

The Potential Benefits of *Akkermansia muciniphila* as a Next-Generation Probiotic in the Maintenance of Overall Liver Health

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Abstract

Background and study aim: The gut-liver axis and gut microbiota, with a particular focus on *Akkermansia muciniphila*, a next-generation probiotic, have been identified as significant factors in preventing the development and progression of liver diseases. This review aims to discuss the potential therapeutic role of *A. muciniphila* in maintaining liver health, focusing on the latest findings from preclinical and clinical studies.

Methods: To achieve the review's purpose, the most common keywords were searched in three online databases (PubMed, bioRxiv, and Google Scholar).

Results: The search approach identified 49 references. Studies have shown that the gut microbiota, including *A. muciniphila*, has the potential to be a therapeutic target for many hepatic disorders. Several studies have demonstrated *A. muciniphila*'s beneficial effects on improving metabolic parameters, including insulin resistance, blood cholesterol levels, and overall liver function.

Conclusions: Further research is necessary to determine the optimal dosage, duration, and administration route of *A. muciniphila* for managing hepatic disorders. While there are promising findings, a more thorough understanding of the underlying mechanisms and the development of effective therapeutic strategies are necessary for successful treatment of liver diseases. (*Acta gastroenterol belg.*, 2025, 88, 141-150).

Keywords: *Akkermansia muciniphila*; liver diseases; NAFLD; gut microbiota; probiotic.

Introduction

Function of the Liver

The liver is a crucial organ that performs various essential bodily functions (Fig. 1.). It neutralizes and eliminates toxins, harmful chemicals, unnecessary substances, and microorganisms from the bloodstream, making it the primary organ for detoxification (1-3). This involves neutralizing and secretion of toxic substances, aided by the liver's filtration function. Additionally, it regulates blood glucose levels by storing glucose in glycogen and releasing it when the body requires additional energy. The liver also helps convert other substances, such as amino acids, into glucose through gluconeogenesis. Moreover, the liver plays a pivotal role in fat metabolism, synthesizing and breaking fatty acids and triglycerides. Processing nutrients from the small intestine facilitates the efficient distribution of essential components throughout the body (1, 2). The liver also produces various plasma proteins, such as albumin, crucial for maintaining oncotic

pressure and transporting bodily substances (2, 4). It also synthesizes proteins involved in blood clotting, which are essential for wound healing and preventing bleeding (2, 5). Furthermore, the liver produces bile, stored in the gallbladder and secreted into the small intestine to aid in fat digestion (1, 2, 6). It also stores vital substances like vitamins (e.g., vitamins A, D, E, K, B12) and minerals (e.g., iron as ferritin) and regulates their release into the bloodstream as needed (7). The liver is a vital organ that performs several critical bodily functions, essential to maintain health and function (1, 2, 7).

When the liver's function is impaired due to liver disease, it can lead to various health complications (1, 2, 7). Therefore, it is essential to maintain liver health by consuming a balanced diet, limiting alcohol intake, and regularly scheduling medical checkups for overall well-being (8, 9).

Liver Diseases and Primary Management

Liver diseases (LD) lead to approximately two million deaths every year, accounting for 4% of all deaths worldwide, which means that LD causes 1 out of every 25 deaths. Two-thirds of liver-related deaths occur in males (10).

Multiple factors, such as genetics, environment, and lifestyle, influence the development of liver diseases. Common risk factors associated with LD include unbalanced diet and obesity, heavy alcohol consumption and smoking, bloodborne viruses (hepatitis B and C), parasitic infections, and chemical pollutants (e.g., pesticides, dioxins, bisphenols). People with multiple risk factors are at a significantly higher risk of developing LD (11-13). Common types of liver disorders include non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver cirrhosis, hepatocellular carcinoma (HCC), and other autoimmune and genetic liver conditions, such as hemochromatosis and primary

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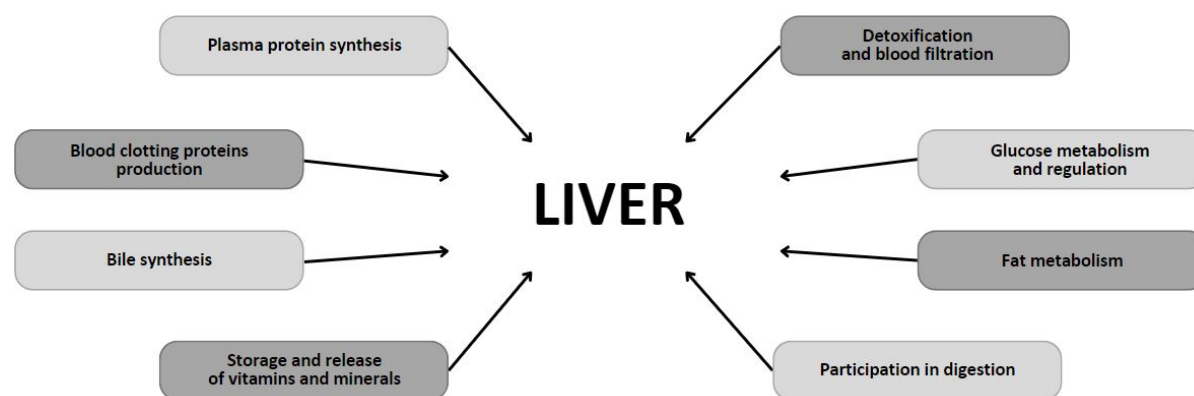


Figure 1. — The main functions of the liver (1, 2, 4, 5, 7).

biliary cirrhosis (12, 14). Typical liver symptoms are reduced appetite, weight loss, and fatigue. Additionally, abdominal pain, nausea, vomiting, fever, alopecia, and cutaneous changes, such as jaundice and pruritus, can also be identified among the symptoms of LD. However, in the advanced stages of certain diseases like alcoholic hepatitis, cirrhosis, and HCC, the severity of symptoms can escalate, potentially leading to complete liver failure and death (15, 16).

Although several treatments are available for liver diseases, making lifestyle changes, explicitly modifying one's diet aimed at caloric restriction and engaging in moderate-intensity physical activity, are crucial. The most effective step in improving the health of patients with liver disorders is to lose weight, especially for obese patients, as obesity is a significant contributor to conditions like NAFLD (17). This can be achieved by adopting the Dietary Approaches to Stop Hypertension (DASH) diet, a reduced-calorie diet enriched with fruits, vegetables, whole grains, low-fat dairy products, fish, and nuts. The DASH diet aims to eliminate sugar and processed foods high in saturated and trans fats (18). Studies have demonstrated its ability to improve liver health by reducing inflammation and oxidative stress, as well as by improving liver enzymes, markers of insulin resistance, serum triglycerides, and very-low-density lipoproteins (VLDLs) levels (19, 20). However, it is important to recognize potential challenges associated with dietary changes. Limiting meat consumption, especially red meat – a key recommendation in the DASH diet – can lead to iron and vitamin B12 deficiencies if not carefully managed (21). Higher dietary calcium consumption, combined with an increased intake of fruits, vegetables, and nuts, may elevate urinary excretion of oxalates, which may potentially be responsible for calcium oxalate kidney stones (22). An alternative dietary approach for the treatment of liver diseases is the Mediterranean diet (MD), which shares similarities with the DASH diet. The main difference lies in the higher allowed fat intake in MD (30-40% of daily caloric consumption) (17, 23). Adherence to the MD has been associated with reduced hepatic fat and improved hepatic insulin

sensitivity (23, 24). Furthermore, an intervention study of untreated NAFLD patients without significant fibrosis has demonstrated additional benefits, including notable improvements in liver imaging, liver fibrosis scores, blood pressure, fasting glucose levels, glycated hemoglobin, and oxidized low-density lipoprotein levels (25).

While reducing weight plays a pivotal role in enhancing liver function, it is crucial to recognize that successful treatment requires a holistic therapeutic approach that addresses other factors influencing liver health. A healthy diet combined with weight loss supports faster and more efficient liver regeneration. Customized dietary plans for liver disease should be tailored to individual patients, focusing on gradual weight loss of up to 1.6 kg per week to avoid worsening liver inflammation (18). Progressive weight loss can reduce fat mass, inflammation, and fibrosis and halt liver disease progression (17).

The Role of Gut Microbiota in Hepatic Disorders

The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement has defined probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (26). Probiotics are live microorganisms like bacteria and yeast that can benefit human health by supporting intestinal microbiota balance. They are crucial for digestive processes, immune function, and overall health (27). Probiotics are commonly used as dietary supplements and are naturally present in certain foods, such as yogurt, kefir, pickled vegetables, and other fermented products (28, 29).

Recent evidence shows that the gut-liver axis and gut microbiota play a critical role in developing and progressing liver diseases. These include NAFLD, NASH, viral hepatitis B, liver cirrhosis, HCC, acute liver injury, acute-on-chronic liver failure (ACLF), autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) (30-32). An imbalance in the gut microbiota, known

as dysbiosis, can disrupt the gut-liver axis, leading to increased intestinal permeability, translocation of microbial components to the liver, and the development or progression of liver disorders. The intestinal microbiota also influences liver regeneration processes (32).

Several randomized clinical trials have demonstrated the efficacy of certain probiotics, primarily *Lactobacillus* and *Bifidobacterium* species, in improving metabolic parameters and liver function tests in patients with NAFLD and hepatic encephalopathy. Probiotics can improve the homeostasis model assessment of insulin resistance (HOMA-IR) index, blood cholesterol levels, tumor necrosis factor- α (TNF- α), and liver function, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity (33-37). Next-generation probiotics (NGPs), such as *Akkermansia muciniphila* (*A. muciniphila*), show promise as therapeutic agents for liver diseases. The definition of NGPs includes “live microorganisms identified on the basis of comparative microbiota analyses that, when administered in adequate amounts, confer a health benefit on the host” (38). They have documented effects on gut barrier function, and recent preclinical and clinical findings suggest their potential as a next-generation probiotic for liver disease treatment (39-41).

Methodology

In this article, we conducted an extensive search across major search engines, including PubMed, bioRxiv, and Google Scholar, to identify English-language studies investigating the relationship between *A. muciniphila* and its potential role in preventing and treating liver diseases while focusing on improving metabolic parameters. Our search strategy involved using specific keywords such as “*Akkermansia muciniphila*”, “*Akkermansia muciniphila* and liver functions”, “*Akkermansia muciniphila* and liver diseases”, and “*Akkermansia muciniphila* in liver disorders”. The comprehensive review encompasses 26 experimental studies and synthesizes insights from 23 theoretical works, all contributing to the understanding of *A. muciniphila*’s impact on overall liver health. These studies have been meticulously referenced to provide a robust foundation for the information presented.

Characterization of *Akkermansia muciniphila*

A. muciniphila is an anaerobic, Gram-negative bacterium that plays a significant role in enhancing its host’s metabolic functions and immune responses (42). It is oval, non-motile, and does not produce endospores (43). This bacterium was first isolated from human feces in 2004 and was named in honour of the esteemed Dutch microbiologist Dr Antoon Akkermans (42). Taxonomically, *A. muciniphila* belongs to the Verrucomicrobia phylum, specifically within the

Verrucomicrobiae class, the Verrucomicrobiales order, the Verrucomicrobiaceae family, and the *Akkermansia* genus (44). *A. muciniphila* is primarily found in the mucus layer of the human gut, with the highest concentration observed in the caecum (42, 43). It constitutes approximately 1-4% of the bacterial population in the colons of infants and healthy adults. However, its prevalence increases with age and progressively declines in the elderly population (45, 46). Furthermore, *A. muciniphila* has also been detected in human breast milk, which serves as a medium for transmitting bacteria from mothers to infants, elucidating its presence in the digestive system of newborns (47). The adaptation of *A. muciniphila* to the mucosal environment is prompted by glucosamine-6-phosphate (GlcN6P) found in mucin, an essential requirement for this bacterium (43).

A. muciniphila’s Role in Liver Diseases

In vitro and in vivo studies

Ongoing research focuses on understanding the role, mechanisms, and effectiveness of *Akkermansia muciniphila* in treating liver diseases. Current findings suggest that this bacterium’s abundance may have several essential functions that improve liver health and protect against various disorders, including obesity and type 2 diabetes, independent risk factors for NAFLD and HCC. These functions include improving the intestinal barrier, regulating metabolism, reducing inflammation, and modulating the intestinal microbiota (Fig. 2.) (45, 48-51).

Improvement of the intestinal barrier

A. muciniphila is a microorganism that lives in the mucosal layers of the human body, particularly in the intestines. It is known for its ability to strengthen the intestinal barrier, which prevents toxins and harmful bacteria from entering the body (45, 48-51). A compromised intestinal mucosa can allow toxic substances to penetrate the bloodstream. However, *A. muciniphila* can help prevent this by degrading mucin, the main glycoprotein in the mucus layer lining the gut. This process releases monosaccharides and amino acids that serve as nutrients for *A. muciniphila* and other gut bacteria to grow optimally (42, 43, 52).

Interestingly, *A. muciniphila* grows more quickly in a mucin-based medium than in one containing glucose, N-acetylglucosamine, and N-acetylgalactosamine (53). It can also adhere to the intestinal epithelium, which helps to strengthen the thickness of the mucus layer and restore a compromised gut barrier (54). Furthermore, *A. muciniphila* produces short-chain fatty acids (SCFAs),

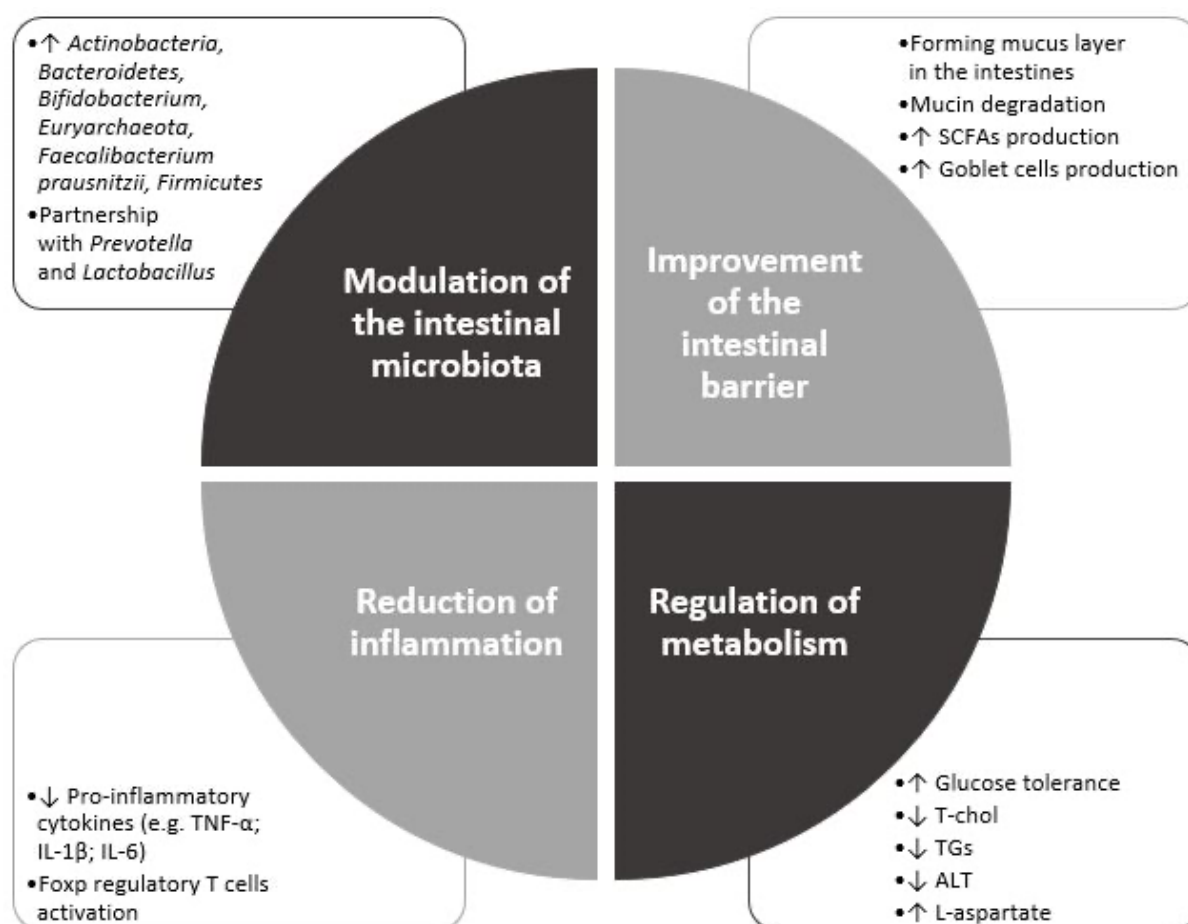


Figure 2. — The role of *A. muciniphila* (42, 43, 45, 48-50, 57, 60, 62, 64, 72, 73). ALT: Alanine aminotransferase; Foxp3: Forkhead box P3 transcription factor; $\text{IL-1}\beta$: Interleukin-1 beta; IL-6 : Interleukin-6; SCFAs: Short-chain fatty acids; T-chol: Total cholesterol; TGs: Triglycerides; $\text{TNF-}\alpha$: Tumor necrosis factor alpha.

improving intestinal barrier permeability. These SCFAs reduce endotoxemia by inhibiting the translocation of lipopolysaccharide (LPS) from the intestine to the circulatory system (49, 55).

Although *A. muciniphila* is typically recognized for its ability to degrade mucin, it has been found to also increase mucin production by boosting the number and density of goblet cells in mice fed a high-fat diet (HFD). This process helps to restore the thickness of the mucus layer and reinforce the integrity of the intestinal barrier (56, 57).

Regulation of metabolism

A. muciniphila is a microbe that regulates host metabolism through various mechanisms (48). One of the most important mechanisms is the neuroendocrine control of hunger and satiety via a hormone secreted by the L cells of the small intestine. This hormone is glucagon-like peptide-1 (GLP-1), and it is secreted in response to the provision of food. GLP-1 plays a role in maintaining glucose homeostasis. *A.*

muciniphila modulates GLP-1 levels by increasing the activity of a G protein-coupled receptor 119 (GPR119), an endocannabinoid receptor agonist called 2-oleoylglycerol. The bacterium also produces the P9 protein, which interacts with the intercellular adhesion molecule-2 (ICAM-2) receptor, activating phospholipase C (PLC). This initiates intracellular calcium signaling, ultimately resulting in the activation of cAMP response element-binding protein (CREB) (57, 58). *A. muciniphila* can produce SCFAs, such as acetate, propionate and butyrate, which can affect glucose and lipid balance (48). Additionally, the outer membrane protein Amuc 1100 of *A. muciniphila* has been shown to decrease body weight and fat mass while improving epithelial tight junctions in HFD-induced obese mice (59).

Various studies conducted on mice have shown that administering *A. muciniphila* may have metabolic benefits. Oral administration of *A. muciniphila* at levels of 108 to 109 colony forming units (CFU)/ml has been linked to reduced levels of total cholesterol (T-chol), serum triglycerides (TGs), and ALT in mice fed a high-fat

diet. In mice treated with *A. muciniphila*, the expression of genes involved in TGs production in liver tissue, such as sterol regulatory element-binding protein (SREBP) and carbohydrate-responsive element-binding protein (chREBP), was lower compared to the control group (60). Additionally, various strains of *A. muciniphila*, which were isolated from human fecal samples, have demonstrated different impacts on HFD-induced hyperlipidemia and hepatic steatosis. Specifically, *A. muciniphila* I (Amuc_GP01) has shown greater efficacy in mitigating hyperlipidemia, liver steatosis, and glucose tolerance compared to *A. muciniphila* II (Amuc_GP25) in HFD-induced obese mice. This suggests that different strains of *A. muciniphila* may exert their effects through distinct pathways, influencing pathological conditions differently (55, 61).

Recent research suggests that *A. muciniphila* may also treat NAFLD by modulating hepatic L-aspartate levels. In an obese mouse model induced by a high-fat and cholesterol (HFC) diet, *A. muciniphila* treatment has been shown to reverse NAFLD symptoms, such as hepatic steatosis and liver injury (62).

A. muciniphila promotes the transport of L-aspartate from the intestine, which elevates the amount of L-aspartate. In hepatocytes, L-aspartate can activate the liver kinase B1 - adenosine monophosphate-activated protein kinase (LKB1-AMPK) signaling pathway, which is critical for maintaining metabolic balance in normal and cancer cells (62, 63). There is also evidence to suggest that this microorganism can help prevent the development and progression of chronic liver diseases, including diabetes, obesity, metabolic-associated fatty liver disease (MAFLD), alcohol-related diseases like NAFLD, which can contribute to the development of liver cirrhosis and cancer (50, 51, 62).

Reduction of inflammation

Studies have shown that *A. muciniphila* can positively impact health by reducing the levels of pro-inflammatory cytokines, such as TNF- α and interleukin-1 β (IL-1 β) (50, 51). Research on mice has also revealed that the presence of colonies of *A. muciniphila* in the ileum can affect the expression of cell signaling and immune-related genes involved in homeostasis and immune support through altered peroxisome proliferator-activated receptors (PPARs)-dependent activities. By activating the forkhead box P3 transcription factor (Foxp3) regulatory T cells, *A. muciniphila* can significantly reduce adipose inflammation (43, 64, 65). Additionally, administration of *A. muciniphila* has been shown to decrease the expression of inflammatory cytokines, such as interleukin-6 (IL-6) in the livers of obese mice, which can help to reduce hepatocyte

damage, liver inflammation, and fibrosis (60). This is particularly important because the liver synthesizes IL-6 and plays a crucial role in influencing the production of acute-phase response proteins, including C-reactive protein (CRP) (66). Furthermore, IL-6 contributes to the progression of chronic hepatitis (especially hepatitis B), cirrhosis, HCC, and liver fibrosis (67).

The release of extracellular vesicles (EVs) by *A. muciniphila* and their role in reducing liver inflammation is exciting. EVs are membranous structures (nanoparticles composed of lipid bilayers) generated by organisms and serve essential functions in intercellular communication and various physiological and pathological processes. These particles typically exhibit a spherical morphology and range in diameter from 20 to 400 nm. EVs derived from the gut microbiota can travel to different host body organs through the circulatory system, triggering diverse immunological responses. The surface components of EVs have the potential to create a proficient interaction between the microbiota and the host's immune response. Gut microbiota, including *A. muciniphila*, also produce EVs. Evidence suggests that *A. muciniphila* and its EVs strongly inhibit liver inflammation and hepatocyte damage (66, 68). Both live *A. muciniphila* and its EVs have demonstrated superior anti-inflammatory effects on the liver tissue of mice treated with HFD/ carbon tetrachloride (CCL4). They influence gene expression related to Toll-like receptors (TLRs) and PPARs, suppressing inflammatory responses. TLRs and PPARs recognize and respond to various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that contribute to inflammation. EVs derived from *A. muciniphila* have reduced the expression of genes *tlr-5* and *tlr-9* in liver tissue. Additionally, at a concentration of 50 μ g, these vesicles significantly increased the mRNA expression of *ppar- α* and *ppar- γ* (66). Furthermore, *A. muciniphila* triggers the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway in peripheral blood mononuclear cells (PBMCs) via the receptors TLR2 and TLR4 (69).

Modulation of the intestinal microbiota

The gut microbiota is crucial in maintaining overall health, including liver health. Dysbiosis, which refers to reduced diversity in the gut environment, can weaken the intestinal membrane permeability and disrupt connections among mucosal cells. This allows the diffusion and activation of potentially inflammatory substances from the intestines, leading to gastrointestinal and other disorders (48). The heightened permeability facilitates the translocation of PAMPs, such as LPS,

bacteria, and inflammatory cytokines from the intestinal lumen into the portal blood and liver, causing endotoxemia and the activation of inflammatory pathways with the activation of TLRs and the secretion of pro-inflammatory cytokines, such as TNF- α , IL-6, and CRP, enhancing liver inflammation, fibrosis, and systemic inflammation. Chronic inflammation that results from imbalances in the intestinal microbiota is considered a key contributor to the progression of chronic liver diseases, such as cirrhosis, hepatic steatosis, autoimmune conditions, and hepatocarcinoma-related complications (70). Disruptions in the microbiota are also observed in individuals with alcohol-associated liver disorders. Studies have shown that alcoholics with increased intestinal permeability experience a decline in the presence of *Ruminococcus* and *Faecalibacterium prausnitzii*. Conversely, patients with NAFLD exhibit an increase in *Proteobacteria*, *Enterobacteriaceae*, and *Escherichia*, whereas individuals diagnosed with primary sclerosing cholangitis exhibit an elevation in *Enterococcus* and *Lactobacillus* (71). Accumulating evidence suggests that the presence of *A. muciniphila* in gut tract supports the diversity of microbial genes and the overall abundance of microbial ecosystems, including *Actinobacteria*, *Bacteroidetes*, *Bifidobacterium*, *Euryarchaeota*, and *Firmicutes* (49, 72). Additionally, the monosaccharides provided by *A. muciniphila* support the expansion of *Faecalibacterium prausnitzii*. Both species exhibit a mutually beneficial (syntrophic) relationship (73). Furthermore, *A. muciniphila* can partner with other gut bacteria, such as *Bacteroides*, *Prevotella*, and *Lactobacillus* (64).

Human Studies

The remarkable potential of *A. muciniphila* as a therapeutic intervention for metabolic syndrome, demonstrated in laboratory models (both in vitro and in vivo), has spurred numerous clinical trials involving human participants (74). The presence of *A. muciniphila* in humans tends to decrease in various pathological conditions, including obesity, diabetes, hypertension, and hypercholesterolemia (75). A substantial body of evidence, including a randomized, double-blind, placebo-controlled pilot study conducted in 2017, supports the beneficial effects of *A. muciniphila* in improving metabolic parameters in overweight or obese individuals with insulin resistance. Live and pasteurized *A. muciniphila* showed improved blood markers related to liver dysfunction and metabolic inflammation. The effective supplementation regimen involved daily oral intake of 10¹⁰ bacteria for three months. Compared to the control group, individuals receiving *A. muciniphila* supplementation experienced weight loss, as evidenced by reduced plasma total cholesterol and fat mass levels.

Moreover, the supplementation positively impacted insulin sensitivity and insulinemia (40). The synergistic effects of *A. muciniphila* supplementation with other probiotics, such as *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis*, and *Anaerobutyricum hallii*, were observed in adult patients diagnosed with type 2 diabetes, improving clinical and metabolic parameters. Notably, *A. muciniphila* supplementation enhanced postprandial glucose control without significant adverse effects. This encouraging finding was derived from a randomized, parallel-group, double-blind, placebo-controlled study. The bacterium was administered in a specially prepared formulation known as WBF-011, encapsulated for oral consumption. Each capsule contained inulin, *A. muciniphila*, *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis*, and *Anaerobutyricum hallii*. Participants were instructed to take three capsules twice daily, within 30 minutes of morning and evening meals, for 12 weeks (41).

The clinical evidence underscores the safe oral administration of *A. muciniphila* in humans (40, 41). Furthermore, the European Union (EU) has approved the use of *A. muciniphila* at a safe dose of 1 x 10¹⁰ cells/day for 12 weeks as a dietary supplement and food for particular medical purposes (76). However, it is essential to consider that mild gastrointestinal side effects may occur when initiating probiotic supplementation. Although infrequent, participants in the study reported occurrences of nausea, flatulence, borborygmi, gastric reflux, and cramps (40).

Approaches for Enhancing the Gut Abundance of *A. muciniphila*

The optimal pH for the growth of *A. muciniphila* is 6.5. Low pH levels hinder its proliferation, making it more prevalent in the distal than the proximal colon. *A. muciniphila* is also sensitive to temperature, and its colony numbers significantly decrease at temperatures exceeding 44°C. Moreover, oxygen in nanomolar concentrations is more beneficial than complete anaerobic conditions (77).

Interestingly, combining *A. muciniphila* with quercetin intake has shown potential in reducing blood glucose levels, plasma insulin, and triglycerides while improving gut-liver bile flow (78). The antioxidant, anti-inflammatory, and prebiotic effect of quercetin may enhance the impact of *A. muciniphila* on liver diseases treatment by modulating gut microbiota and related gut-liver axis activation, counteracting inflammasome initiation response and reticulum stress pathway induction. This effect leads to the reduction of intrahepatic lipid accumulation through the blockage of lipid metabolism gene expression deregulation,

cytochrome P450 family 2 subfamily E member 1 (CYP2E1)-dependent lipoperoxidation and related lipotoxicity (78, 79). Polyphenols found in grapes, cranberries, and procyanidins from apples can also increase the abundance of *A. muciniphila* colonies in the gut (80, 81). Additionally, dietary strategies involving caloric restriction and supplementation with substances, such as resveratrol, pomegranate extract, polydextrose, yeast fermentate, sodium butyrate, and inulin have been observed to enhance the abundance of *A. muciniphila*. Conversely, diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols have been associated with a decreased abundance of *A. muciniphila* (80, 82). Furthermore, the use of certain drugs, such as metformin in patients with diabetes or atorvastatin in patients with hypercholesterolemia, has been shown to promote the abundance of *A. muciniphila* through the enrichment of mucin degradation and SCFAs secretion (83, 84).

Although increasing the abundance of *Akkermansia muciniphila* in the gut might have positive health benefits, it is essential to consider the potential risks associated with such interventions. One study has shown that over-colonized *A. muciniphila* in the presence of cancer cells decreased the thickness of the intestinal mucus layer, compromising the intestinal barrier and promoting inflammation. Thus, it would eventually aggravate the development of colitis and colorectal cancer (85). This finding suggests that increasing *A. muciniphila* abundance may not always be beneficial. It highlights the importance of a personalized approach when considering strategies to manipulate the gut microbiota.

Future perspectives and conclusions

The gut microbiota plays a significant role in the development of liver diseases. Researchers have made progress in understanding how intestinal microbes contribute to these diseases and have designed therapeutic approaches, such as probiotics and prebiotics, to target the modulation of the intestinal microbiota. These approaches have shown promise in treating liver disorders by enhancing intestinal barrier function, reducing inflammation, and mitigating liver damage. Recent studies have highlighted the effectiveness of *A. muciniphila*, a type of gut bacteria, in improving metabolic disorders, positioning it as a promising “next-generation beneficial microbe”. Both live, and pasteurized *A. muciniphila* and its components have demonstrated beneficial effects. Studies have found changes in *A. muciniphila* abundance in animal models and human patients with metabolic diseases, highlighting its therapeutic benefits and the effectiveness of interventions to increase its presence. Therefore, *A. muciniphila* stands out as one of the most promising microbes for host metabolism due to its positive impact on metabolic disorders in animals and humans.

The potential of *A. muciniphila* as a next-generation probiotic to address liver issues is highly promising. Future studies should focus on establishing the optimal dosage, duration, and administration method of *A. muciniphila* for liver diseases management. However, it is crucial to emphasize the necessity of seeking professional advice from a physician or nutritionist before using *A. muciniphila* supplements or making significant dietary changes.

Further research is imperative to fully understand the precise mechanisms involved and to develop effective therapeutic strategies to enhance overall liver health. Ongoing research will continue to shed light on the potential of *A. muciniphila* in the treatment of liver diseases.

Abbreviations

ACLF: Acute-on-chronic liver failure; AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; *A. muciniphila*: *Akkermansia muciniphila*; AST: Aspartate aminotransferase; CCL4: Carbon tetrachloride; CFU: Colony forming unit; chREBP: Carbohydrate-responsive element-binding protein; CREB: cAMP response element-binding; CRP: C-reactive protein; CYP2E1: Cytochrome P450 family 2 subfamily E member 1; DAMPs: Damage-associated molecular patterns; DASH: Dietary Approaches to Stop Hypertension; EU: European Union; EVs: Extracellular vesicles; Foxp3: Forkhead box P3 transcription factor; GlcN6P: Glucosamine-6-phosphate; GLP-1: Glucagon-like peptide-1; GPR119: G protein-coupled receptor 119; HCC: Hepatocellular carcinoma; HFC: High-fat and cholesterol; HFD: High-fat diet; HOMA-IR: Homeostasis model assessment of insulin resistance; ICAM-2: Intercellular adhesion molecule-2; IL-1 β : Interleukin-1 beta; IL-6: Interleukin-6; ISAPP: International Scientific Association for Probiotics and Prebiotics; LD – Liver disease; LKB1-AMPK: Liver kinase B1 - adenosine monophosphate-activated protein kinase; LPS: Lipopolysaccharide; MAFLD: Metabolic-associated fatty liver disease; MD: Mediterranean diet; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; NGPs: Next-generation probiotics; PAMPs: Pathogen-associated molecular patterns; PBC: Primary biliary cholangitis; PBMCs: Peripheral blood mononuclear cells; PLC: Phospholipase C; PPARs: Peroxisome proliferator-activated receptors; PSC: Primary sclerosing cholangitis; SCFAs: Short-chain fatty acids; SREBP: Sterol regulatory element-binding protein; T-chol: Total cholesterol; TGs: Triglycerides; TNF- α : Tumor necrosis factor alpha; TLRs: Toll-like receptors; VLDLs: Very-low-density lipoproteins.

Declarations

Author's contribution: K. Rachwał, K. Mierczak; *Formal analysis:* K. Rachwał, K. Mierczak; *Software:* K. Rachwał, K. Mierczak; *Supervision:* K. Rachwał, K. Mierczak; *Validation:* T. Popławski; *Visualization:* K. Mierczak; *Writing - original draft:* K. Rachwał, K. Mierczak; *Writing - review & editing:* K. Rachwał, K. Mierczak, T. Popławski.

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