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Kefir: Unveiling the science behind a traditional fermented food - A narrative review of its composition, bioactivities, and therapeutic potential

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Abstract

Kefir, a traditional fermented milk beverage originating from the Caucasus Mountains, has garnered significant global interest due to its purported health benefits. This comprehensive review synthesizes current scientific knowledge on kefir, bridging traditional wisdom with modern research. We begin by detailing the complex microbiological composition of kefir grains, which host a unique symbiotic consortium of lactic acid bacteria, acetic acid bacteria, and yeasts embedded in a polysaccharide and protein matrix. The fermentation process yields a diverse array of bioactive compounds, including peptides, exopolysaccharides (kefiran), and short-chain fatty acids, which are responsible for its biological activities. We critically evaluate the evidence supporting kefir's multifaceted bioactivities, such as its antimicrobial, anti-inflammatory, immunomodulatory, antioxidant, and anti-proliferative properties. Furthermore, the review explores the potential therapeutic applications of kefir and its metabolites in managing metabolic syndromes, gastrointestinal disorders, and certain cancers, primarily based on *in vitro* and *in vivo* studies. Finally, we discuss the challenges in standardizing kefir production and the need for more robust, well-designed human clinical trials to fully validate its health-promoting claims and elucidate its mechanisms of action. This review underscores kefir's potential as a promising functional food and a source for next-generation probiotic formulations and therapeutic agents.

Introduction

The evolution of mankind has been accompanied by dietary changes, which have been shown to be essential to that evolution and to human welfare. In addition to being necessary for survival, nutrition is also important for the health and balance of the human body [1]. The development of innovative foods with clear health advantages has been encouraged by rising consumer demand for healthy foods and understanding of the influence of dietary practices on human wellbeing. A large variety of innovative functional foods are now available on the market, with dairy products and beverages playing an essential role [2]. Fermented foods and drinks were among the earliest processed foods that humans consumed [3]. By giving the user

beneficial bacteria and nutritional advantages due to modifications made to the food matrix during fermentation, fermented foods can contribute to health benefits [4]. Several species and even separate strains of microorganisms may be found in certain artisanal fermented foods, and the dynamics of the population throughout processing are highly complicated [3]. Kefir a fermented milk beverage and water kefir, often referred to as "aquakefir" or "sugary kefir" a fermented non-dairy beverage, are two artisanal fermented drinks that are of particular interest because to their natural and artisanal manufacture, which is compatible with sustainable technology [5]. Kefir is a low-alcohol fermented drink that is acidic and frothy due to the fermentation carbonation of kefir grains with milk or water [6,7]. Its

origins can be traced back to the Balkans, Eastern Europe, and the Caucasus, and its consumption has spread to other regions of the world over time due to its health-giving benefits [8]. Kefir grains are cauliflower-like florets that are white to yellowish-white in color and made of a protein and carbohydrate matrix with a microbial population [9]. Both milk kefir and water kefir are typically made from distinct probiotic-containing gelatinous particles called “milk kefir grains” and “water kefir grains.” These grains are used to make a pair of beverages produced by fermentation, each of which has unique physical, chemical, and microbiological compositions. Both milk and water kefir have useful characteristics. Milk kefir offers considerable levels of protein as well as probiotics and prebiotics, whereas water kefir can be a highly essential probiotic, prebiotic, and antioxidant source for vegans and persons who are allergic to dairy products [10]. Numerous research on the potential health benefits of kefir as a natural beverage containing probiotic bacteria and useful organic compounds have been published in the last few years. Probiotics are living bacteria that, when treated in adequate quantities, provide a health benefit to the host, according to the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). Furthermore, data suggests that kefir’s exopolysaccharide, kefiran, has important physicochemical properties and biological activities that add value to the products [11]. In addition, several biotechnological advancements have previously been proposed to create a kefir-like beverage with enhanced sensory, nutritional, and functional properties [12]. While numerous reviews have summarized the general health benefits of kefir, a comprehensive and critical synthesis of the latest advancements is lacking. Specifically, there is a need to consolidate recent findings on the molecular mechanisms behind its bioactivity, the clinical translation of these effects in human trials, and the emerging innovations in kefir production. This review aims to bridge this gap by not only providing an up-to-date overview of kefir’s composition and properties but also by offering a critical perspective on the challenges and future directions for its application as a functional food and potential therapeutic agent.

Composition and nutritive value of kefir grains

Kefir grains contain bacteria and fungus embedded in kefiran, a durable insoluble polysaccharide matrix consisting of glucose and galactose (Figure 1) [13]. This carbohydrate is bacterial in nature, generated by lactobacilli (*Lactobacillus paracasei*, *Lactobacillus kefirii*, *Lactobacillus parabuchneri*, and *Acetobacter lovaniensis*) and yeast (*Saccharomyces cerevisiae* and *Kluyveromyces lactis*) that accumulate on matrix polysaccharide and protein [14]. The kefir grains’ external surfaces seemed smooth and glossy to the human eye. According to Mei et al. [15], SEM analyses revealed that grain surfaces were quite rough. In the inner portion of the grain, a variety of lactobacilli (long and curved), yeasts and fibrillar material were observed. The short lactobacilli and yeast were observed on the outer portion [16]. The inner region had a lower microbial cell density than the outside portion. Nonetheless, Brazilian kefir grains were examined by Leite et al. [17] which discovered rod-shaped bacteria in both the inner and outer grain regions, with yeasts being more prevalent in the outside portion. Whereas, Guzelseydim, et al. [18] found a diversity of lactobacilli but no yeast in the interior. A considerable number of long, curved bacteria may be found in the polysaccharide matrix zone between

the smooth and rough sides. These bacteria may be responsible for the kefiran that makes up the matrix [13]. According to research, the grain folding structure is caused by the fact that most LABs are hydrophilic and have a negative charge on their cell surface. *Lactobacillus kefirifaciens* HL1 and *Lactobacillus HL2* kefir are hydrophobic with a positively charged cell surface, enabling for self-aggregation [19]. As reported by Xie et al. [20], proteins on the bacterial cell wall surface and polysaccharides on the yeast cell wall both play key roles in co-aggregation and microbial adherence, as well as that, the yeast applied improves aggregation, adhesion, and survival in hostile environments.

In terms of nutritional content, Kefir’s nutritional benefit stems from its diverse chemical composition, which includes minerals, sugars, carbs, proteins, peptides, vitamins, and lipids (Table 1). Even so, this composition varies greatly and is impacted by milk composition, the origin and composition of the grains used, fermentation time/temperature, and storage conditions [21]. Kefir has a significant amount of vitamins such as carotene, vitamins A, K, B1, B2, B5, C, B12, and folic acid. It is a source of amino acids like ammonia, serine, lysine, alanine, threonine, tryptophan, valine, lysine, methionine, phenylalanine, and isoleucine and minerals (Mg, Ca, P, Zn, Cu, Fe, Co, Mn, etc.) [14]. According to Sarkar [22], kefir contains at least 6% sugars, 3.5% fat, 3% proteins, and 0.7% ash, but the most abundant part is the moisture which represent 90%. Based to research, lysine is the most prevalent essential amino acid (376 mg/ 100 g), whereas tryptophan is the least abundant (70 mg/100 g) [23]. The primary by-products of the lactic fermentation process are lactic acid, CO₂, and ethanol. Aldehydes, traces of acetone, isoamyl alcohol, formic, propionic, and succinic acids, as well as a number of folates, are also present in kefir. Kefir’s pH ranges from 4.2 to 4.6; its ethanol concentration is between 0.5 and 2% (v/v); its lactic acid content is between 0.8 and 1% (w/v); and its CO₂ level is between 0.08 and 0.2% (v/v) [21]. Peptides are recognized as a distinct and essential class of molecules produced during milk fermentation, accounting for a large portion of the health advantages of fermented milk products [24]. Experiments on Tibetan kefir enabled the purification of a peptide F3 with antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [25]. As per to Ebner et al. [26] studies, they were identified 236 peptides in bovine kefir produced from casein proteolysis and they were shown to have antibacterial, antioxidant, angiotensin-converting enzyme (ACE)-inhibitory, immunomodulatory, and antithrombotic properties. As well as that, they reported 35 peptides in bovine milk kefir that have an antihypertensive impact via ACE inhibition [27]. In addition to its chemical composition, the fermentation process increases the nutritional value of kefir by producing additional bioactive compounds such catechin, vanillin, ferulic acid, and salicylic acid [24]. Moreover, Kefir is a suitable alternative for lactose-intolerant people, or those who cannot digest large amounts of lactose, the main sugar in milk. The fermenting process reduces the lactose level of kefir while increasing the-galactosidase concentration [28]. As stated by altay et al. [29] researches, the presence of biogenic amines in kefir samples was caused by LAB activity. All samples included putrescine, cadaverine, and spermidine, whereas tyramine was discovered to be an abundant biogenic amine. High levels of biogenic amines are linked to the deterioration of fermented milk’s sensory characteristics and are regarded as an essential measure of quality and acceptability. The presence of a high concentration of bioactive amines

in fermented food is associated with an unpleasant bitter taste [30]. Despite the detailed characterization of kefir grains, a significant challenge lies in the profound variability of their microbial composition, which is highly dependent on geographical origin, substrate, and propagation techniques. This heterogeneity directly impacts the consistency of the final product's nutritional and bioactive profile, posing a major hurdle for industrial standardization and reproducible health outcomes. Future research should focus on standardizing fermentation protocols and correlating specific microbial consortia with defined health benefits to ensure product efficacy and reliability.

Kefir a powerful probiotic

Probiotics are live microbial dietary supplements that benefit the host by enhancing microbial equilibrium [14]. Probiotics are widely used as bio-ingredients in many functional fermented foods, and their beneficial benefits on human health and nutrition are continually growing [31]. By promoting the release of soluble factors or the generation of Short-Chain Fatty acids (SCFAs), probiotics may reduce the development of pathogenic bacteria, strengthen the gut's defences against pathogen invasion, enhance epithelial barrier function, or treat disease processes [32]. The genus *Bifidobacterium* and the diverse group of LAB (*Lactobacillus*, *Enterococcus*) are the most often utilized probiotic bacteria; nevertheless, in recent years, yeasts and other microorganisms have also been explored as possible probiotics [31]. Probiotics must be alive in order to build a symbiotic equilibrium in the host's digestive tract, emphasizing the relevance of microbial viability throughout gastrointestinal transit, particularly in the case of oral delivery [33]. Microbial survival rate is affected by treatment regimen, hence the use of symbiotic matrices for probiotic application and microbial viability maintenance has grown in importance [34]. Probiotic bacteria are susceptible to a variety of physicochemical stressors, including pH, acidity, temperature, and preservatives [35]. One of the most popular probiotics and a potent nutritional is kefir. Microorganisms develop in kefir grains, producing enzymes and other biogenic components that cause physicochemical changes in the environment. As a result, kefir has been increasingly used for medicinal purposes, as it has a high concentration of natural probiotics and is easily digestible [33]. Farnworth [36] claims that kefir is consumed daily in many hospitals in Russia because it is regarded as a "general health promoter," works well to recover from digestive diseases, and is advised for mothers to consume during weaning. Furthermore, they demonstrated that some bacteria isolated from kefir were resistant to bile and low pH conditions and could cling to intestinal epithelium [37]. Additionally, research conducted by Xie et al. [20] have shown that yeasts included in kefir increase LAB aggregation and adherence to epithelial cells; they also improve LAB gastrointestinal tolerance. Kefir grains can be considered as a natural repository of safe and definitely probiotic strains due to their diverse microbiota [4].

Molecular mechanisms of kefir's bioactivity

A comprehensive understanding of kefir's health benefits requires elucidating its molecular mechanisms of action, which operate through a complex interplay of microbial and host pathways. The modulation of the gut microbiota is a foundational event; kefir's probiotics and their metabolites, particularly short-chain fatty acids (SCFAs) like butyrate, promote a beneficial microbial community enriched in *Bifidobacterium* and *Lactobacillus* species. Butyrate, in turn, serves as a primary energy source for colonocytes, strengthening intestinal barrier

function by upregulating tight junction proteins, thereby reducing endotoxemia and systemic inflammation [38]. Concurrently, kefir's immunomodulatory effects are initiated when its structural components, such as exopolysaccharides and peptides, act as ligands for innate immune receptors like Toll-Like Receptors (TLRs) on antigen-presenting cells. This interaction primarily modulates the **NF- κ B signaling pathway**, leading to a calibrated cytokine response that enhances defense mechanisms while curtailing excessive inflammation [39]. In oncology, kefir's antiproliferative properties extend beyond apoptosis induction to involve the regulation of critical cell signaling pathways. Bioactive compounds in kefir have been shown to inhibit the PI3K/AKT/mTOR pathway, a central driver of cell survival and growth, while simultaneously activating tumor suppressor pathways like p53 and stress-related MAPK pathways, collectively inducing cell cycle arrest and apoptosis in malignant cells [40]. Furthermore, the gut-brain axis serves as a critical conduit for kefir's neuroprotective effects. Kefir-associated microbes influence central nervous system function by producing neurotransmitters (e.g., GABA, serotonin), modulating the Hypothalamic-Pituitary-Adrenal (HPA) axis to reduce cortisol levels, and sending vagal nerve signals that decrease neuroinflammation, thereby improving cognitive function and emotional regulation [41]. These interconnected molecular pathways underscore kefir's role as a potent modulator of host physiology at a systemic level.

Biological properties of Kefir

Consumers nowadays prefer food with functional characteristics that can improve their health. The notion of "functional foods" has influenced consumer views of healthful foods [42]. That's why researches on the advantages of kefir are getting deeper. Indeed, the diverse microbial consortium of kefir grains is responsible for the large number of metabolites generated, which contribute to a variety of health-promoting benefits (Figure 2) [43].

Antimicrobial effect of kefir

Kefir's antibacterial effects are due to a variety of parameters, including nutritional competition and the intrinsic activity of organic acids, H₂O₂, acetaldehyde, CO₂, and bacteriocins created during the fermentation process [44]. Obviously, Golowczyk et al. [37] confirmed that the kefir grain-isolated *Lactococcus lactis* strain DPC3147 generated a bacteriocin known as lacticin 3147 that was antimicrobial against *Escherichia coli*, *Listeria monocytogenes*, *Salmonella typhimurium*, and *Salmonella enteritidis*. Additionally, Bacteriocin F1, an antimicrobial peptide isolated from Tibetan kefir and composed of 18 amino acids, displayed bacteriostatic activity against *Escherichia coli* at 62.5 g/mL. The antibacterial action is mediated through *E. coli* cell outer and inner membrane permeability. Bacteriocin F1 has the extra benefit of being resistant to heat, pH, and protease treatment, implying its use in food preservation [25]. Moreover, *Lactobacillus plantarum* C4 isolated from kefir protects against *Yersinia enterocolitica* infection of the intestine [24]. Ismail et al. [45] demonstrated that kefir suspension had a greater inhibitory activity against *Streptococcus faecalis* and *Fusarium graminearum*. Thus, Kefir concentrations ranging from 7 to 10% (w/w) were able to totally block *Aspergillus flavus* sporulation and, as a result, aflatoxin B1 synthesis, demonstrating kefir's antifungal effects against filamentous fungi. This is explained by the fact that organic acids are formed during the fermentation of kefir, which can change the aflatoxin B1 molecule, turning it into less dangerous forms such as aflatoxicol and aflatoxin B, and

B2a. In this context, kefir looks to be a safe food preservation option, giving protection against aflatoxin B1 toxicity [21].

Anti-inflammatory effect of kefir

Complications of neuroinflammatory illnesses and inflammation in chronic conditions are the leading causes of morbidity and death worldwide. Growing data from both in vitro and in vivo research has demonstrated significant antiinflammatory and immunomodulatory potentials, with kefir therapy demonstrating an increase in anti-inflammatory mediators while decreasing pro-inflammatory cytokines [11]. Rosa et al. [46] discovered that administering kefir for a duration of ten weeks led to a decrease in the expression of the inflammatory cytokine IL-1 in adipose tissue. Simultaneously, it increased the expression of the anti-inflammatory cytokine IL-10 and lowered the levels of oxidative markers such as malondialdehyde (MDA) and hydroperoxides. Furthermore, in this study, they were discovered that the freeze-dried extract of Tibetan kefir polysaccharide exhibited potent inhibition of the hyaluronidase enzyme. Moreover, Kefiran has demonstrated the ability to scavenge nitric oxide, similar to quercetin, a well-known antioxidant [46].

Exopolysaccharide treatment generated by *Lactobacillus kefiranofaciens*, to mice triggered a mucosal response in the gut by enhancing IgA production in small and large intestines, as well as promoting systemic immunity through the generation of cytokines in the intestinal fluid and blood serum [47]. Several in vivo studies have also revealed that kefir peptides have potent immunostimulant properties. In NF- κ B luciferase+/+ transgenic mice, kefir peptides generated from kefir grain fermentation with milk proteins were reported to have anti-inflammatory effects on PM4.0-induced lung inflammation. Thus, they found a decrease in PM4.0-induced inflammatory cell infiltration and the generation of inflammatory mediators such as TNF-, IL-1, and IL-4 in lung tissue. This was accomplished by inhibiting NF- κ B signalling [48].

Antioxidant activity of kefir

Antioxidants act as scavengers of free radicals. They protect the body from damage caused by unstable molecules or free radicals created by stress and other environmental forces. Kefir exhibits robust antioxidant activity. For instance, research has shown that kefir has the ability to scavenge free radicals, such as DPPH and superoxide radicals, and inhibit lipid peroxidation. Moreover, consumption of kefir increases the level of glutathione peroxidase and reduces the level of malondialdehyde, which are involved in controlling oxidative stress [14]. According to Yilmaz-Ersan et al. [49] indicated that kefir samples fermented with kefir grains demonstrated superior antioxidant effectiveness, as assessed through DPPH and ABTS assays, compared to kefir samples fermented with starter cultures. Likewise, the exopolysaccharide isolated from Tibetan kefir grains during milk fermentation exhibited substantial antioxidant activities in vitro. Additionally, it provided protection to proteins from oxidative damage in a concentration-dependent manner [50]. The research conducted by Ghoneum and Felo [51] which based on the evaluation of the antioxidant properties of a *Lactobacillus kefir* (PFT) in oxidative stress-induced rats aged 10 months; they revealed that the consumption of PFT resulted in a notable increase in the activities of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Additionally, PFT led to a reduction in oxidative stress biomarkers including nitric oxide and malondialdehyde, and a reversal of decreases in total antioxidant capacity, glutathione levels,

and anti-hydroxyl radical content.

Anticancer properties of kefir

Recent investigations have revealed promising anticancer properties of kefir and its bioactive compounds. The antiproliferative effects of kefir are attributed to multiple mechanisms, including apoptosis induction, cell cycle arrest, and inhibition of metastatic potential. *Lactobacillus kefir* P-IF, isolated from Turkish kefir grains, demonstrated significant cytotoxic activity against human colon cancer cells (HT-29) through the induction of apoptosis and G0/G1 cell cycle arrest [6]. Furthermore, kefiran, the primary exopolysaccharide of kefir grains, exhibited selective cytotoxicity against various cancer cell lines while showing minimal toxicity to normal cells [52]. The peptides derived from kefir fermentation have also shown remarkable anticancer potential. Studies by Wang et al. [53] identified specific bioactive peptides that demonstrated anti-proliferative effects against breast cancer cells (MCF-7) and cervical cancer cells (HeLa). The mechanism involves the modulation of pro-apoptotic and anti-apoptotic gene expression, leading to programmed cell death in malignant cells [54]. Additionally, recent research has highlighted the role of kefir in enhancing the efficacy of conventional chemotherapy while reducing its adverse effects, suggesting potential applications as an adjuvant therapy in cancer treatment [55].

Metabolic health benefits

Glycemic control and diabetes management

The impact of kefir consumption on glucose metabolism has gained considerable attention in recent years. Clinical studies have demonstrated that regular kefir consumption significantly improves glucose tolerance and insulin sensitivity in both healthy individuals and patients with type 2 diabetes mellitus. The mechanism involves the modulation of incretin hormones, particularly Glucagon-Like Peptide-1 (GLP-1), which enhances insulin secretion and delays gastric emptying [56]. A randomized controlled trial conducted by Ostadrahimi et al. [57] showed that 8-week consumption of probiotic kefir significantly reduced fasting blood glucose, hemoglobin A1C, and improved insulin resistance in patients with type 2 diabetes. The beneficial effects were attributed to the diverse probiotic strains present in kefir, particularly *Lactobacillus casei* and *Lactobacillus acidophilus*, which modulate gut microbiota composition and enhance short-chain fatty acid production [58].

Lipid profile modulation

Kefir consumption has been consistently associated with favorable changes in lipid metabolism. Multiple studies have reported significant reductions in total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, and triglycerides, accompanied by increases in High-Density Lipoprotein (HDL) cholesterol [59]. The cholesterol-lowering (hypocholesterolemic) properties of kefir are mediated through three primary and interconnected biological mechanisms. First, certain probiotic bacteria within kefir have the ability to bind to bile acids in the intestine. Since bile acids are synthesized from cholesterol, their increased excretion forces the liver to draw upon existing cholesterol reserves to produce new bile acids, thereby reducing circulating cholesterol levels [60]. Second, the fermentation process generates specific bioactive metabolites, which can inhibit the activity of HMG-CoA reductase, the rate-limiting enzyme in the endogenous cholesterol synthesis pathway in the liver [61]. Finally, the fermentation of dietary fibers by kefir's probiotics

produces Short-Chain Fatty Acids (SCFAs), particularly propionate. Upon absorption, propionate travels to the liver where it further suppresses hepatic cholesterol synthesis [62]. Thus, kefir acts through a synergistic combination of enhancing cholesterol excretion, directly inhibiting its production, and modulating hepatic metabolic pathways. Recent meta-analyses have confirmed that kefir consumption leads to a mean reduction of 7-12% in total cholesterol and 8-15% in LDL cholesterol, with effects becoming apparent after 4-8 weeks of regular consumption [63].

Cardiovascular health effects

The cardiovascular benefits of kefir extend beyond lipid profile improvements. Kefir consumption has been associated with significant reductions in blood pressure, particularly in individuals with hypertension. The antihypertensive effects are primarily attributed to Angiotensin-Converting Enzyme (ACE) inhibitory peptides generated during milk protein fermentation [64]. Recent studies have identified specific bioactive peptides in kefir with potent ACE inhibitory activity, including peptides derived from β -casein and κ -casein hydrolysis. These peptides demonstrate IC50 values ranging from 0.15 to 2.8 mg/mL, indicating strong antihypertensive potential [65]. Additionally, kefir consumption improves endothelial function through enhanced nitric oxide production and reduced oxidative stress, contributing to overall cardiovascular health [66].

Neuroprotective properties

Emerging research illuminates the significant neuroprotective potential of kefir, primarily mediated through its influence on the gut-brain axis. The mechanisms by which kefir's probiotics confer these benefits are multifaceted. Firstly, specific bacterial strains present in kefir are capable of producing key neurotransmitters, such as GABA, serotonin, and dopamine, which can directly modulate neuronal excitability and mood [67]. Furthermore, kefir consumption contributes to a reduction in systemic and neuroinflammatory markers, thereby creating a less hostile environment for neurons and mitigating damage associated with inflammation [68]. A third critical pathway involves the strengthening of the Blood-Brain Barrier (BBB); probiotics enhance its integrity and reduce permeability, which protects the brain from circulating toxins and inflammatory agents [69]. Collectively, these interconnected pathways neurotransmitter production, anti-inflammatory action, and BBB fortification, underscore kefir's promising role in supporting brain health and preventing neurological decline. Recent animal studies have demonstrated that kefir consumption improves cognitive function, reduces anxiety and depression-like behaviors, and provides protection against neurodegenerative diseases. The neuroprotective effects are mediated through the modulation of microglial activation, reduction of pro-inflammatory cytokines, and enhancement of Brain-Derived Neurotrophic Factor (BDNF) expression [70]. Furthermore, Tanure et al. [71] demonstrated that kefir peptides significantly improved memory performance and reduced neuroinflammation in aged mice models.

Recent innovations in kefir production and processing

Novel fermentation substrates

Recent research has explored the use of alternative substrates for kefir production to enhance nutritional value and expand consumer accessibility. Plant-based milk alternatives, including oat, rice, soy, and almond milk, have been successfully fermented using kefir grains, resulting in vegan-friendly

products with comparable probiotic content [72]. Studies have shown that the fermentation of plant-based substrates by kefir grains produces unique bioactive compounds not found in traditional milk kefir. For instance, oat kefir contains higher levels of β -glucans, which contribute to cholesterol-lowering effects, while soy kefir is enriched with isoflavones that exhibit estrogenic and antioxidant activities [73]. Moreover, Randazzo et al [74] demonstrated that coconut milk kefir showed enhanced antimicrobial properties compared to traditional milk kefir (Figure 3).

Microencapsulation technologies

Microencapsulation has emerged as a pivotal strategy to enhance the viability of kefir probiotics, which are often vulnerable to the harsh conditions encountered during industrial processing and storage. This technology functions by entrapping the sensitive microorganisms within protective matrices, effectively shielding them from detrimental factors such as low pH, high temperatures, and oxygen exposure. Significant advances have been made in refining these techniques. For instance, alginate-based encapsulation has proven highly effective in significantly improving the survival rates of specific strains like *Lactobacillus kefir* when subjected to simulated gastric fluids [75]. Similarly, the spray-drying technique, when optimized with protective compounds like whey proteins or maltodextrins, enables the production of stable kefir powders with markedly higher probiotic viability [76]. Furthermore, coacervation methods, which involve the phase separation of polymers, provide superior control over the release of bacteria and enhance the retention of their bioactive metabolites throughout the manufacturing process [77]. Collectively, these microencapsulation technologies are crucial for ensuring that the health-promoting, live probiotics in kefir reach the consumer in a viable and active state.

Functional ingredient fortification

Contemporary food science research is increasingly focused on the strategic fortification of kefir to amplify its intrinsic health benefits and create advanced functional foods. This approach involves supplementing kefir with bioactive ingredients that work synergistically with its native probiotics and metabolites. A key area of investigation is the incorporation of prebiotic fibers such as inulin, fructooligosaccharides (FOS), and Galactooligosaccharides (GOS), which selectively stimulate the growth and activity of kefir's beneficial microorganisms, creating a potent synbiotic product [78]. Furthermore, to significantly boost kefir's antioxidant capacity, studies have successfully enriched it with plant-based extracts from sources like green tea, turmeric, and berries, which provide concentrated phenolic compounds that help combat oxidative stress [13]. For enhanced natural preservation and potential antimicrobial health benefits, essential oils from oregano, thyme, and rosemary have been integrated, leveraging their potent bioactive properties [79]. Lastly, some research explores the direct addition of exogenous bioactive peptides, which can further augment kefir's profile with targeted benefits such as improved antihypertensive or immune-modulatory effects [80]. Through these fortification strategies, kefir is transformed from a probiotic beverage into a tailored nutritional vehicle designed to address specific health and wellness needs.

Clinical applications and therapeutic potential

Gastrointestinal disorders

The therapeutic potential of kefir is increasingly supported by clinical evidence, particularly in the management of gas-

gastrointestinal disorders. Systematic reviews of randomized controlled trials substantiate its efficacy, demonstrating significant benefits across a spectrum of conditions. For individuals with Irritable Bowel Syndrome (IBS), kefir consumption has been associated with a notable reduction in symptom severity scores and an improved quality of life [81]. In the context of Inflammatory Bowel Disease (IBD), clinical studies indicate that kefir can contribute to decreased systemic inflammatory markers and support mucosal healing [82]. Furthermore, kefir serves as an effective adjunct therapy for antibiotic-associated diarrhea, not only accelerating recovery time but also reducing the incidence of severe complications like *Clostridioides difficile* infections [83]. Its well-established role in alleviating lactose intolerance symptoms, by improving lactose digestion through its microbial lactase activity, further underscores its digestive benefits [84]. These multifaceted therapeutic effects are primarily mediated through kefir's ability to restore a healthy balance of the gut microbiota, enhance the integrity of the intestinal barrier, and modulate local immune responses, collectively promoting gastrointestinal homeostasis.

Immune system modulation

A growing body of immunological research indicates that regular consumption of kefir contributes to a robust and balanced immune system by modulating both innate and adaptive immune responses. The probiotics and metabolites present in kefir interact with the Gut-Associated Lymphoid Tissue (GALT), which houses a significant portion of the body's immune cells, leading to systemic effects. Key mechanisms include the enhancement of innate immunity through the activation of macrophages, boosting their phagocytic capacity to clear pathogens and their production of key signaling molecules called cytokines [21]. Furthermore, kefir has been shown to stimulate the activity of Natural Killer (NK) cells, thereby enhancing their ability to identify and destroy virally infected or cancerous cells [85]. On the adaptive immunity front, kefir components help modulate T-cell responses, promoting a balanced interplay between Th1 and Th2 pathways and supporting the activation of regulatory T-cells, which are crucial for preventing excessive inflammation and autoimmune reactions [86]. Finally, a critical line of defense is strengthened at the mucosal level, where kefir intake has been demonstrated to boost the production of secretory immunoglobulin A (sIgA), an antibody essential for neutralizing pathogens at the intestinal barrier [87]. Collectively, these actions enhancing frontline defenses, fine-tuning targeted immune responses, and fortifying the mucosal barrier, underscore kefir's significant potential as a dietary modulator of immune function.

Current challenges and limitations

Despite the promising evidence supporting kefir's health benefits, several significant challenges and limitations must be addressed to translate traditional knowledge into evidence-based applications and standardized products. A critical analysis of the current literature reveals key areas requiring further investigation and innovation.

Limitations of existing studies and standardization hurdles

A primary limitation hindering the validation of kefir's effects is the scarcity of large-scale, long-term, Randomized Controlled Trials (RCTs) in human populations. Many claims are based on in vitro studies or animal models, which do not always directly translate to human physiology. Furthermore, a major

confounding factor across studies is the profound variability in the microbial composition of kefir grains, which is influenced by geographical origin, substrate, and propagation methods. This heterogeneity leads to inconsistent compositional profiles of the final beverage, making it difficult to compare results between studies and establish causal links between specific microbial strains or metabolites and observed health outcomes. Future research must prioritize the precise molecular characterization of the kefir used in clinical interventions, reporting detailed metagenomic and metabolomic data to ensure reproducibility and reliability.

Technical and industrial challenges

The industrial-scale production of kefir with guaranteed probiotic viability and consistent quality remains a challenge. The preservation of live microorganisms during processing, storage, and gastrointestinal transit is difficult. While microencapsulation technologies offer promising solutions, they face their own limitations, including potential alterations to the sensory properties of the final product, scalability issues, and increased production costs [88]. Developing cost-effective encapsulation methods that robustly protect probiotics without compromising consumer acceptance is a key area for future technological development.

Safety and regulatory considerations

The artisanal nature of kefir grains, while advantageous for microbial diversity, raises questions regarding the safety of uncharacterized microbial strains, particularly for immunocompromised individuals. Although kefir has a long history of safe consumption, rigorous safety assessments for specific autochthonous strains are necessary. Moreover, the regulatory landscape for health claims associated with fermented foods is complex. Obtaining authorized health claims from bodies like the European Food Safety Authority (EFSA) or the U.S. Food and Drug Administration (FDA) requires a high level of scientific evidence, which is currently limited for kefir due to the aforementioned standardization issues [89].

Conclusion and future perspectives

Kefir represents a remarkable example of how traditional fermented foods can contribute to modern healthcare through their complex microbiological compositions and diverse bioactive compounds. The extensive research conducted over the past decade has firmly established kefir's potential as a functional food with significant therapeutic applications. The growing body of evidence supporting kefir's health benefits, coupled with increasing consumer awareness of the gut-health connection, positions kefir as a key player in the functional food market. However, several challenges remain, including standardization of production methods, quality control measures, and the need for well-designed clinical trials to establish optimal dosing regimens and treatment protocols.

Future research should focus on elucidating the mechanisms underlying kefir's health effects, developing standardized production methods, and conducting large-scale clinical trials to establish evidence-based therapeutic applications. The integration of omics technologies, including genomics, proteomics, and metabolomics, will provide deeper insights into kefir's mode of action and facilitate the development of next-generation probiotic products.

As our understanding of the human microbiome continues to evolve, kefir's role in maintaining and restoring microbial balance will likely expand, positioning this ancient fermented beverage as a cornerstone of modern preventive and therapeutic nutrition. The convergence of traditional knowledge and modern scientific methods promises exciting developments in kefir research, with potential applications extending far beyond conventional nutritional supplementation.

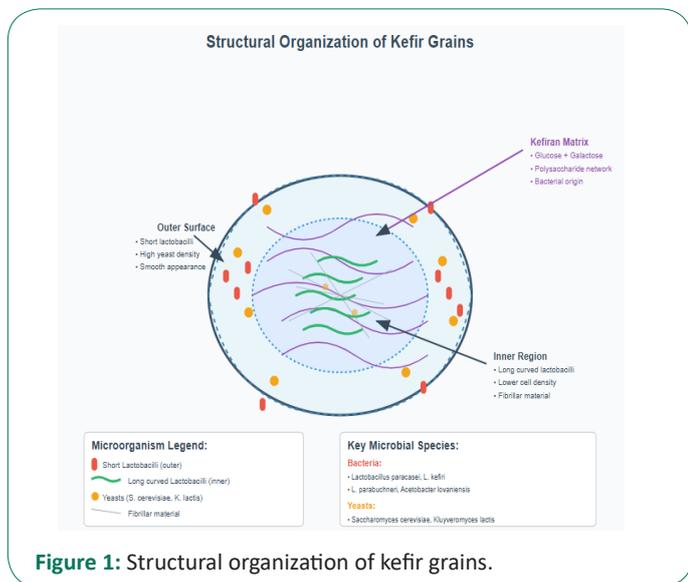


Figure 1: Structural organization of kefir grains.



Figure 2: Biological activities of kefir.

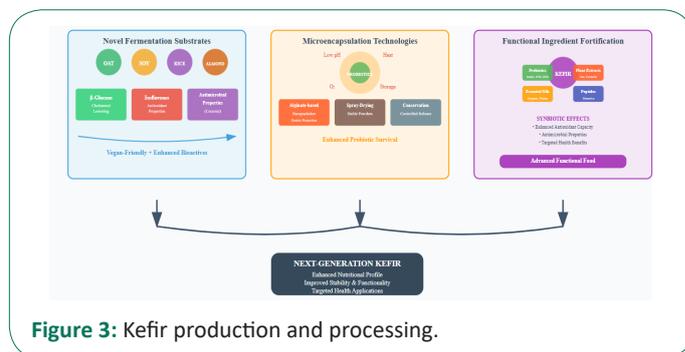


Figure 3: Kefir production and processing.

Table 1: Nutritional composition and bioactive properties of milk kefir.

	Proteins	~3%	-	Sarkar (2008)
	Lipids	~3.5%	-	Sarkar (2008)
	Carbohydrates	≥ 6%	-	Sarkar (2008)
	Ash	~0.7%	-	Sarkar (2008)
Vitamins and Minerals	Vitamins (A, K, B1, B2, B5, C, B12, Carotene, Folic Acid)	Variable	Nutritional Value	Sharifi et al. (2017)
	Minerals (Mg, Ca, P, Zn, Cu, Fe, Co, Mn)	Variable	Nutritional Value	Sharifi et al. (2017)
Essential Amino Acids	Lysine	376 mg/100g	Most abundant essential amino acid	Liutkevičius and Šarkinas (2004)
	Tryptophan	70 mg/100g	Least abundant essential amino acid	Liutkevičius and Šarkinas (2004)
	Other EAA*: Serine, Alanine, Threonine, Valine, Methionine, Phenylalanine, Isoleucine	Variable	-	Sharifi et al. (2017)
Physicochemical Parameters	pH	4.2-4.6	-	Rosa et al. (2017)
	Lactic acid	0.8-1% (w/v)	Fermentation product	Rosa et al. (2017)
	Ethanol	0.5-2% (v/v)	Fermentation product	Rosa et al. (2017)
	CO ₂	0.08-0.2% (v/v)	Fermentation product	Rosa et al. (2017)
	Lactose	-	Improved digestibility (lactose intolerance)	Arslan (2015)
	β-galactosidase	-	Lactose hydrolysis	Arslan (2015)
Bioactive Peptides	Peptide F3 (Tibetan Kefir)	ND	Antibacterial activity (E. coli, S. aureus)	Miao et al. (2016)
	β-casein-derived peptides	236 identified peptides	Antibacterial, Antioxidant, ACE-inhibitory, Immunomodulatory, Antithrombotic	Ebner et al. (2015)
	Antihypertensive peptides	35 identified peptides	ACE inhibition	Amorim et al. (2019)
Phenolic Compounds	Catechin, Vanillin, Ferulic acid, Salicylic acid	Products of fermentation	Antioxidant activity	Farag et al. (2020)

Biogenic Amines	Putrescine, Cadaverine, Spermidine	ND	Products of LAB metabolism	Altay et al. (2013)
	Tyramine	Most abundant amine	Quality indicator; bitter taste at high concentrations	Altay et al. (2013); Takahashi and Kohno (2016)
Other Metabolites	Aldehydes, Acetone, Isoamyl alcohol	Traces	Volatile aromatic compound	Rosa et al. (2017)
	Organic acids (Formic, Propionic, Succinic)	Variable	Fermentation products	Rosa et al. (2017)
	Folates	Variable	Nutritional value	Rosa et al. (2017)

Declarations

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