Review Article

Hepatoprotective Properties of Water Kefir: A Traditional Fermented Drink and Its Potential Role

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Abstract

The liver is extremely vulnerable to damage because of its role in metabolism. Toxin, metabolic syndrome, alcohol, microorganisms, and autoimmune diseases can be the cause of liver damage. While different etiologies can cause liver disease, pathophysiologically, there are similarities in the role of free radicals, inflammatory mediators, and gut microbiome during the disease development. Therefore, ingredients with antioxidant, antiinflammatory, and antidysbiotic properties have the potential to act as hepatoprotectors; and water kefir is one of them. Water kefir is a traditional fermented drink made from water kefir grains, sugar, and dried fruit. Water kefir is dominated by lactic acid bacteria and yeast as a fermented beverage, and several species of this group of microorganisms have been shown as probiotics. According to researches, water kefir has strong antioxidant, antiinflammatory, and hepatoprotective effects. Even so, there are still few researches reported about water kefir as a hepatoprotective agent. Several studies, on the other hand, showed promising results. This review discusses the relationship between the pathophysiology of liver disease and the pharmacological activity of water kefir and other probiotics in general, which leads to the potential prospect of water kefir research as a hepatoprotective agent.

Keywords: *Antioxidant, hepatoprotector, inflammation, probiotic, water kefir*

Introduction

The liver is the largest visceral organ in the human body, accounting for 2–5% of an adult's weight.[1] The liver's primary function is to absorb, store, and deliver nutrients to other organs. When performing its functions, it also absorbs potentially harmful substances such as drugs, microorganisms, or bacterial products distributed by portal blood.[2] As a result, the liver is extremely vulnerable to hepatotoxic substance damage.

The global burden of mortality and disease includes liver disease.[3] The centers for disease control and prevention (CDC) states that approximately 1.8% of adults, or 4.5 million, were diagnosed with liver disorders in 2018. Every year, approximately 2 million people die as a result of liver disease, 1 million as a result of cirrhosis complications, and 1 million of hepatocellular carcinoma and viral hepatitis. When it comes to leading causes of mortality, cirrhosis comes in at number 11, while liver cancer comes in at number 16, accounting for about 3.5 percent of all deaths. Cirrhosis is one of the 20 most serious health problems in the world, resulting in disability-adjusted life years and years of life lost totaling 1.6% and 2.1% of the global burden. Over 75 million people suffer from alcohol use disorder and are at risk of developing liver disease. Over 2 billion adults are overweight or obese, with more than 400 million in diabetics; both of which are risk factors for hepatocellular carcinoma and non-alcoholic fatty liver disease. The global burden of viral hepatitis keeps on increasing, and drug-induced liver disease remains to be the major cause of acute hepatitis.[4]

The Caribbean, Latin America, North Africa, and the Middle East have the highest regional percentages of deaths from liver disease, while East Asia and the Pacific, Egypt, Mongolia, Moldova, and South Asia have the highest number of deaths. Because of its large population, India is responsible for one-fifth (18.3%) of all cirrhosis deaths worldwide, while China accounts for 11%. Deaths are increasing in Central Asian countries and Russia, while in Europe, deaths increased in the UK but decreased in Italy and France. Cirrhosis affects men more than women worldwide, though the ratio

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is nearly equal in Moldova and Russia.[5] Cirrhosis causes differ by region. In industrialized countries and Western, alcoholic and non-alcoholic fatty liver diseases are more prevalent than viral hepatitis; however, in China and other Asian countries, hepatitis B remains the leading cause.[6] In Mongolia, hepatitis B and C viruses cause 99% of cases of cirrhosis, and 20% of patients are co-infected with both. Chronic liver disease and cirrhosis are the 12th main cause of death in the United States, and the fourth major cause of death in patients aged 45–64 years.[7]

Treatment for cirrhosis is based on the etiology and severity of liver damage. Cirrhosis symptoms and complications can be prevented or treated with therapy aimed at slowing the progression of liver scar tissue. The high number of people suffering from liver disorders, as well as the fatal consequences of this disease, are not matched by the treatment available to overcome them. Natural and herbal therapies are frequently used by patients due to their potential for hepatoprotection. According to a survey conducted in the United States, 41% of patients with liver disease used complementary and alternative medicine. The most commonly used herbs for the liver disease were milk-thistle seed extract (silymarin) and garlic, followed by ginseng, green tea, ginkgo, echinacea, and St. John's wort. However, liver transplantation is still the standard of care for end-stage liver disease patients. But until now, donor liver availability has remained a major issue.[8]

Pathophysiologically, it is known that, while different etiologies can cause liver disease, there are similarities in the role of free radicals, inflammatory mediators, and gut microbiota during the development process. As a result, ingredients with antioxidant, antiinflammatory, and antidysbiotic properties have the potential to act as hepatoprotectors, and water kefir is one of them. Water kefir had a strong antioxidant effect with an IC_{50} of 92.65 ppm and showed antiinflammatory activity.[9] Another study concluded that water kefir had the potential as an antioxidant[10] and as a hepatoprotector against paracetamol-induced liver damage.[11,12] Water kefir is made up of a complex biofilm formed by various symbiotic bacteria and yeasts on the surface of the polysaccharide dextran matrix, a polymer of 1–6 linked glucose.[13] The microorganism composition in water kefir has been studied.[14-17] Compared to other fermented products such as milk kefir or yoghurt, research on water kefir is still in its infancy. However, the health benefits of drinking water kefir have been empirically supported by centuries of human consumption. Thus far, the following pharmacological effects of water kefir have been investigated: gastroprotective, antioxidant, antihyperglycemic, hepatoprotective, and antiinflammatory.[9-12,18] Due to the lack of a review article on this subject, the objective of this review article was to explore the theoretical potential of water kefir as a hepatoprotective agent using studies on water kefir or its microorganisms.

Patophysiology of Liver Disease

Any disease that affects the liver is referred to as liver disease.[19] This condition is characterized by jaundice, coagulopathy, and hepatic encephalopathy (HE), followed by multiorgan failure.[20] Acute and chronic liver disease can be distinguished based on the onset. If the symptom occurs within 6 months, the patient has acute liver disease; but if the symptoms last longer than 6 months, the patient has chronic liver disease.[19] However, this definition is too narrow and does not encompass the entire patient population. Acute liver failure is currently defined as a condition in which an acute liver attack results in rapid clinical deterioration, with HE occurring within 26 weeks following the first symptoms of liver dysfunction (jaundice). If HE occurs 26 weeks or more after the occurrence of liver disease symptoms, it is considered as chronic liver disease.[20]

Chronic liver disease can be caused by alcohol, metabolic syndrome, hepatitis B or C viruses, or the presence of autoimmune diseases.[21] The first possible response is inflammation (hepatitis), followed by fat changes (steatosis), or both (steatohepatitis). At this stage, the liver can still regenerate, and the condition is potentially reversible. However, if the underlying issue of liver damage is not addressed, the damage can develop into fibrosis and, eventually, liver cirrhosis.[19]

As shown in Figure 1, when there are damaged or apoptotic hepatocytes, HSCs are activated. The main pathway that can activate HSCs is the release of reactive oxygen species and fibrogenic mediators, as well as immune system stimulation. Damaged hepatocytes and Kupffer cells stimulate the release of reactive oxygen species, which play a role in HSCs activation and inflammatory cell recruitment. These reactive oxygen species can also cause the release of cytokines such as tumor necrosis factor alpha (TNF-α), which can cause inflammation and apoptosis. Because activated HSCs can secrete inflammatory chemokines, a vicious circle develops in which fibrogenic and inflammatory cells stimulate each other, promoting the process of liver damage and repair. Fibrogenic mediators are substances produced by other cells that can activate HSCs. Kupffer cells, hepatocytes, epithelial cells, sinusoidal endothelial cells, platelets, and neutrophils are examples of those cells. The main fibrogenic mediators are platelet-derived growth factor and transforming growth factor beta (TGF-β); other mediators include monocyte chemotactic protein type, endothelin, angiotensin, and adipokines such as leptin, TNF-α, TGF-β, TIMP-1, collagen 1, and integrins.[21-23]

Cirrhosis occurs when liver fibrosis becomes so severe that the architecture of the liver changes. As cirrhosis progresses, scar tissue substitutes normal hepatocytes. The appearance of the liver becomes nodular, disrupting the free flow of blood to all parts of the liver and reducing the

liver's ability to perform its functions.[19] Cirrhosis develops from healthy liver tissue after about 15–20 years, with an increase in ECM of up to 6 times that of normal liver.[21]

The pathophysiology of acute liver disease is determined by its etiology. Acetaminophen hepatotoxicity, a well-known pathophysiology of acute liver disease, caused by excessive amounts of the metabolite N-acetyl-para-benzo-quinone imine (NAPQI). NAPQI, a highly toxic and reactive compound, is a byproduct of acetaminophen metabolism via the CYP 2E1 cytochrome pathway. NAPQI will be detoxified by glutathione, a naturally occurring antioxidant. When the level of acetaminophen is excessive, the production of NAPQI also increases, resulting in a decrease in glutathione production, mitochondrial oxidative stress, and hepatocellular necrosis.[20,24]

The pathophysiology of liver disease is also linked to a dysbiosis or composition imbalance of the gut microbiome.[25-27] The gut microbiome's qualitative (imbalance between harmful and beneficial microbiomes) and quantitative (change in total microbiota) effects on liver health. These changes have the potential to alter the composition of microbiota-produced products such as short-chain fatty acids and bile acids.[25] Dysbiosis can also induce intestinal inflammation, intestinal barrier damage, and microbial product translocation.[28]

Hepatoprotective Potential of Water Kefir

Water kefir is a traditional fermented drink made from water kefir grains, sugar, and dried fruit. The exact origin of water kefir is unknown, but two theories have been proposed: the first is that water kefir grains were brought to Europe from the Caucasus by soldiers returning from the Crimean war in the late nineteenth century[29], and the second is that water kefir grains formed naturally from the Opuntia cactus in Mexico.[30] Water kefir is also known as Tibi grains, Ginger beer plant, African bees, California bees, Balm of Gilead, Ale nuts, Sugary kefir grains, or Japanese beer seeds.[30-32]

Water kefir is made up of a complex biofilm formed by various symbiotic bacteria and yeasts on the surface of the polysaccharide dextran matrix, a polymer of 1–6 linked glucose.[13] The microorganism composition in water kefir has been studied.[14-17] Different water kefir grain sources may have different microorganism compositions. However, lactic acid bacteria, most of which are Lactobacillus species, such as *Lactobacillus casei/paracasei, Lactobacillus nagelii,* and *Lactobacillus hilgardii*; and yeast, such as *Saccharomyces cerevisiae*, *Dekkera bruxellensis, Hanseniaspora valbyensis, Lachancea fermentati, Zygotorulaspora Florentina,* dominate the microorganism composition of water kefir. There are also Bifidobacteria, such as *Bifidobacterium aquikefiri*, and acetic acid bacteria, such as *Acetobacter fabarum*, in small amounts. In addition to these microorganisms, many unknown microorganisms are thought to be present in the water kefir symbiosis. According to Verce *et al*.[17] (2019), there were novel Oenococcus species and the possibility of novel Lactobacillus species related to *L. hordei* and *L. mali*. Ethanol and lactic acid are the primary metabolites of fermented water kefir, with minor amounts of glycerol, acetic acid, and mannitol. Several aromatic and volatile compounds are also produced, including ethyl hexanoate, ethyl acetate, ethyl octanoate, ethyl decanoate, and isoamyl acetate (relative to their threshold values).[33]

Lactic acid bacteria predominate in most probiotic products, and water kefir is no exception. Several probiotic strains have been shown to be hepatoprotective in animal models. *Lactobacillus plantarum* AR501 improved antioxidant status in hepatic injury mice by increasing the gene expression of nuclear factor erythroid 2-related factor 2 and upregulating several antioxidant genes including glutathione S-transferase (GSTO1), heme oxygenase-1 (HO-1), glutamate cysteine ligase, and NAD (P) H: quinone oxidoreductase-l (NQO1).[34] In alcoholic liver disease animals, *L. paracasei* repairs liver damage by inhibiting TNF-α production and repairing the gut microbiome.[35] In cases of acute liver injury, pretreatment with *L. casei* reduced serum gamma-glutamyltranspeptidase, total bile acids, IL-5, IL-10, G-CSF, and Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES). Intestinal microbiome balance improves as well, resulting in less harmful metabolite production, downregulation of retinol metabolism and Peroxisome Proliferator Activated Receptor (PPAR) signaling, and upregulation of pyruvate metabolic pathways in the liver.[36] As a probiotic, *L. rhamnosus* was able to improve intestinal fatty acid absorption in NAFLD animal models resulting in decreased body weight, body fat mass, and hepatic lipid accumulation.[37] Probiotics' mechanism of action in repairing liver damage is generally due to their antioxidant, antiinflammatory, and antidysbiotic properties. In the case of liver damage, oxidative stress and inflammation are important factors to consider, and they interact with one another.

Water kefir has been shown to have strong antioxidant properties.[9,10] Many studies have shown that lactic acid bacteria had promising antioxidant activity *in vitro*[38–41] and *in vivo*[34,41,42] as shown in Table 1. Several probiotic strains could reduce oxidative stress through various mechanisms. To begin with, antioxidant enzymes like SOD, CAT, and GPx are directly neutralizing oxidants in the intestinal tract. Immune system stimulation may also help to reduce inflammation and protect against oxidative stress caused by cytokines. Inhibiting intestinal pathogens is another method of reducing inflammation and the oxidative damage that goes along with it. Antioxidants and postprandial lipids are linked to oxidative damage and are frequently responsible for a variety of food-related pathologies, and probiotics can increase the absorption of both micro and macronutrients,

Table 1: Antioxidant activity of probiotics

Author (Year)	Bacterial Species	Method	Result
Kleniewska *et al*. (2016)[44]	*Lactobacillus casei* (combined with inulin)	Human plasma was evaluated for catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) activity, and ferric reducing ability of plasma (FRAP) after 7 weeks of treatment.	Synbiotics containing *L. casei* and inulin increased CAT, SOD, and GPx activity. This combination increased the total antioxidant capacity in the study group compared to that of the control group, as shown by plasma FRAP evaluation
Finamore *et al*. (2018)[45]	*Lactobacillus casei* Shirota (LS)	Experiments were carried out using *in vitro* model of enterocytes.	*L. casei* pretreatment of enterocytes prevented membrane disruption and the accumulation of cellular reactive oxygen species (ROS), modulated the expression of the gastrointestinal antioxidant enzyme glutathione peroxidase (GPX2), and reduced phosphorylation of p65, favoring the involvement of the Nuclear Factor-Erythroid-2 (Nfr2) pathway and nuclear factor kappa B in the activation of antioxidant ceruloplasmin
Zhang *et al*. (2017)[46]	*Lactobacillus curvatus* and *Lactobacillus paracasei*	Experiments were carried out using *in vitro* method by measuring the reducing power, DPPH free radical scavenging activity, hydroxyl radical scavenging capacity, antilipid peroxidation, and antioxidase activity.	DPPH• scavenging activity was higher in *L. curvatus* SR6 and *L. paracasei* SR10-1 exhibited higher antilipid peroxidation ability and OH• scavenging activity. The catalase activity of the cell-free extracts was greater than 1.00 U/mL, while the superoxide dismutase activity of the cell culture fluid was greater than 47.00 U/mL.
Chooruk *et al*. (2017)[47]	201 *Lactobacillus* strains	A total of 201 *Lactobacillus* strains were investigated for antioxidant activities: free radical scavenging (DPPH), inhibition of linoleic acid peroxidation (TAALA), superoxide dismutase (SOD), and glutathione (GSH).	Except for *L. oris* and *L. gasseri*, all of the *Lactobacillus* strains tested had strong antioxidative characteristics. *L. fermentum*, *L. paracasei*, and *L. rhamnosus* strains with strong DPPH and TAALA activities (>60%) were found to be more resistant to oxidative stress than *L. salivarius*, *L. oris*, and *L. gasseri* strains.
Livinska *et al*. (2016)[39]	378 strains of LAB isolated from various sources	The strains derived from plant surfaces (phylloplane) were evaluated for their antioxidative activity, polyphenolic and thiol-producing ability, and total antioxidative activity of the screened isolates.	Antioxidant activity was found in 22 strains, with some strains being able to create fenolic and thiol compounds that act as antioxidants.
Unban *et al*. (2021)[48]	A total of 133 isolates of lactic acid bacteria (LAB) isolated from fermented tea leaves (Miang)	A total of 133 isolates of lactic acid bacteria (LAB) isolated from Miang were evaluated for probiotic potential and selected strains were tested for antioxidant activity evaluation using DPPH scavenging activities method.	*L. pentosus* showed the highest cell antioxidant properties.
Abubakr *et al*. (2012)[49]	Lactic acid bacteria isolated from six fruit samples.	Lactic acid bacteria were isolated from six different types of fruits and put into skim milk. DPPH scavenging activities and ferrous chelating activity were used to assess the antioxidant activity of the whey fraction from fermented skim milk.	*L. plantarus* and *Leuconostoc mesenteroides* showed antioxidant activity.
Grompone *et al*. (2012)[50]	*Lactobacillus rhamnosus*	*C. elegans* were given a variety of LAB strains (a total of 78) after being treated by oxidative stress, and nematode vitality was measured (3 mM and 5 mM H_2O_2).	*L. rhamnosus* CNCM I-3690 protected worms by improving their viability by 30% and lengthening their average lifetime by 20%.
Amaretti *et al*. (2013)[51]	Thirty-four strains of lactic acid bacteria (7 Bifidobacterium, 11 *Lactobacillus*, 6 Lactococcus,	Thirty-four lactic acid bacteria strains were tested *in vitro* for antioxidant activity against ascorbic and linolenic acid	The antioxidant mixture successfully reduced doxorubicin-induced oxidative stress when supplied at doses of at

Contd...

Table 1: Contd...

Author (Year)	Bacterial Species	Method	Result
	and 10 *Streptococcus thermophilus*)	oxidation (TAA (AA) and TAA (LA)), trolox-equivalent antioxidant capacity (TEAC), intracellular glutathione (TGSH), and superoxide dismutase (SOD).	least 10 (8) CFU/day, according to plasma antioxidant activity, reactive oxygen molecules level, and glutathione concentration.
Yang *et al*. (2020)[41]	*Pediococcus pentosaceus* SC28 and Levi*lactobacillus brevis* KU15151	The antioxidant activity of samples was determined using the 2,2-diphenyl-1-picrylhydrazyl assay, 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonate, and *β*-carotene bleaching assay.	In three antioxidant assays, *L. brevis* KU15151 showed better adhesion activity to HT-29 cells and antioxidant effects than *P. pentosaceus* SC28.

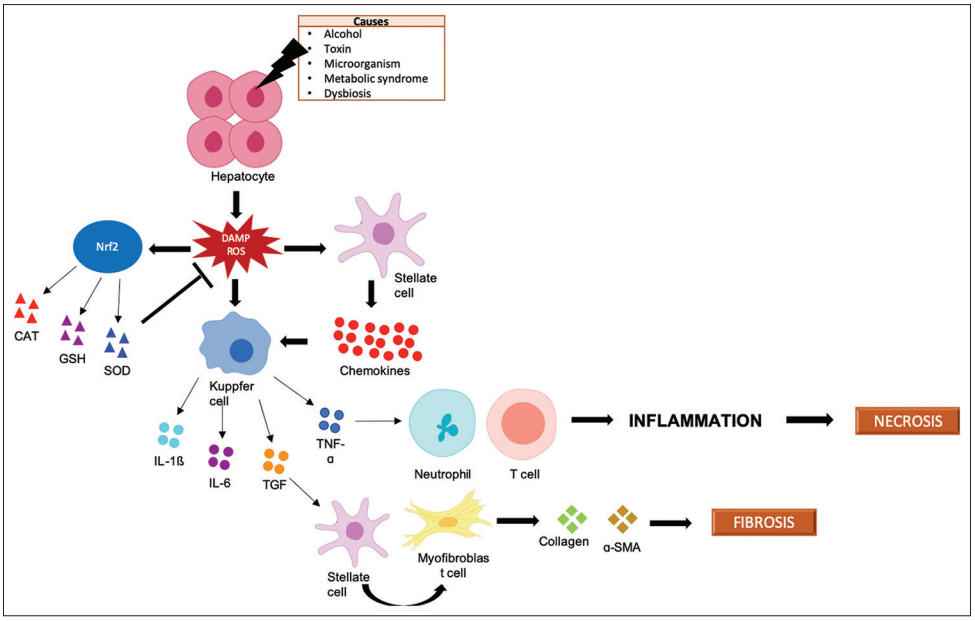

Figure 1: Pathophysiology of liver disease

including antioxidants.[42] Glutathione, lipids, and proteinaceous components of *L. casei's* intracellular content are antioxidant agents.[43]

Water kefir has been shown to be effective in reducing inflammation in animals.[9,52] Lactobacillus strains were discovered to have antiinflammatory properties in addition to antioxidant activity, as shown in Table 2. *L. rhamnosus* and *L. gasseri* had the ability to inhibit the release of inflammatory mediators such as TNF, IL-6, IL-1, and IL-10.[53] *L. mucosae* and *L. fermentum* administration reduced lipid peroxide levels and increased antioxidant activity in animal models of acute inflammation. Furthermore, antiinflammatory cytokine genes are being up-regulated while pro-inflammatory cytokine genes are being downregulated.[54] *L. casei* was also able to reduce histology and proliferation index scores in colorectal cancer animal models. Furthermore, it can function as an immunomodulator by downregulating IL-22 and an antiproliferative cytokine by upregulating caspase-7, caspase-9, and Bik.[55] Probiotics could also inhibit nitric oxide formation.[56]

Water kefir contains yeast in addition to lactic acid bacteria. Yeast cells are made up of high-nutritional-value carbohydrates, proteins, lipids, vitamins, and minerals.[61] Although research on yeast is not as extensive as that of bacteria, yeast has the potential to be a medicine. Yeast has antioxidant activity, according to research.[61-64] Yeast has two free radical defense mechanisms: enzymatic defenses like catalase and superoxide dismutase, and non-enzymatic defenses like glutathione (GSH).[65]

Yeast has also been shown to have antiinflammatory properties. *Candida kefyr*, a yeast isolated from milk kefir, showed antiinflammatory activity in the central nervous system in an experimental autoimmune encephalomyelitis animal model (EAE). *C. kefyr* administration improved EAE by optimizing microflora, which was accompanied by an increase in Tregs and CD103 positive regulatory dendritic cells in the Mesenteric Lymph Nodes (MLN) and a decrease in Th17 cells in the intestinal lamina propria.[66] In animal models of colitis, several strains of *S. cerevisiae* demonstrated antiinflammatory activity. The alleged mechanism of action is to strengthen the gastrointestinal

Table 2: Antiinflammatory activity of probiotics

Author (Year)	Bacterial Species	Method	Result
Grompone *et al*. (2012)[50]	*Lactobacillus rhamnosus*	*L. rhamnosus* was co-cultured with HT-29 cells and co-culture systems with HT-29 cells and DC in the presence of LPS, which were triggered by pro-inflammatory cytokines.	This strain displayed a marked antiinflammatory profile. Finally, in a mouse model of colitis, this *Lactobacillus* strain decreased inflammation.
Guo *et al*. (2013)[57]	Lactococcus lactis subsp. Lactis	*Lactococcus lactis* subsp. Lactis culture broth was used to identify and purify exopolysaccharide (EPS). To make selenium-exopolysaccharide, selenium chloride oxide (SeCl (2) O) was added to the EPS (Se-EPS). The antioxidant activity was tested both *in vitro* and *in vivo*.	Superoxide anions and hydroxyl radicals were scavenged by EPS and Se-EPS. They also boosted catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) activity in mice's serum and livers, while lowering malondialdehyde (MDA) levels.
Oh *et al*. (2018)[53]	*L. rhamnosus*, 4B15 dan *L. gasseri* 4M13	A total of 22 *Lactobacillus* strains isolated from infant feces were tested for probiotic potential, as well as resistance to low pH and bile salts. The selected *Lactobacillus* strains were evaluated, including antioxidation, inhibition of glucosidase activity, cholesterol-lowering, and antiinflammation.	The two selected strains significantly inhibited the release of inflammatory mediators such as TNF-α, IL-6, IL-1, and IL-10 when RAW 264.7 macrophages were stimulated with LPS.
Ayyanna *et al*. (2018)[54]	*Lactobacillus mucosae* AN1 and *Lactobacillus fermentum* SNR1	*L. mucosae* AN1 and *L. fermentum* SNR1 were tested for antiinflammatory properties in carrageenan (acute) and full Freund's adjuvant-induced inflammation (chronic) models.	The probiotic strains had antiinflammatory effects by upregulating while pro-inflammatory cytokine genes were downregulated and the probiotic groups exhibited lower levels of lipid peroxide formation and higher antioxidant activities.
Rochat *et al*. (2007)[58]	*Lactobacillus casei*	The antioxidative effects of *L. casei* were evaluated in a murine model of dextran sodium sulfate (DSS)-induced moderate colitis.	Mice treated with both *L. casei* strains showed a significant reduction in caecal and colonic inflammatory scores compared to the control group.
Jacouton *et al*. (2017)[55]	*Lactobacillus casei* BL23	*Lactobacillus casei* BL23, a probiotic strain known for its antiinflammatory and anticancer properties, was evaluated for its effect on the risk of cancer.	*L. casei* BL23 significantly reduced the development of CRC in mice; specifically, *L. casei* BL23 treatment reduced histological scores and proliferative index values. *L. casei* BL23 also had an immunomodulatory effect and antiproliferative effect.
Kim *et al*. (2021)[56]	*Enterococcus faecium*, *Lactobacillus reuteri, Lactobacillus fermentum*, and *Pediococcus pentosaceus*	The antioxidant activity of lactic acid bacteria isolated from canine and feline feces was tested. Followed by the evaluation of antiinflammatory activity of the chosen strains.	Nitric oxide inhibition was observed in the selected strains, as well as inhibition of inducible nitric oxide synthase and cyclooxygenase expression.
Brandi *et al*. (2020)[59]	six LAB lysates, belonging to the genus *Lactobacillus*	Six Lactobacillus lysates were characterized for their wound healing, antiinflammatory, antipathogen, and proteomic activity.	The lactobacilli lysates induced specific proteome modulation of the exposed keratinocytes, involving dysregulation of proteins and pathways associated with wound healing and antiinflammatory effects.
Lee *et al*. (2017)[60]	*Leuconostoc mesenteroides* and *Lactobacillus sakei*	Two LAB strains isolated from Kimchi were tested for antiinflammatory activity in mice with acid-induced acute colitis. To induce acute colitis in C57BL/6 model mice, a 3% dextran sulfate sodium treatment was given for 7 days.	Necropsy and histopathology analysis revealed that both *L. mesenteroides* and *L. sakei* supplementation alleviated the symptoms of acute colitis. Furthermore, the combination had a synergistic effect on colitis.

epithelial cells and the intestinal barrier.[67] In an animal model of inflammatory bowel disease, the beta-glucan fraction derived from *C. albicans* demonstrated strong antiinflammatory potential.[68] The following research revealed that yeast beta-glucan had bile acid binding, antioxidant, and antiinflammatory activity.[69]

Yeast, like bacteria, is one of the components of the gut microbiome. Several yeast strains have been shown to have probiotic potential. *S. cerevisiae* var. *boulardii* is the most well-known probiotic yeast.[70,71] *S. boulardii* is a probiotic yeast that has been shown high effectivity in fighting various gastrointestinal infections in both mouse

and human models. It works by modulating host immunity and competing with pathogenic bacteria. In comparison to other yeasts, *S. boulardii* can also survive in mammalian hosts. Preclinical and clinical studies have shown that using this yeast is safe, with systemic infection being extremely rare.[72]

One of the important factors influencing liver health is the state of the gut microbiome.[25,73,74] Probiotics, particularly those containing lactic acid bacteria, could help to improve the composition of the gut microbiome.[75] The fact that some severe liver disease complications, such as HE, can be effectively managed with various probiotics, prebiotics, and antibiotics lends credence to the importance of the gut microbiome in liver disorders.[76] Despite these facts, research on water kefir probiotic as a hepatoprotector has not been widely conducted.

Conclusion

Pathophysiologically, free radicals, inflammatory mediators, and the gut microbiome play an important role during liver damage development. According to the researches, water kefir showed a promising potency as a hepatoprotective agent due to its strong antioxidant, antiinflammatory, and probiotic properties. However, there are still limited researches reported about water kefir as a hepatoprotective agent. Because of the high prevalence and mortality rates of liver disease, as well as the limitations of liver disease therapy, further research on water kefir as a hepatoprotective agent is necessary.

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Conflicts of interest

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