B, Keller S & Jahreis G (2005) Cholesterol metabolism is affected by calcium phosphate supplementation in humans. *J Nutr* **135**, 1678–1682.
107. Lorenzen JK & Astrup A (2011) Dairy calcium intake modifies responsiveness of fat metabolism and blood lipids to a high-fat diet. *Br J Nutr* **105**, 1823–1831.
108. Denke MA, Fox MM & Schulte MC (1993) Short-term dietary calcium fortification increases fecal saturated fat content and reduces serum lipids in men. *J Nutr* **123**, 1047–1053.
109. Salari A, Ghodrat S, Gheflati A, *et al.* (2021) Effect of kefir beverage consumption on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. *Complement Ther Clin Pract* **44**, 101443.
110. Hills RD Jr, Pontefract BA, Mishcon HR, *et al.* (2019) Gut microbiome: profound implications for diet and disease. *Nutrients* **11**, 1613.
111. Rothschild D, Weissbrod O, Barkan E, *et al.* (2018) Environment dominates over host genetics in shaping human gut microbiota. *Nature* **555**, 210–215.
112. Sairenji T, Collins KL & Evans DV (2017) An update on inflammatory bowel disease. *Prim Care* **44**, 673–692.
113. Flynn S & Eisenstein S (2019) Inflammatory bowel disease presentation and diagnosis. *Surg Clin North Am* **99**, 1051–1062.
114. Lee M & Chang EB (2021) Inflammatory bowel diseases (IBD) and the microbiome-searching the crime scene for clues. *Gastroenterology* **160**, 524–537.
115. Chassaing B & Darfeuille-Michaud A (2011) The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. *Gastroenterology* **140**, 1720–1728.
116. Jeong DY, Kim S, Son MJ, *et al.* (2019) Induction and maintenance treatment of inflammatory bowel disease: a comprehensive review. *Autoimmun Rev* **18**, 439–454.
117. Slattery C, Cotter PD & O'Toole PW (2019) Analysis of health benefits conferred by lactobacillus species from kefir. *Nutrients* **11**, 1252.
118. Leite AM, Leite DC, Del Aguila EM, *et al.* (2013) Microbiological and chemical characteristics of Brazilian kefir during fermentation and storage processes. *J Dairy Sci* **96**, 4149–4159.
119. Dallas DC, Citerne F, Tian T, *et al.* (2016) Peptidomic analysis reveals proteolytic activity of kefir microorganisms on bovine milk proteins. *Food Chem* **197**, 273–284.
120. Kim JE & Kim HS (2019) Microbiome of the skin and gut in atopic dermatitis (AD): understanding the pathophysiology and finding novel management strategies. *J Clin Med* **8**, 444.
121. Nie P, Li Z, Wang Y, *et al.* (2019) Gut microbiome interventions in human health and diseases. *Med Res Rev* **39**, 2286–2313.
122. Gensollen T & Blumberg RS (2017) Correlation between early-life regulation of the immune system by microbiota and allergy development. *J Allergy Clin Immunol* **139**, 1084–1091.
123. Stinson LF, Sindi ASM, Cheema AS, *et al.* (2021) The human milk microbiome: who, what, when, where, why, and how? *Nutr Rev* **79**, 529–543.
124. Guo Q, Goldenberg JZ, Humphrey C, *et al.* (2019) Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev* **4**, CD004827.
125. Depoorter L & Vandenplas Y (2021) Probiotics in pediatrics. A review and practical guide. *Nutrients* **13**, 2176.
126. Jiang W, Ni B, Liu Z, *et al.* (2020) The role of probiotics in the prevention and treatment of atopic dermatitis in children: an updated systematic review and meta-analysis of randomized controlled trials. *Paediatr Drugs* **22**, 535–549.
127. Turck D, Bernet JP, Marx J, *et al.* (2003) Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr* **37**, 22–26.
128. Nguyen QN, Himes JE, Martinez DR, *et al.* (2016) The impact of the gut microbiota on humoral immunity to pathogens and vaccination in early infancy. *PLoS Pathog* **12**, e1005997.


https://doi.org/10.1017/S0954422423000070 Published online by Cambridge University Press

129. Mosaddad SA, Tahmasebi E, Yazdanian A, *et al.* (2019) Oral microbial biofilms: an update. *Eur J Clin Microbiol Infect Dis* **38**, 2005–2019.
130. Dashper SG, Mitchell HL, Le Cao KA, *et al.* (2019) Temporal development of the oral microbiome and prediction of early childhood caries. *Sci Rep* **9**, 19732.
131. Patidar D, Sogi S, Singh V, *et al.* (2018) Salivary levels of *Streptococcus mutans* and *Streptococcus sanguinis* in early childhood caries: an *in vivo* study. *J Indian Soc Pedod Prev Dent* **36**, 386–390.
132. Fatahi A, Soleimani N & Afrough P (2021) Anticancer activity of kefir on glioblastoma cancer cell as a new treatment. *Int J Food Sci* **2021**, 8180742.
133. Rafie N, Golpour Hamedani S, Ghiasvand R, *et al.* (2015) Kefir and cancer: a systematic review of literatures. *Arch Iran Med* **18**, 852–857.
134. Gracia CR & Freeman EW (2018) Onset of the menopause transition: the earliest signs and symptoms. *Obstet Gynecol Clin North Am* **45**, 585–597.
135. Potter B, Schrager S, Dalby J, *et al.* (2018) Menopause. *Prim Care* **45**, 625–641.
136. Lane JM, Russell L & Khan SN (2000) Osteoporosis. *Clin Orthop Relat Res* **372**, 139–150.
137. The North American Menopause Society (2021) Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause* **28**, 973–997.
138. Lopez OL & Kuller LH (2019) Epidemiology of aging and associated cognitive disorders: prevalence and incidence of Alzheimer's disease and other dementias. *Handb Clin Neurol* **167**, 139–148.
139. Querfurth HW & LaFerla FM (2010) Alzheimer's disease. *N Engl J Med* **362**, 329–344.
140. Kinney JW, Bemiller SM, Murtishaw AS, *et al.* (2018) Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y)* **4**, 575–590.
141. Luca M, Di Mauro M, Di Mauro M, *et al.* (2019) Gut microbiota in Alzheimer's disease, depression, and type 2 diabetes mellitus: the role of oxidative stress. *Oxid Med Cell Longev* **2019**, 4730539.
142. Chen Z & Zhong C (2014) Oxidative stress in Alzheimer's disease. *Neurosci Bull* **30**, 271–281.
143. Megur A, Baltriukiene D, Bukelskiene V, *et al.* (2020) The microbiota–gut–brain axis and Alzheimer's disease: neuroinflammation is to blame? *Nutrients* **13**, 37.
144. Jiang C, Li G, Huang P, *et al.* (2017) The gut microbiota and Alzheimer's disease. *J Alzheimers Dis* **58**, 1–15.
145. Doifode T, Giridharan VV, Generoso JS, *et al.* (2021) The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. *Pharmacol Res* **164**, 105314.
146. Cryan JF, O'Riordan KJ, Cowan CSM, *et al.* (2019) The microbiota–gut–brain axis. *Physiol Rev* **99**, 1877–2013.
147. Alasmari F, Alshammari MA, Alasmari AF, *et al.* (2018) Neuroinflammatory cytokines induce amyloid beta neurotoxicity through modulating amyloid precursor protein levels/metabolism. *Biomed Res Int* **2018**, 3087475.
148. Watanabe S, Narisawa Y, Arase S, *et al.* (2003) Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. *J Allergy Clin Immunol* **111**, 587–591.
149. Fieten KB, Totte JEE, Levin E, *et al.* (2018) Fecal microbiome and food allergy in pediatric atopic dermatitis: a cross-sectional pilot study. *Int Arch Allergy Immunol* **175**, 77–84.
150. Lee SY, Lee E, Park YM, *et al.* (2018) Microbiome in the gut–skin axis in atopic dermatitis. *Allergy Asthma Immunol Res* **10**, 354–362.
151. Carasi P, Racedo SM, Jacquot C, *et al.* (2015) Impact of kefir derived *Lactobacillus kefiri* on the mucosal immune response and gut microbiota. *J Immunol Res* **2015**, 361604.
152. Kim D-H, Jeong D, Kang I-B, *et al.* (2017) Dual function of *Lactobacillus kefiri* DH5 in preventing high-fat-diet-induced obesity: direct reduction of cholesterol and upregulation of PPARα in adipose tissue. *Mol Nutr Food Res* **61**, 1700252.
153. Chen YP & Chen MJ (2013) Effects of *Lactobacillus kefiranofaciens* M1 isolated from kefir grains on germ-free mice. *PLoS One* **8**, 7467–7477.
154. Chen YP, Hsiao PJ, Hong WS, *et al.* (2012) *Lactobacillus kefiranofaciens* M1 isolated from milk kefir grains ameliorates experimental colitis *in vitro* and *in vivo*. *J Dairy Sci* **95**, 63–74.
155. Dobson A, O'Sullivan O, Cotter PD, *et al.* (2011) High-throughput sequence-based analysis of the bacterial composition of kefir and an associated kefir grain. *FEMS Microbiol Lett* **320**, 56–62.
156. Marsh AJ, O'Sullivan O, Hill C, *et al.* (2013) Sequencing-based analysis of the bacterial and fungal composition of kefir grains and milks from multiple sources. *PLoS One* **8**, e69371.
157. Walsh AM, Crispie F, Kilcawley K, *et al.* (2016) Microbial succession and flavor production in the fermented dairy beverage Kefir. *mSystems* **1**, e00052–16.
158. Bourrie BCT, Cotter PD & Willing BP (2018) Traditional kefir reduces weight gain and improves plasma and liver lipid profiles more successfully than a commercial equivalent in a mouse model of obesity. *J Funct Foods*, **46**, 29–37.
159. Bourrie BCT, Ju T, Fouhse JM, *et al.* (2021) Kefir microbial composition is a deciding factor in the physiological impact of kefir in a mouse model of obesity. *Br J Nutr* **125**, 129–138.
160. Reagan-Shaw S, Nihal M & Ahmad N (2008) Dose translation from animal to human studies revisited. *FASEB J* **22**, 659–661.
161. Diniz Rosa D, Gouveia Peluzio do MC, Pérez Bueno T, *et al.* (2014) Evaluation of the subchronic toxicity of kefir by oral administration in Wistar rats. *Nutr Hosp* **29**, 1352–1359.


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