Gastrointestinal Tract

REVIEW ARTICLE

Influence of human milk oligosaccharides *vs.* lactulose on the gut microbiome in patients with hepatic encephalopathy

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ABSTRACT

Hepatic encephalopathy (HE) is a neuropsychiatric disorder associated with liver dysfunction. This literature review explores the therapeutic potential of nutritional and microbiome-based interventions in managing HE, particularly minimal hepatic encephalopathy. Nutritional therapy, along with probiotics, prebiotics, and fecal microbiota transplants, has shown efficacy in reducing ammonia levels, improving cognitive function, and enhancing health-related quality of life. Additionally, the safety of 6'-sialyllactose, a human milk component, has been confirmed in clinical trials, supporting its potential use in HE treatment. Emerging evidence also suggests that bacteriophages within the gut microbiome are linked to cognitive impairment in cirrhotic patients, indicating that microbiome modulation could provide new therapeutic avenues. These findings highlight the promise of nutritional and microbiome-based strategies in managing HE and emphasize the need for further research to fully integrate these approaches into clinical practice.

Key words: hepatic encephalopathy, sialyllactose, human milk oligosaccharide, prebiotics, microbiota

INTRODUCTION

Hepatic encephalopathy (HE), also known as portosystemic encephalopathy, is a wide spectrum of neuropsychiatric abnormalities in patients who are suffering from liver failure or portosystemic shunt. It is characterized by a transient cognitive decline, personality changes, and behavioral abnormalities, and is associated with various neurological dysfunctions. Cirrhosis is the primary disease linked to hepatic encephalopathy, and its global incidence is on the rise. As of 2024, Cirrhosis is the 4th leading cause of death from non-communicable diseases worldwide, but it ranks 10th in developed countries.[1–3] Its prevalence in the United States is estimated at around 2.2 million.[3] Which is on the increase primarily due to the rising incidence of Nonalcoholic fatty liver disease (NAFLD), Hepatitis C virus (HCV), and Hepatocellular carcinoma (HCC).[4,5] The real problem lies in managing hepatic encephalopathy due to the complexity of its pathogenesis, most studies being conducted on animal models, and a wide range of presentations.[6] Unlike patients with overt HE, some patients develop a milder form of HE or minimal hepatic encephalopathy (MHE) that presents with mild signs of altered brain function.[7] The exact mechanisms behind MHE are complex and not yet fully understood. Research involving cirrhotic patients and animal models with MHE suggests that an imbalance in gut microbiota triggers systemic inflammation, elevated ammonia levels, and endotoxemia. These factors, in turn, contribute to neuroinflammation in the brain through the gut-liver-brain axis, and predispose to complications like spontaneous bacterial peritonitis, and gastrointestinal bleeding.[8] The role of gut microbiota dysbiosis is crucial

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in developing MHE.[9,10] Current clinical treatments for MHE, such as lactulose, rifaximin, probiotics, synbiotics, and fecal microbiota transplantation, primarily work by correcting gut microbiota imbalances.[11–13] While managing HE is challenging. A promising yet unproven compound appears to be Human Milk Oligosaccharides(HMO), which is a long-chain carbohydrate, a non-nutritive bioactive prebiotic, that possesses antibacterial effects and can disrupt biofilms that bacteria use for protection, thereby influencing the gut microbiome and enhancing the effectiveness of antimicrobial agents.[14] Benefits of HMOs have been shown in different subgroups of patients, mainly pediatric, improvements in gastrointestinal function, and cognitive function, and selectively encouraging the growth of beneficial bacteria (probiotics).[15,16] What are the challenges that face HMOs to be used as a treatment for HE and can it be compared to a better-understood and widely studied oligosaccharide, lactulose?

PATHOGENESIS OF HEPATIC ENCEPHALOPATHY

The pathogenesis of HE is an interplay of various metabolic factors. The primary suspect is ammonia. Unfortunately, ammonia levels cannot be used to direct the management, diagnosis or correlating it to HE severity.[17,18] The main source of ammonia is the gut microbiome through the breakdown of proteins from dietary intake acting on urea through urease. In healthy hepatic cells, ammonia can be processed Primarily through transamination followed by deamination from amino groups of nitrogenous bases such as purines and pyrimidines.[19] However, in cirrhotic liver ammonia bypasses the liver directly to the bloodstream which is toxic to brain and muscle cells.[19] Thus, leading to transient attacks of brain edema, in the short term, and brain atrophy, in the long term.[20] The effects of ammonia on muscles manifest as sarcopenia, loss of muscle mass, and power, which is an indicator of poor morbidity and survival rates.[21–24] Patients who suffer from sarcopenia present with low BMI, elevated myostatin levels, and reduced irisin levels. In a subgroup analysis between CHILD A and CHILD BC groups, serum irisin levels were the most significant predictor of cirrhosis-related mortality in the 4th year In the CHILD A group, whereas in the CHILD BC group, higher serum myostatin levels were more predictive of mortality, independent of sarcopenia status.[25]

SYSTEMIC INFLAMMATION AND NEUROTOXICITY

Hyperammonemia and frequent infections are the main causes of morbidity and mortality in HE cases.[26] However, cytokines and pro-inflammatory mediators play a major role in weakening the innate immune system that constitutes the blood-brain barrier. The result is a vicious cycle of infection or inflammation that puts stress on the immune system which responds to the stressor by releasing more pro-inflammatory mediators like tumor necrosis factor alpha (TNF)-α, interferon-gamma (IFN)-γ, interleukins like IL1, IL-6, IL-12. These cytokines influence leukocytes, specifically the neutrophils, to activate and contribute to further transcription of more inflammatory mediators. The result is the development of the systemic inflammatory response syndrome (SIRS) which is defined as (1) temperature > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg; and (4) white blood cell count > 12,000/m^3 or < 4000/m^3, or >10% immature (band forms). This syndrome developed irrespective of infection status but in response to the severity of the underlying cause.[27]

Hyperammonemia can alter the synaptic transmission in the hippocampus by altering membrane receptors of GluA2 and GluA1.[28] A more recent *in vivo* study in 2023 found that another novel piece of the puzzle, miR-122-5p, and miR-183-5p, identified for the first time to be able to affect the blood-brain barrier (BBB) causing structural and functional changes.[25] The study also identified the targets of these miRNAs to be occludin and integrin β1 which are junctional proteins on the surface of endothelial cells that form the BBB. These results align with the growing evidence of another older study that proposed the relationship between the mi-R-183 family and the progression of liver fibrosis.[25]

GUT MICROBIOTA

The gut microbiome is a collection of many bacteria, viruses, and fungi that are considered a part of the innate immune system.[29–31] That is directly evidenced by the immune homeostasis achieved through limiting pathogen overgrowth, modulating the immune response, and regulating the environment around them.[30,32] Any deficiency in these protective organisms results in disorders in the surrounding environment, altering metabolic pathways, and overgrowth of opportunistic pathogens, this phenomenon is termed dysbiosis. A well-known example of this is *Clostridium difficile* (CD) infection after recent antibiotic use.[33,34] Furthermore, patients with recurrent CD achieved clinical remission 2 to 4 weeks after Fecal Microbiota Transplantation(FMT) was 57% (95% CI 49% to 64%) with a low risk of heterogeneity (I^2 = 37%). Moreover, analysis found that FMT significantly reduced Crohn's disease activity index scores 4 to 8 weeks after the intervention(95% CI −1.12 to −0.20; I^2 = 0).[35] This poses an interesting question: can the innate immune system be trained? Can this

generalist form of immunity adapt to the influences around it?

DYSBIOSIS IN DIFFERENT LIVER PATHOLOGIES COMPARED TO HE

It is suggested that there is a link between the severity of nonalcoholic fatty liver disease (NAFLD) and dysbiosis. Fifty-seven patients with biopsy-confirmed NAFLD were studied and subcategorized based on taxonomic composition of gut microbiota using 16S ribosomal RNA gene sequencing of stool samples and found that Bacteroides as independently associated with NASH and *Ruminococcus* with significant fibrosis.[36] That is directly observed in two other studies that found a similar result which is the abundance of firmicutes, bacteroidetes, and proteobacteria species in the same patient group with a correlation to liver fibrosis.[37,38]

Bajaj *et al.* demonstrated the ability to estimate the degree of dysbiosis and correlate it to the severity of cirrhosis by introducing the concept of cirrhosis/dysbiosis ratio (CDR). The study found that the CDR was significantly lower in healthy individuals compared to those with cirrhosis.[39] Probiotics, prebiotics, and synbiotics are functional food components that modulate gut microflora, benefiting the host's health. Probiotics alter the intestinal flora by reducing the number of urease-producing bacteria, which decreases the production of toxic substances, especially ammonia. This has been shown to improve MHE and prevent overt hepatic encephalopathy (OHE) by lowering blood ammonia levels.[40] An interesting prebiotic is lactulose, one of the most well-studied oligosaccharides, it was found that combining lactulose with Rifaximin was more effective than lactulose alone for reducing the risk of overt HE recurrence and HE-related hospitalization in adults.[41] An unexpected finding was found in hospital patients with liver disease, who were treated with lactulose. Their microbiome supported Bifidobacteria species expansion which led to reduced incidence of infection and improved 90-day survival. That finding demonstrated that oligosaccharides can impact complications like infection rates and muscle wasting.[42,43]

Patients who are suffering from liver cirrhosis face two complications known for their high mortality rates and low life quality, spontaneous bacterial peritonitis and esophageal variceal bleeding. Both of these complications have something in common, dysbiosis and intestinal epithelial barrier dysfunction secondary to cirrhosis.[44,45] A hallmark of these disorders is reduced portal vein blood flow and intestinal vascular constriction directly leading to high intestinal permeability and leakage. This leads us to an important detail, patients with liver failure need constant monitoring and specific adjustments to their gut microbiome because of secondary biliary dysfunction resulting in favoring *Escherichia coli* and *Enterococcus faecalis* species.[46] These species are notorious for altering pH in their environment, thus facilitating ammonia absorption and transition from the colon lumen to the blood.[47]

PREBIOTICS, SYNBIOTICS AND PROBIOTICS—WHAT ARE THEY AND HOW DO THEY WORK?

Probiotics are living organisms that feed on bioactive non-digestible non-nutritious molecules, known as prebiotics. These microorganisms play a vital role in maintaining homeostasis. A commonly used prebiotic is oligosaccharides like inulin and oligofructose. In a well-balanced diet, a mixture of probiotics and prebiotics is referred to as synbiotics, which showed miraculous health benefits in improving insulin sensitivity, and weight reduction according to one randomized controlled trial.[48]

Other health benefits include but are not limited to the resolution of diarrhea or constipation, better bile salt conjugation, anti-inflammatory and anti-bacterial properties, combating allergies, and finally some positive effects on aging, fatigue, and diabetes.[49]

GUT-LIVER-BRAIN AXIS—FINAL PIECE OF THE PATHOGENESIS PUZZLE

It is well established that probiotics can improve cognitive function and decrease venous ammonia levels, even with combinations of bacterial species like Clostridium butyricum combined with *Bifidobacterium infantis* in minimal hepatic encephalopathy, which also showed a significant decrease in harmful *Enterococcus* and *Enterobacteriaceae*.[47] Probiotic treatment can be combined with nutritional therapy for maximum effect. Sharma *et al.*, demonstrated that nutritional therapy is an effective intervention for patients with MHE. It not only significantly improves cognitive function and health-related quality of life (HRQOL) but also leads to beneficial changes in nutritional status, biochemical markers such as ammonia and myostatin levels, and reductions in endotoxins and inflammatory cytokines. Furthermore, therapy reduces the progression to overt hepatic encephalopathy.[44,50,51]

To support nutritional and probiotic therapy, this SR/MA evaluated the effectiveness of microbiome therapies, including probiotics, synbiotics, and FMT, in treating HE. The analysis included 21 randomized controlled trials with a total of 1746 participants. The findings demonstrated that microbiome therapies significantly improved MHE, reduced the development of overt HE,

and decreased the frequency of serious adverse events. Additionally, these therapies lowered ammonia levels, neurocognitive test scores, and hospitalization rates compared to placebo or no treatment. The study concluded that microbiome therapies are more effective than placebo in improving MHE, preventing progression to overt HE, and reducing related health complications.[52]

In a neurological disorder with different pathophysiological mechanisms from HE, gut microbiome even showed promise in patient-specific Alzheimer's disease management through symbiotics and fecal microbiota transplantation according to this review.[53] The gut microbiota plays a crucial role in various physiological processes, including short-chain fatty acid production, vitamin biosynthesis, bile salt transformation, and the conversion of complex dietary polysaccharides into more readily absorbable carbohydrates. Furthermore, certain bacterial species within the gut can produce neurotransmitters, such as GABA, noradrenaline, and dopamine, highlighting the potential impact of the gut microbiome on neurological and cognitive functions.[54]

In a randomized controlled trial, 70 participants were given a six-week regimen of a multi-strain probiotic (MSP) containing four strains: *Limosilactobacillus fermentum* LF16, *Lacticaseibacillus rhamnosus* LR06, *Lactiplantibacillus plantarum* LP01, and *Bifidobacterium longum* 04, with a total dosage of 4 × 10□ live cells per day. The results showed significant improvements in depression, anxiety, and mood scores along with increased plasma serotonin levels.[55] A table showing a summary of the main studies and its findings (Table 1).

COMPOSITION AND CONCENTRATION OF HUMAN MILK OLIGOSACCHARIDES

The composition of human milk is primarily water (approximately 87%), with smaller amounts of proteins (around 1%), fats (3%–5%), and carbohydrates, which make up about 7% of its composition (Figure 1). The major carbohydrate in human milk is lactose, but an essential subset of carbohydrates, known as human milk oligosaccharides (HMOs), contributes to its complexity and bioactivity.[56–60]

A NOVEL PREBIOTIC FOR HE, HUMAN MILK OLIGOSACCHARIDE

Human milk oligosaccharides are a diverse group of complex carbohydrates found in abundance in human breast milk, second only to lactose in terms of concentration. These unique structures are not digestible by human enzymes, but instead serve as a prebiotic,

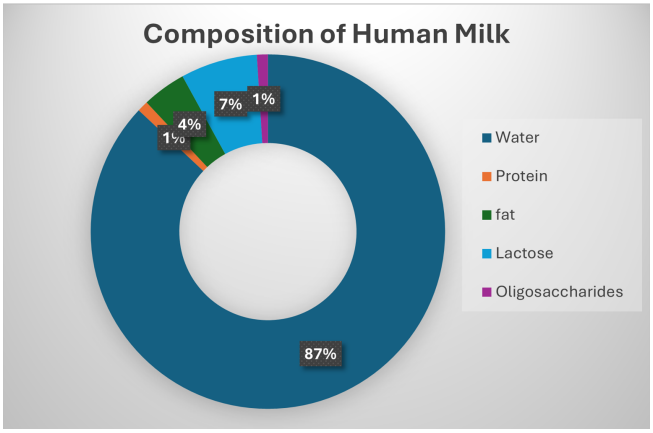

Figure 1. A pie chart illustrating the composition of human milk.

selectively fostering the growth of beneficial bacteria in the infant gut microbiome.[60] One of the primary bacterial groups that can metabolize human milk oligosaccharides is the *Bifidobacterium* species. These anaerobic bacteria are considered a hallmark of a healthy infant gut, as they facilitate the development of the immune system and protect against pathogenic microorganisms.[61]

The main source of HMO is from the mother's colostrum. As a result, the composition and diversity of human milk oligosaccharides can vary significantly between individuals, and even within a single mother's milk over time.[64] This heterogeneity may contribute to the establishment of a unique gut microbiome in each infant, as different oligosaccharide structures can selectively enrich distinct microbial communities. Furthermore, other factors such as gestational age, host genetics, and maternal diet may also play a role in shaping the infant gut microbiome, even in the presence of human milk oligosaccharides.[62]

An earlier study involving 125 cirrhotic patients received either *Bifidobacterium* with fructooligosaccharides (FOS) or lactulose for 60 days. After 30 days patients who were treated with Bifidobacterium plus FOS had significantly better cognitive performance, with lower scores on the Trail Making Test B and higher scores on the Symbol Digit Modalities Test and Block Design Test compared to those treated with lactulose. After 60 days, the *Bifidobacterium* plus FOS group continued to show superior outcomes, with significantly reduced fasting ammonia levels and improved results on cognitive tests. The study concludes that *Bifidobacterium* + FOS is an effective alternative to lactulose in cirrhotic patients, offering benefits in lowering blood ammonia levels and enhancing cognitive function.[63]

HMO IN OTHER CONDITIONS

Table 1: A table showing a summary of the main studies and its findings

Title	Findings	Sources
Pathogenesis of HE	Ammonia is the primary factor but not directly correlate to HE severity	[17–19]
	Ammonia bypasses the liver in cirrhosis, causing brain and muscle damage, leading to edema and sarcopenia.	[19–22]
	Sarcopenia in HE patients is linked to higher morbidity, characterized by low BMI, high myostatin, and low irisin levels	[25]
Systemic inflammation & neurotoxicity	Hyperammonemia and infections cause morbidity in HE	[26]
	Cytokines such as TNF-α, IFN-γ, and IL-1, IL-6, IL-12 are involved in a vicious inflammatory cycle, leading to SIRS	[27]
	Novel miRNAs (miR-122-5p, miR-183-5p) affect the blood-brain barrier (BBB), contributing to HE neurotoxicity.	[28,25]
Gut microbiota in HE	Dysbiosis is linked to NAFLD, cirrhosis, and liver fibrosis, characterized by shifts in gut microbiome composition (e.g., Firmicutes, Bacteroides)	[36–41]
Probiotics, prebiotics, synbiotics	Probiotics reduce urease-producing bacteria, lowering ammonia production and improving outcomes in HE (MHE & OHE)	[40–43]
	Prebiotics like lactulose combined with rifaximin were more effective than lactulose alone in preventing HE recurrence	[41]
Gut-liver-brain axis	Probiotic therapies (e.g., Clostridium butyricum, Bifidobacterium infantis) improve cognitive function and reduce ammonia levels.	[47–49]
	Nutritional therapy and probiotics together improve cognitive function, HRQOL, and reduce inflammatory markers in MHE	[50,51]
Microbiome therapy in HE	A systematic review/meta-analysis of 21 RCTs showed microbiome therapies (*e.g.*, probiotics, FMT) significantly improve MHE, reduce OHE, and decrease adverse events.	[52]
Gut microbiome & neurological disorders	Gut microbiome therapies show promise in managing Alzheimer's disease and other neurological disorders through symbiotics and FMT.	[53,54]
Probiotics in mental health	A 6-week trial of a multi-strain probiotic improved depression, anxiety, and mood scores, along with increased serotonin levels	[55]

Beyond HE, HMOs have shown potential in other conditions like irritable bowel syndrome (IBS). This is evident with 2'-O-fucosyllactose (2'FL) and lacto-N-neotetraose (LNnT) supplementation on the gut microbiota and metabolite profiles in patients with IBS. The intervention led to moderate changes in fecal microbiota composition, while mucosal microbiota composition remained unchanged. Both fecal and mucosal levels of Bifidobacterium species, including *Bifidobacterium adolescentis* and *Bifidobacterium longum*, increased following 2'FL/LNnT intake. The supplementation also influenced fecal and plasma metabolite profiles, with these changes being linked to the increased abundance of bifidobacteria, although it did not affect urine metabolite profiles or host mucosal gene expression. This concludes that 2'FL/LNnT supplementation effectively modulates the gut microbiota and metabolite environment in IBS patients, potentially contributing to health improvements.[64]

In another study involving adults with prediabetes and insulin resistance (PreDM-IR) examined the effects of red raspberry (RRB) supplementation, with or without a fructo-oligosaccharide (FOS) prebiotic, on cardiometabolic risk biomarkers and gut microbiota composition. Participants consumed either RRB alone or RRB + FOS daily for 4 weeks, with a 4-week washout between periods. The results showed that RRB supplementation reduced hepatic insulin resistance by 30.1% and lowered plasma total and LDL cholesterol levels. Adding FOS further improved β-cell function, though it did not significantly affect cholesterol levels. Gut microbiota analysis revealed that RRB increased Eubacterium eligens and decreased *Ruminococcus gnavus*, while RRB + FOS increased *Bifidobacterium* spp. and decreased *Blautia wexlerae*. Notably, *R. gnavus* was positively correlated with hepatic insulin resistance, while *E. eligens* and *Bifidobacterium catenulatum* were negatively correlated with cholesterol levels. These findings suggest that changes in specific gut bacteria linked to RRB and FOS supplementation may contribute to metabolic improvements in PreDM-IR, highlighting the potential for targeted dietary interventions to modulate gut microbiota and improve cardiometabolic health.[65]

SAFETY AND ADVERSE EFFECTS

The safety of HMOs, specifically 2'FL and LNnT, was evaluated at various doses up to 20 grams daily for 2 weeks. HMO supplementation was found to be safe and well-tolerated, as indicated by the gastrointestinal symptoms rating scale. Notably, no participants discontinued the study prematurely due to adverse effects. Additionally, 16S rRNA sequencing revealed that HMO supplementation significantly altered the gut microbiota, notably increasing the abundance of beneficial bacteria such as *Actinobacteria* and *Bifidobacterium*, while reducing the relative abundance of *Firmicutes* and *Proteobacteria*.

These findings suggest that HMO supplementation is an effective strategy to positively influence gut microbiota by promoting the growth of beneficial bifidobacteria.[66]

Another study evaluated participants who consumed either 1 or 3 bottles daily of the test product, which included yogurt strains and probiotic strains *Lactobacillus paracasei* and *Lactobacillus rhamnosus*. Safety was evaluated through various health parameters, including adverse events, metabolic profiles, and digestive symptoms. The results showed no significant safety differences between the test and control groups across all parameters. Gut microbiota analysis revealed that the probiotic strains were detectable only during the consumption period, with higher levels in those consuming 3 bottles per day. While the overall gut microbiota structure remained unchanged after 4 weeks, a few bacterial genera exhibited differential responses to the product. Metagenomic analysis indicated that the probiotics contributed functionally to the gut microbiome.[67]

Additionally, a study investigating the safety of 6'-sialyllactose (6'-SL), a component abundant in human milk, compared it with a placebo (maltodextrin). Participants received 3 grams of 6'-SL powder or placebo twice daily for 12 weeks. The study found no serious adverse effects, such as life-threatening complications or significant changes in clinical chemistry tests (e.g., aspartate aminotransferase, alanine aminotransferase, and creatinine) between the 6'-SL and placebo groups. While some gastrointestinal issues like diarrhea and bloating were reported, their frequency was similar between both groups. These findings suggest that 6'-SL is safe for human use, supporting its potential for therapeutic applications.[68]

ETHICAL CONSIDERATIONS, SAFETY, AND COST-BENEFIT ANALYSIS

Human milk is considered the gold standard for oligosaccharide structure and diversity, providing numerous benefits. However, due to practical and ethical constraints, these compounds cannot be easily obtained in large quantities for research purposes. Consequently, colostrum or milk from dairy animals can serve as an alternative source of oligosaccharides, which can be utilized for the development of functional foods and clinical applications.[61]

INNOVATIVE RESEARCH DIRECTIONS AND PERSONALIZED MEDICINE

While lactulose treatment does not significantly change fecal microbiome composition, it may improve dysbiosis and alter microbial metabolic functions.[69] The effects of lactulose on human microbiota composition are both patient- and dose-dependent. Interestingly, a combination of Bifidobacterium and fructo-oligosaccharides (FOS) has shown promise in reducing blood ammonia levels and improving psychometric tests in HE patients, potentially offering an alternative to lactulose treatment.[63,70]

CLINICAL IMPLICATIONS AND KNOWLEDGE GAPS

This review shines a light on the importance of a personalized approach specifically through nutritional and microbiome-based therapy to guide clinical and pharmacological management.

Further research is needed to elucidate the specific mechanisms by which human milk oligosaccharides can influence liver function and the gut microbiome in the context of hepatic encephalopathy. Nevertheless, the existing evidence highlights the potential of this novel therapeutic strategy to improve clinical outcomes in patients with advanced liver disease and associated complications.

CONCLUSION

This literature review highlights the significant potential of HMOs and other prebiotics, such as FOS, in modulating gut microbiota and improving clinical outcomes in various health conditions, including HE, IBS, and cardiometabolic disorders. Studies indicate that HMOs, particularly 2'FL and LNnT, not only promote the growth of beneficial gut bacteria like Bifidobacterium species but also exert positive effects on cognitive function, metabolic health, and immune responses. Additionally, safety evaluations demonstrate that these prebiotics are well-tolerated and can be administered without significant adverse effects, further supporting their therapeutic potential.

In hepatic encephalopathy, the inclusion of HMOs and Bifidobacterium-based interventions has shown promise in improving cognitive function and reducing blood ammonia levels, offering an alternative to traditional treatments like lactulose. Moreover, in other conditions such as IBS and prediabetes, prebiotics have been shown to modulate gut microbiota composition, reduce insulin resistance, and improve lipid profiles, underscoring their role in personalized medicine.

Microbiome-based treatments, including probiotics, synbiotics, and fecal microbiota transplant (FMT), have shown substantial benefits in the treatment of hepatic encephalopathy. These therapies are effective in reversing MHE, reducing the incidence of OHE, and lowering ammonia levels. They also decrease hospital-

ization rates and the frequency of serious adverse events compared to placebo treatments. The positive outcomes suggest that modulating the gut microbiome can be an effective strategy for improving cognitive function and overall health in patients with HE.

Clinical trials have demonstrated the safety of 6'-SL, a component found abundantly in human milk. While some gastrointestinal issues, such as diarrhea and bloating, were reported, they were not significantly different from those experienced with a placebo. Importantly, no severe adverse effects or significant clinical chemistry changes were noted, supporting the use of 6'-SL for therapeutic purposes. These findings reinforce the safety profile of 6'-SL and its potential for broader applications in clinical settings.

Emerging research highlights a notable link between gut microbiome components, particularly bacteriophages, and cognitive function in patients with cirrhosis. Changes in bacteriophage profiles associated with specific bacteria correlate with cognitive impairment and variations in MHE status. These observations suggest that bacteriophages could influence cognitive outcomes through their effects on neuroactive metabolites produced by gut bacteria. This connection opens new avenues for exploring microbiome modulation as a potential therapeutic approach for improving cognitive function in patients with hepatic encephalopathy.

DECLARATIONS

Author contributions
Kareem Wael Raafat and Ismail Elkhattib were co-first authors.

Use of large language models, AI and machine learning tools
None declared.

Informed consent
Not applicable.

Ethical approval
Not applicable.

Conflicts of interest
There is no conflict of interest among the authors.

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No additional data is available.

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