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Akkermansia muciniphila: A key player in gut microbiota-based disease modulation

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ABSTRACT

Akkermansia muciniphila (*A. muciniphila*), a mucin-degrading bacterium residing in the gut's mucus layer, has emerged as a key modulator of host physiology with significant implications for health and disease. Growing evidence shows that *A. muciniphila* influences host metabolism, strengthens gut barrier integrity, modulates microbial composition, and regulates immune responses. This review synthesizes current literature on *A. muciniphila*, emphasizing its role in conditions such as metabolic disorders, inflammatory bowel disease (IBD), *Clostridioides difficile* infection (CDI), cancer, cardiovascular disease, and aging. In metabolic disorders, *A. muciniphila* improves insulin sensitivity, reduces adiposity, and increases GLP-1 secretion through mechanisms involving short-chain fatty acid (SCFA) production and TLR2 activation. It also restores microbial balance and reduces inflammation in type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). In IBD, it enhances mucus secretion, tight junction integrity, regulatory T cell expansion, and suppresses pro-inflammatory cytokines. In CDI, it promotes epithelial protection and colonization resistance by enriching butyrate producers. In cancer, it boosts immune checkpoint inhibitor efficacy by enhancing IL-12 and T cell activation. It also reduces vascular inflammation and calcification in cardiovascular disease via propionate production. In aging, *A. muciniphila* improves metabolic health, reduces chronic inflammation, promotes SCFA production, and preserves blood–brain barrier integrity. Both live and pasteurized forms are effective, with pasteurized, particularly Amuc_1100, showing enhanced benefits. Broader application requires large-scale trials, better understanding of host and strain variability, and development of personalized, synergistic therapies.

1. Introduction

The human intestine hosts a diverse community of microbial species, recognized as the "gut microbiota". The gut microbiota has long been estimated to comprise approximately 10^{14} microorganisms, suggested that the bacterial cells outnumber human cells by more than 10-fold (Bäckhed et al., 2005; Gill et al., 2006). However, more recent estimates indicate a near 1:1 ratio, with the average adult harboring about 38 trillion bacterial cells and 30 trillion human cells (Sender et al., 2016). Given the intimate symbiotic relationship and the substantial microbial contributions, the host and its microbiota are frequently conceptualized as a "superorganism" (Gill et al., 2006; Turnbaugh et al., 2007). These microbes play vital roles in digestion, immune system modulation, metabolic regulation, and neurological communication. It is essential for maintaining health and pathogenicity, with disruptions in this delicate balance, known as dysbiosis, being linked to various diseases. These include irritable bowel syndrome (Canakis et al., 2020), cardiovascular disease, liver dysfunction, and psychological disorders (Liang et al., 2018).

Two major phyla dominate the gut microbiota, *Bacteroidetes* and *Firmicutes*, accounting for 90 % of the total microbial population. The remaining microbiota includes members of *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* (Rinninella et al., 2019). Among these, *Akkermansia muciniphila* (*A. muciniphila*), a strict anaerobic bacterium, was first isolated from human feces by Derrien et al. (2004). *A. muciniphila* resides predominantly in the mucus layer of the gastrointestinal tract, particularly in the caecum. It is present in 90 % of healthy individuals and constitutes 3–5 % of the gut microbiota from early life (Belzer and de Vos, 2012). It stably colonizes the gut within the first year of life but shows a significant decline in elderly individuals and those with inflammatory and metabolic disorders, including diabetes, cancer, obesity, and inflammatory bowel diseases (Zhao et al., 2023).

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Mucin, a glycoprotein secreted by the intestinal lining, serves as the primary nutrient source for *A. muciniphila.* Using mucin-degrading enzymes such as α- and β-D-galactosidase and

α-L fucosidase, *A. muciniphila* breaks down mucin to obtain carbon and nitrogen (Davey et al., 2023). This process produces essential metabolites, including short-chain fatty acids (SCFAs), which confer competitive survival advantages to other beneficial gut bacteria while protecting against pathogens (van der Lugt et al., 2019). Additionally, *A. muciniphila* stimulates mucin production, strengthens the mucous barrier, supports gut microbiota integrity, and promotes metabolic and immune functions (Rodrigues et al., 2022).

These discoveries underscore *A. muciniphila* as a promising candidate for next-generation probiotics. This review aims to highlight the role of *A. muciniphila* in microbiota-associated diseases and conditions, including metabolic disorders, inflammatory diseases, *Clostridioides difficile* infection, cardiovascular disease, and aging. It summarizes current research on *A. muciniphila* up to 2025 and identifies key knowledge gaps especially its relationship with the gut-microbiome and host-bacterium interaction mechanisms. By integrating recent findings and proposing future research directions, this review provides a timely and valuable contribution to the field.

2. Classification and characteristics

2.1. Taxonomy

A. muciniphila is a member of the Verrucomicrobia (phylum), Verrucomicrobiae (class), Verrucomicrobiales (order), Verrucomicrobiaceae (family), Akkermansia (genus), and muciniphila (species) (Ottman et al., 2016). *A. muciniphila* was first identified as a novel species in 2004, marking the initial successful cultivation of a Verrucomicrobia species inhabiting the gut (Derrien et al., 2004). However, advancements in genomic research have shown that *Akkermansia* comprises over 25 candidate species with diversity in strain functionality (González et al., 2023; Guo et al., 2017; Karcher et al., 2021). Current initiatives approximate range of three to seven phylogroups notably AmI-III, each characterized by distinct metabolic profiles, high nucleotide diversity, oxygen tolerance and sulfur utilization, which influence their ability to colonize the gastrointestinal tract (Becken et al., 2021; Guo et al., 2017). *Akkermansia* species inhabit the gut's mucosal layer, with AmII and AmIII strains showing distinct SCFA production, mucin degradation, and vitamin B_{12} synthesis capabilities (Kirmiz et al., 2020). Well, human guts are not purely inhabited by a single strain but due to the competition among the group of strains, one of the particular strains flourishes and amplify, which leads to the confinement of other strains (Truong et al., 2017) and resulting in host-specific strain dominance (Karcher et al., 2021). Notably, all species isolated from different mammals have a core ability to survive in the mucosal habitat but their ability to synthesize short-chain fatty acids (SCFAs), their physiology, growth on mucin and genomic structures make them unique from each other (Geerlings et al., 2021).

2.2. Morphology and Metabolic characteristics

Akkermansia strains are primarily isolated from human and rodent feces (Zhai et al., 2019). Until 2017, only two strains ATCC BAA-835T and *A. glycaniphila Pyt* had complete genome sequencing (Ouwerkerk et al., 2017). Currently, metagenome analysis of human gut microbiota of different age groups, body parts, diet and regions helps to analyze bacterial genomes and out of 3810 samples, 1159 contained genomes of *A. muciniphila* from various geographic regions and age groups, which proves how this bacterium evolves and varies (Almeida et al., 2021; Nayfach et al., 2019). This gram-negative bacterium is non-motile, non-spore-forming, and oval-shaped, with a diameter ranging from 0.6 to 1.0 μm (Derrien et al., 2004). Its colonies are generally small, round, and translucent. This bacterium has a genomic G+C content of approximately 55.8 % and exhibits optimal growth under strictly anaerobic conditions at 37°C, suggesting its adaptation to the human intestinal environment (Ottman et al., 2017). Its outer membrane features specific proteins and pili-like structures that facilitate adherence to mucin and interaction with the host (Plovier et al., 2017; van der Lugt et al., 2019).

A. muciniphila predominantly utilizes mucin as its primary energy source. However, it can also be cultured in medium supplied with glucose, defined amino sugars (N-acetylglucosamine and N-acetyl galactosamine), when additional protein sources are available, and mucin-derived components enhance its growth (Depommier et al., 2019). Glucosamine-6-phosphate (GlcN6P), a mucin-derived metabolite, is critical for *Akkermansia*'s growth and its adaptation to the mucosal niche (van der Ark et al., 2018). The primary metabolic characteristics involve mucin degradation via glycosyl hydrolases, sulfatases, and proteases, resulting in oligosaccharide fermentation into acetate. Cross-feeding interactions then contribute to the production of butyrate and propionate. Remarkably, *A. muciniphila* can thrive in the absence of added vitamins, with some strains even capable of producing vitamin B12 (Kirmiz et al., 2020).

3. Roles and mechanisms of *A. muciniphila* in gut microbiota-associated diseases and conditions

The roles of *A. muciniphila* in gut microbiota-associated diseases and conditions, including metabolic disorders (obesity, type 2 diabetes, non-alcoholic fatty liver disease), inflammatory bowel disease, *Clostridioides difficile* infection, cancer, cardiovascular disease, and aging, are discussed individually and in Fig. 1.

3.1. Metabolic disorders

3.1.1. Obesity

Due to its multifaceted roles in gut health and metabolism, *A. muciniphila* has been shown to aid in managing and preventing metabolic syndrome. Obesity, characterized by excess body weight, increased insulin production, insulin resistance, and chronic inflammation, is a major component of this syndrome (Hildebrandt et al., 2023). Studies indicate that *A. muciniphila* positively influences lipid metabolism and inflammation, thereby mitigating the effects of obesity and metabolic syndrome (Xu et al., 2020). The study (Hasani et al., 2021) demonstrated that *A. muciniphila* is associated with reduced adiposity and improved insulin sensitivity in obese individuals. This bacterium helps by enhancing gut barrier integrity through the upregulation of tight junction proteins such as occludin and zonula occludens-1 (ZO-1). This process subsequently contributes to the reduction of metabolic endotoxemia and systemic inflammation, which are critical aspects of gut dysfunction associated with obesity and regulate fat storage and energy expenditure (Everard et al., 2013). A key mechanism involves its production of short-chain fatty acids (SCFAs), engage with G-protein-coupled receptors, specifically GPR41 and GPR43, which help modulate fat metabolism and energy balance (Plovier et al., 2017). Similarly, Ghaffari et al. (2023) highlighted the critical role of the gut microbiome, including *A. muciniphila,* in harvesting energy from the diet. Individuals with higher *A. muciniphila* levels tend to have lower body fat and improved metabolic health. Additionally, another study by Zeng et al. (2025) demonstrated that *A. muciniphila* supplementation may benefit obesity by improving insulin sensitivity and reducing visceral fat accumulation. Moreover, it has been shown that pasteurized *A. muciniphila* and its outer membrane protein Amuc_1100 activate Toll-like receptor 2 (TLR2), thereby inducing anti-inflammatory responses and improving metabolic parameters without necessitating live bacterial colonization (Plovier et al., 2017).

Referring to the modulation of gut microbiome, *Akkermansia* not only influences the availability of nutritional resources and

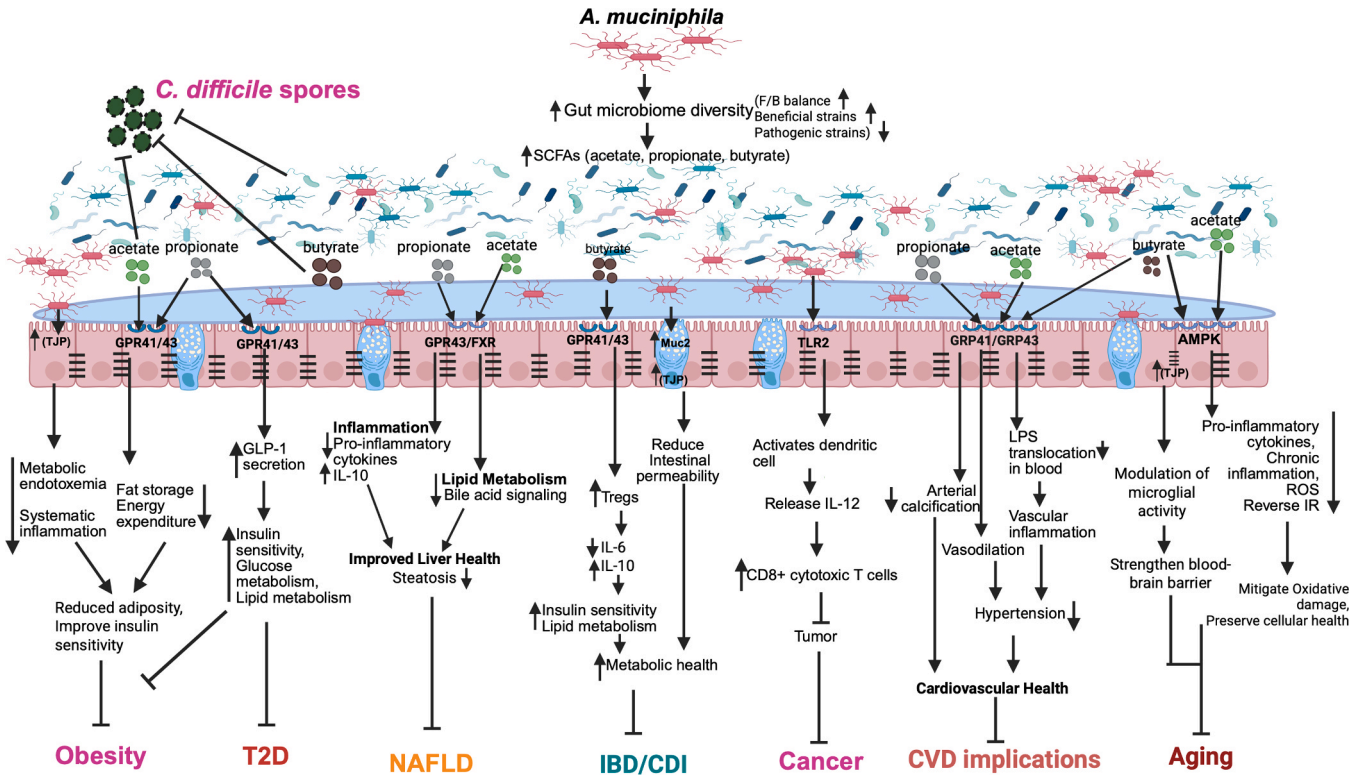

Fig. 1. Effects of *A. muciniphila* on gut microbiota-associated human diseases and conditions through modulation of the gut microbiome and gut metabolites, particularly short-chain fatty acids (SCFAs). T2D, type 2 diabetes; NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular disease; IBD, inflammatory bowel disease; *C. difficile*, *Clostridioides difficile*; GPR41/43, G-protein-coupled receptors 41/43; GLP-1, glucagon-like peptide-1; IL-10/6, interleukins 10/6; IR, insulin resistance; TJP, tight junction protein; AMPK, AMP-activated protein kinase; CD8 +, cluster of differentiation 8; ROS, reactive oxygen species; TLR2, Toll-like Receptor 2; FXR, Farnesoid X receptor; LPS, lipopolysaccharide; F/B, *Firmicutes*-to-*Bacteroidetes* ratio.

environmental factors affecting gut microbiota, but also enhance trophic resources for the gut community through the degradation of extracellular mucins (Belzer et al., 2017). The mucolytic activity of *A. muciniphila* involves mucin-degrading enzymes, as well as the production of SCFAs such as acetate and propionate, which neighboring microbial communities can utilize for their benefit (Lopez-Siles et al., 2018). For instance, the mucolytic enzymes stimulated by *A. muciniphila* increased in the presence of the butyrogenic gut commensal *Anaerostipes caccae* (Chia et al., 2018). Additionally, the monosaccharides metabolized by *A. muciniphila* promote the growth of *Faecalibacterium prausnitzii*, which synthesizes butyrate, an anti-inflammatory SCFA vital for the health of colon, from acetate and lactate. The co-residence of *A. muciniphila* and *F. prausnitzii* in the mucosa establishes a syntrophic relationship, and both these varieties are depleted in inflammatory bowel disease (Lopez-Siles et al., 2018). *A. muciniphila* contributes to the production of these metabolites albeit incompletely, thereby fostering metabolic cross-feeding interactions within the gut ecosystem.

Furthermore, supplementation with *A. muciniphila* has been shown to increase bacterial gene density and microbial network complexity, influencing key components of the gut microbiota, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Euryarchaeota* (Dao et al., 2016). *A. muciniphila* can form alliances with *Bacteroides-Prevotella*, *Bacteroidetes*, *Firmicutes*, and *Lactobacillus*. Consequently, colonization by *A. muciniphila* promotes mucosal health, shapes gut microbiota toward anti-inflammatory profiles, increases the abundance of *A. muciniphila*, and its microbial allies leads to significant shifts in overall gut microbiome composition.

3.1.2. Type 2 diabetes (T2D)

Type 2 diabetes, a metabolic disorder defined by insulin resistance, persistent hyperglycemia, and low-grade inflammation, is another condition where *A. muciniphila* demonstrates therapeutic potential (Zatterale et al., 2019). It helps maintain gut homeostasis and modulates metabolic factors associated with type 2 diabetes. For instance, *A. muciniphila* enhances the absorption of gut hormones such as GLP-1, which is crucial for insulin secretion, glucose metabolism, and improved glycemic regulation (Angelini et al., 2024; Zeng et al., 2025). This phenomenon is partially mediated by the production of short-chain fatty acids (SCFAs), particularly propionate, which induces the secretion of GLP-1 and enhances insulin sensitivity. It was noted that pasteurized *A. muciniphila* has shown even greater benefit, such as reduced fat mass (Choi et al., 2021). Furthermore, *A. muciniphila* can improve the efficacy of some antidiabetic drugs like metformin by enhancing the gut microbial profile and reducing inflammation, which amplifies the drug's effectiveness while mitigating its side effects (Lee et al., 2021). Similarly, *A. muciniphila* influences metabolic pathways, including insulin sensitivity and lipid metabolism. Its presence is associated with improved metabolic health, suggesting a role in managing obesity and type 2 diabetes (Hasani et al., 2021).

A key insight into the gut microbiome is its association with T2D, which is commonly linked to higher levels of pathogenic bacteria, including *Ruminococcus, Fusobacterium,* and *Blautia*, as well as lower levels of SCFA-producing bacteria such as *Bifidobacterium, Bacteroides, Faecalibacterium,* and *Roseburia* (Gurung et al., 2020). Studies have shown that both humans and mice with T2D exhibit reduced levels of *A. muciniphila* (Everard et al., 2013; Yassour et al., 2016). While the exact composition of a healthy human gut microbiota remains unclear, high microbial richness is generally considered beneficial. Administration of *A. muciniphila* in mice has been shown to enhance gut microbiota diversity, as indicated by increases in Shannon index, Ace, and Chao1 metrics (Li et al., 2025). Intestinal homeostasis is largely determined by the richness and diversity of gut microbiota, a balance that

A. muciniphila helps to maintain. Among the 19 identified bacterial phyla in the human intestine, *Firmicutes* and *Bacteroidetes* are the most abundant (Qin et al., 2010), and the *Firmicutes/Bacteroidetes* ratio has been recognized as a key indicator of health status, including in conditions such as T2D (Magne et al., 2020). Interestingly, *A. muciniphila* has been shown to prevent diabetes and NAFLD in mice experiencing *Firmicutes/Bacteroidetes* dysbiosis (Hänninen et al., 2018) (Pérez-Monter et al., 2022). It is also important to note that while *Firmicutes* and *Bacteroidetes* contribute to SCFA production, they may not be directly involved in *A. muciniphila*'s regulation of SCFAs (Magne et al., 2020). Additionally, colonization with *A. muciniphila* has been associated with an increased abundance of potential probiotic bacteria, including *Lactobacillus* and *Verrucomicrobia* (Xia et al., 2022)

3.1.3. Non-alcoholic fatty liver disease (NAFLD)

The gut-liver axis, a bidirectional interaction between the gut microbiota and the liver, plays a pivotal role in liver health and the development of liver diseases (Pabst et al., 2023; Zheng and Wang, 2021). *A. muciniphila*, a symbiont gut bacterium, has shown therapeutic potential in maintaining liver health and preventing conditions such as NAFLD and liver fibrosis. Chronic liver diseases, including NAFLD, are often inflammatory in nature (Feng et al., 2024). By producing SCFAs like acetate and propionate (Rodrigues et al., 2022), *A. muciniphila* regulates pro-inflammatory cytokines and promotes the release of anti-inflammatory cytokines such as IL-10 (Kang et al., 2024). NAFLD is characterized by hepatic steatosis, defined as fat accumulation exceeding 5 % of liver weight (Li et al., 2020). *A. muciniphila* helps regulate lipid metabolism by attenuating bile acid signaling via receptors such as Farnesoid X Receptor (FXR), thereby enhancing lipid digestion and reducing liver fat deposition (Di Ciaula et al., 2022). This results in decreased steatosis and improved liver health.

At the gut microbiome level, a previous study demonstrated that when mice were fed a high-fat diet, the *Firmicutes/Bacteroidetes* ratio was significantly lower compared to that in the *A. muciniphila*-treated group. Additionally, the rarefaction curve analysis revealed that species richness was significantly lower in the non-*A muciniphila*-treated group than in the *A. muciniphila*-treated group. These findings suggest that *A. muciniphila* contributes to the modulation of the *Firmicutes/Bacteroidetes* ratio and enhances gut microbiota diversity. This effect may be attributed to SCFAs, such as propionic acid and acetic acid, which are derived from mucin breakdown by *A. muciniphila*. Consequently, *A. muciniphila* treatment promotes gut microbiota diversity (Lukovac et al., 2014; Derrien et al., 2011).

3.2. Inflammatory bowel disease (IBD)

The intestinal barrier, also known as the epithelial barrier, is crucial for regulating the influx of nutrients, electrolytes, and water through the intestine while preventing the entry of toxic substances, including bacteria and toxins, into the bloodstream (Vancamelbeke et al., 2017). Inflammatory bowel disease is a chronic condition characterized by the host immune system attacking elements of the digestive tract (Diez-Martin et al., 2024).

Significant research has highlighted the beneficial effects of *A. muciniphila* in patients with IBD. Individuals with IBD often experience increased intestinal permeability, also known as "leaky gut," due to disruptions in the tight junction proteins of the gut. *A. muciniphila* is effective in synthesizing mucus, a protective slimy layer that forms a barrier above the intestinal tissue (Kim et al., 2021). This mucus layer prevents pathogenic bacteria and fungi from entering the bloodstream and helps preserve the structure of epithelial cells (Martens et al., 2018). Involved in synthesizing mucin and glycoprotein, *A. muciniphila* enhances mucus production, strengthens the gut's defense mechanisms, and reduces intestinal permeability (Yu et al., 2022).

Tight junction proteins form complexes that prevent the penetration of toxic substances into the intestinal mucosa (Hollander and Kaunitz, 2020). *A. muciniphila* regulates the expression of tight junction proteins, such as occludin, enhancing the barrier against bacteria and endotoxins responsible for causing inflammation in IBD patients (Liu et al., 2023). The short-chain fatty acids (SCFAs) produced during the degradation of mucin by *A. muciniphila*, in conjunction with butyrate-producing bacteria through cross-feeding mechanisms, facilitate the induction of $Foxp3^{+}$ regulatory T cells, which reduce the levels of IL-6 and other pro-inflammatory cytokines, enhance IL-10 production, and strengthen the gut barrier, collectively contributing to the mitigation of intestinal inflammation (Zhang et al., 2024). Additionally, *A. muciniphila* has been implicated in modulating immune response by promoting the generation of regulatory T cells (Tregs) and inhibiting cytokine secretion (Mei et al., 2024). Tregs play a critical role in immune tolerance inflammation control (Ni et al., 2021). Chronic inflammation in IBD is often associated with elevated levels of cytokines such as TNF- α, IL 6 and CRP (Shahini and Shahini, 2023), which can impair insulin signaling and glucose uptake, contributing to insulin resistance. By reducing inflammatory markers like TNF-α and IL-6, *A. muciniphila* exerts an anti-inflammatory effect, thereby improving insulin sensitivity (Luo et al., 2021). IBD also impacts lipid metabolism, resulting in hypertriglyceridemia, hypercholesterolemia, and an imbalance of fatty acid metabolism, which collectively increases cardiovascular risk in IBD patients. *A. muciniphila* helps lower triglyceride and cholesterol levels, positively altering lipid profiles (Kim et al., 2020). Elevated plasma triglyceride and cholesterol levels, particularly in IBD patients with metabolic syndrome or obesity, are well-documented. Besides, visceral fat is closely linked to metabolic diseases, systemic inflammation, and insulin resistance, all of which exacerbate IBD (Stürzl et al., 2021). This fat releases pro-inflammatory molecules, including adipokines such as leptin and cytokines, which prolong inflammation and worsen insulin resistance (Ahmed et al., 2021). *A. muciniphila* has been shown to reduce visceral fat stores, thereby mitigating inflammation and improving metabolic conditions (Abuqwider et al., 2021). By regulating lipid metabolism, *A. muciniphila* also protects against cardiovascular diseases, which are prevalent among IBD patients (Gofron et al., 2024).

Dysbiosis, an imbalance in gut microbiota composition, is another hallmark of IBD (Santana et al., 2022). *A. muciniphila* supports the restoration of the gut microbial community, strengthening gut barrier function and reducing inflammation (Cheng and Xie, 2021). Studies have demonstrated that administrating *A. muciniphila* can affect both the abundance and diversity of gut microbiota, which are disrupted in IBD. Potential pathogenic bacterial genera linked to IBD include *Escherichia coli* and *Helicobacter* species, while IBD is also characterized by a reduction in beneficial bacteria such as *Lactobacillus, Bifidobacterium*, and *A. muciniphila* itself (Yang et al., 2021). A direct relationship between *A. muciniphila* and cytokine IL-10 upregulation has been found with IL-10 levels correlating with species enriched by *A. muciniphila*, including *Verrucomicrobia, Akkermansia, and Ruminococcaceae*. Meanwhile, *A.muciniphila* administration has been shown to reduce *Bacteroidetes*, a bacterial group associated with colitis (Bian et al., 2019).

3.3. Clostridioides difficile infection (CDI)

Clostridioides difficile (*C. difficile*) infection is a severe, hospital-acquired gastrointestinal disease caused by the pathogenic *C. difficile* in the gut microbiota (Bien et al., 2013). It is characterized by diarrhea, inflammation, and potentially fatal complications such as toxic megacolon (Sehgal et al., 2021). CDI has emerged as a significant public health concern due to the severity of symptoms, high morbidity rates, and its prevalence among immunocompromised and hospitalized individuals (Fu et al., 2021).

A hallmark of CDI is the disruption of the intestinal epithelium, which facilitates the translocation of toxins such as toxin A and toxin B, leading to inflammation and tissue damage (Alam and Madan, 2024). *A. muciniphila* has been shown to enhance mucus secretion by activating goblet cells and upregulating mucin-associated genes, including *MUC2*

(Li et al., 2023). This increased mucus production creates a physical barrier that minimizes the interaction between *C. difficile* toxins and epithelial cells. Additionally, *A. muciniphila* strengthens tight junctions within the intestinal epithelium, reducing gut permeability and preventing the translocation of toxins and pathogens into the host system (Chelakkot et al., 2018). *A. muciniphila* has also been shown to reduce tissue damage and improve epithelial barrier function, offering a protective effect against the deleterious consequences of CDI (Wu et al., 2022).

One of the primary factors contributing to CDI is the disruption of the host's normal gastrointestinal microbiota, often associated with antibiotic use (Seekatz et al., 2022). Microbiota analysis of CDI patients reveals a less diverse gut bacterial community enriched with pathogenic species, a state of dysbiosis that fosters *C. difficile* overgrowth and recurrent infections (Martinez et al., 2022). Emerging research indicates that *A. muciniphila* can mitigate the effects of CDI on gut homoeostasis and the immune system. *A. muciniphila* has been reported to decrease pathogen colonization in the gut through competitive exclusion (van der Lugt et al., 2019). Furthermore, its enzymatic activity in breaking down mucin generates oligosaccharides and other metabolites that support the growth of other commensal bacteria, thereby enriching microbiota diversity and reducing *C. difficile* colonization. The role of *A. muciniphila* in microbiome composition during *Clostridium difficile* infection (CDI) was investigated using a mouse CDI model (Wu et al., 2022). Gut microbiome analysis revealed that *A. muciniphila* supplementation significantly reduced colonization by opportunistic pathogens, including *Enterococcus, Escherichia–Shigella,* and *Proteobacteria*, which promote inflammation (Shin et al., 2016) and create conditions favorable for *Clostridium* invasion, as well as *Clostridioides* and *Clostridium sensu stricto*. Additionally, the *A. muciniphila*-treated group exhibited an increased relative abundance of butyrate-producing bacteria, such as *Blautia* (family *Lachnospiraceae*, order *Lachnospirales*), *Parabacteroides*, and *Akkermansia*, all of which contributed to a reduction in *C. difficile* compared to the control group without *A. muciniphila* administration (Ghimire et al., 2020).

3.4. Cancer

A. muciniphila demonstrated significant potential in preventing and treating cancer through immunomodulation, restoration of gut microbiota balance, and enhancement of cancer therapy efficacy (Faghfuri and Gholizadeh, 2024). Immune checkpoint inhibitors such as programmed death-1 (PD-1) inhibitors and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors are novel therapeutic strategies for cancers including melanoma, lung cancer, and others (Patwekar et al., 2024). *A. muciniphila* contributes to anti-tumor immunity by interacting and activating the dendritic cells, induce them to produce interleukin-12 (IL-12), boosts the activation of cytotoxic T lymphocytes (CD8 +), which helps the body's immune response against tumors (Smith et al., 2021). Additionally, *A. muciniphila* has been shown to improve tumor sensitivity to chemotherapy and radiation by modulating the immune system and reducing inflammation. Its protective role in the gut helps mitigate the gastrointestinal side effects of cancer therapies, thereby enhancing patient compliance and overall quality of life (Sougiannis et al., 2021). Experimental data on *A. muciniphila* in intestinal inflammation demonstrate its ability to promote barrier restoration and inflammation regulation. However, its effects in colorectal cancer models remain conflicting. Some studies have linked *A. muciniphila* to a reduction in tumor mass, while others suggest it may promote tumor growth. Gubernatorova et al. (2023) compared various experimental protocols using *A. muciniphila* in intestinal cancer models and concluded that high doses, particularly after antibiotic treatment, induce dysbiosis, impair intestinal barrier function (S. Qu et al., 2023), and exacerbate inflammation, contributing to cancer progression (Wang et al., 2022). Conversely, lower doses of *A. muciniphila* or its derivatives administrated without disrupting the native microbiota-−demonstrated beneficial impact on disease progression (Qu et al., 2021; Wang et al., 2023). This aligns with clinical trials showing a correlation between *A. muciniphila* density and checkpoint therapy response, where moderate, but not high levels of *A. muciniphila* in stool were associated with better prognosis (Derosa et al., 2022). Thus, precise microbiota modulation with *A. muciniphila* may offer a promising therapeutic approach for inflammatory bowel diseases and colorectal cancer. Additionally, *A. muciniphila* levels in colitis-induced mice increased further upon supplementation with Amuc_1100 (an outer membrane protein of *A. muciniphila*) and *Bacteriodes cidifaciens* (Wang et al., 2020).

3.5. Cardiovascular disease (CVD)

Cardiovascular diseases, including atherosclerosis and hypertension, remain among the leading causes of mortality worldwide (Roth et al., 2020). The gut microbiota has been identified as a key regulator of cardiovascular health (Witkowski et al., 2020), and *A. muciniphila* has emerged as a promising candidate for the prevention and management of CVDs. One of the ways *A. muciniphila* supports cardiovascular health is through the production of SCFAs, which act on acetate receptors in the gut and vascular system to induce vasodilation, thereby reducing hypertension (Lakshmanan et al., 2022). Furthermore, by preventing the translocation of lipopolysaccharides (LPS) into the bloodstream, *A. muciniphila* reduces vascular inflammation, which can further lower blood pressure and improve overall cardiovascular health (Nesci et al., 2023). The study by (Li et al., 2016) demonstrated that *A muciniphila* reduces atherosclerotic lesions by alleviating metabolic endotoxemia-induced inflammation and restoring gut barrier integrity in mouse models.

A. muciniphila holds significant therapeutic potential for treating cardiovascular diseases, but only live bacteria should be introduced to achieve beneficial outcomes. One key effect of *A. muciniphila* in reducing cardiovascular disease risk is its role in opposing arterial calcification, a major component of atherosclerosis. In atherosclerotic plaques, calcium salts accumulate, leading to arterial stiffening and hypertension. SCFAs such as propionate and butyrate, produced by gut bacteria, influence arterial calcification-propionate has antioxidant properties that reduce calcification, whereas butyrate exacerbates it (Deleu et al., 2021). Notably, supplementation with live *A. muciniphila* promotes propionate production, thereby offering protection against arterial calcification.

The interaction between *A. muciniphila* and vascular lesions has also been described. ApoE-deficient mice, supplementation with *A. muciniphila* reduced metabolic endotoxemia-induced inflammation by strengthening the gut barrier, leading to decreased intestinal permeability and remission of atherosclerosis (Li et al., 2016). Additionally, a study on patients with coronary artery disease found that non-responders statin therapy had lower levels of *A. muciniphila* and *Lactobacillus* in their gut microbiota (Wang et al., 2021). This suggests that enhancing the availability of these probiotic species could help improve blood lipid management in patients with coronary artery disease.

3.6. Potential roles and mechanisms of A. muciniphila in anti-aging

A. muciniphila has emerged as a potential modulator of the aging process due to its ability to influence gut health, metabolic balance, and systemic inflammation. Aging is typically associated with significant alterations in structure and function of gut microbiota, including a reduction in microbial diversity, impaired gut integrity, and decreased production of anti-inflammatory molecules, which contribute to a chronic low-grade inflammatory state known as "inflammaging" (Ling et al., 2022).

One of the key mechanisms by which *A. muciniphila* exerts anti-aging effects is through the synthesis and elevation of SCFAs, particularly acetic acid (Zeng et al., 2023). SCFAs, the fermentation products of dietary fiber by gut microbiota, have widespread impacts on aging,

inflammation, and metabolism (Vinelli et al., 2022). These compounds suppress pro-inflammatory cytokines, reducing chronic inflammation and oxidative stress-both hallmarks of aging (Baechle et al., 2023). SCFAs also enhance antioxidant capacity and reduce reactive oxygen species (ROS) formation, thereby mitigating oxidative damage and preserving cellular and tissue health (Ferrer et al., 2024).

Metabolic dysfunction is another key aspect of aging, often characterized by insulin resistance, fat accumulation, and lipid metabolism changes (Johnson and Stolzing, 2019). *A. muciniphila* has been shown to prevent the development of diabetes and enhance glucose metabolism (Hasani et al., 2021). It increases SCFAs levels, which improve insulin sensitivity and modulate lipid homeostasis (Li et al., 2023). Moreover, *A. muciniphila* interacts with host signaling pathways, such as AMP-activated protein kinase (AMPK) pathway, which plays a central role in energy metabolism (Mei et al., 2024). These metabolic benefits suggest that supplementation with *A. muciniphila* can help prevent age-related metabolic decline and associated diseases.

Neuroinflammation and cognitive decline are also closely linked to aging (Wu et al., 2021). Gut dysbiosis and increased intestinal permeability, both of which worsen with age, contribute to systemic inflammation that can adversely affect brain health (Wu et al., 2021). By reducing systemic inflammation, fortifying the mucosal barrier, and preserving gut barrier integrity, *A. muciniphila* may limit inflammatory markers that impact central nervous system (Misera et al., 2024). Although direct studies are limited, it may enhance cognitive function indirectly through producing short-chain fatty acids (SCFAs), such as butyrate, through cross-feeding interactions with other gut microbes (Lopez-Siles et al., 2018). SCFAs exhibit neuroprotective properties by modulating microglial activity, promoting anti-inflammatory M2 polarization and suppressing pro-inflammatory M1 responses (Dalile et al., 2019; Xu et al., 2023). Additionally, SCFAs strengthen blood–brain barrier integrity by upregulating tight junction proteins, including occludin and claudin-5, thereby restricting the entry of inflammatory cytokines into the brain (Braniste et al., 2014). While direct studies on *A. muciniphila* and cognitive aging are limited, its known functions suggest it may play a role in maintaining brain health and cognitive function during aging.

Aging is also closely associated with Hyperglycemia and Insulin resistance (IR), which in older individuals leads to an acceleration of 4BL cell expansion and a decline in *Akkermansia* levels. IR occurs following the activation of CCR2 + monocytes, which drive the conversion of B1a cells into 4BL cells, resulting in gut dysbiosis and a reduction in butyrate production. Supplementation with *Akkermansia* has been shown to reverse IR by increasing its abundance in the gut, thereby restoring insulin responsiveness in aged mice and macaques. A similar effect on IR has also been observed following butyrate supplementation or depletion of CCR2 + monocytes and 4BL cells (Jian et al., 2023). These findings suggest that *Akkermansia* administration may prevent the activation of CCR2 + monocytes, thereby blocking the conversion of B1a cells into 4BL cells. Consequently, *Akkermansia* represents a promising therapeutic strategy for aging-induced IR and metabolic dysfunction with aging. Although *A. muciniphila* has not yet been established as an anti-aging probiotic, its beneficial effects on immunity, metabolism, and the gut–brain axis highlight its strong potential for aging-related interventions.

4. Current studies on the translational applications of *A. muciniphila*

4.1. Effects of live and pasteurized A. muciniphila

Probiotics are live bacterial cultures consumed to confer health benefits by colonizing the gastrointestinal tract (Plaza-Diaz et al., 2019). Live *A. muciniphila* is metabolically active, allowing it to directly interact with host cells by synthesizing SCFAs, enhancing mucus production, and promoting the growth of other beneficial gut bacteria (Zhang et al., 2019). These functions contribute to gut homeostasis by maintaining mucus layer thickness, improving gut barrier integrity, and reducing inflammation (Mo et al., 2024). Additionally, live *A. muciniphila* modulates bile acid metabolism, regulates glucose levels, and influences lipid metabolism, all of which are essential for maintaining metabolic health. However, there are limitations to using live probiotics. They are sensitive to environmental conditions such as temperature, humidity, and oxygen exposure during storage, transport, and consumption (Barbosa et al., 2022). Moreover, the acidic environment of the stomach can reduce the viability of live *A. muciniphila*, decreasing the bacterial count that successfully reaches the intestines (Zhang et al., 2019). These factors, along with the inherent instability of live bacteria, limit their therapeutic applications.

To address these challenges, pasteurized *A. muciniphila*, a heat inactivated form of the bacterium, has been developed. While pasteurized *A. muciniphila* is no longer metabolically active, its structure integrity and bioactive molecules are preserved (Abbasi et al., 2024). Heat inactivation the surface proteins and molecules responsible for health benefits (Niu et al., 2024). Pasteurization of *A. muciniphila* does not comprise its ability to modulate immune response, strengthen the intestinal barrier, and suppress inflammation (Ashrafian et al., 2021). Some key bioactive components retained after pasteurization include Amuc_1100, a membrane protein that plays a significant role in reducing inflammation and protecting the gut (Si et al., 2022), and P9, a secreted protein shown to enhance GLP-1 secretion and improve glucose regulation (Yoon et al., 2021). These protein remains functional in the pasteurized form, allowing the bacterium to maintain therapeutic potential.

Comparative studies between live and pasteurized *A. muciniphila* suggest that the pasteurized form may be more effective under certain conditions (Peng et al., 2023). In animal models, pasteurized *A. muciniphila* demonstrated superior effects in enhancing insulin sensitivity, reducing adipose tissue, and decreasing systemic inflammation compared to its live counterpart (Ashrafian et al., 2021). The bioactive surface proteins in the pasteurized form facilitate its interaction with host cells and tissues, underscoring its therapeutic utility. Additionally, pasteurized *A. muciniphila* offers practical advantages. It is more stable, safe and has a longer shelf life compared to the live strain, making it easier to store and transport (Ashrafian et al., 2021). Its ability to reach target sites in the body without degradation enhances its clinical applicability (Cani et al., 2022). These features make pasteurized *A. muciniphila* a promising candidate for therapeutic interventions targeting metabolic disorders, type 2 diabetes, obesity, and gastrointestinal barrier dysfunction.

4.2. Trials conducted in mice and humans

Experimental studies in both mice and humans have provided evidence of the therapeutic potential of *A. muciniphila* in treating liver diseases, gut disorders, and inflammatory bowel diseases (Table 1). In a study by Fang et al., (2023), C57BL/6 mice with alcoholic liver disease (ALD) were administered live *A. muciniphila* orally. The results demonstrated a reduction in serum oxalic acid levels and an increase in ornithine levels. Furthermore, pathogenic bacteria such as *Escherichia coli* and *Helicobacter hepaticus* were significantly reduced. These findings indicate the potential of *A. muciniphila* in mitigating ALD in mouse models.

Kim et al. (2020) conducted a similar study, using C57BL/6 mice to evaluate the effects of *A. muciniphila* on fatty liver disease. The administration of *A. muciniphila* led to a significant decrease in serum triglycerides and alanine aminotransferase levels, suggesting its efficacy in treating fatty liver disease in mice. In another study conducted by Bian et al. (2019), the effects of *A. muciniphila* were assessed in a colitis model. Colitis was induced in C57BL/6 mice using 2 % dextran sulfate sodium (DSS). Once colitis was established, the mice were divided into two groups receiving either *A. muciniphila* or phosphate buffer saline.

Table 1
Summary of studies investigating the effects of *A. muciniphila* on various diseases.

Diseases	Treatment	Model	Dose	Outcome/ Mechanism	References
Obesity	Live or pasteurized (ATCC BAA−835)	Human (obesity)	Orally 1×10^{10} *A. muciniphila* either live or pasteurized (3 months)	Both live and pasteurized *A. muciniphila* • Improved insulin sensitivity • Lowered insulin and cholesterol levels • Slightly reduced body weight and fat mass • Decreased markers of liver dysfunction and inflammation Pasteurized form performed better than live Akk	(Depommier et al., 2020)
	Pasteurized *A. muciniphila* BAA-835T with HFD	Mice (C57BL/6)	Orally 2×10^8 CFU 5 weeks	• Decreased body weight and fat gain • Increased energy expenditure, oxygen consumption, physical activity, and fecal energy loss • Reduced carbohydrate transporter expression and modulating lipid-droplet regulation	(Wu et al., 2020)
T2D	*A. muciniphila* WST01	Mice (GF)	Orally 2×10^8 CFU 2 weeks	• Lowered blood glucose levels and inflammation • Improve insulin sensitivity • Boosted energy expenditure and improved gut barrier function	(Zhang et al., 2025)
NAFLD	Live *A. muciniphila*, *Amuc_1100*	Male mice (C57BL/6)	Orally 1.5×10^9 CFU (*Akk*) *100 ug Amuc_1100* 10 weeks	• Lowered serum LPS mass and inflammatory cytokines • Regulated gut microbiota and improved intestinal barrier integrity	(Qu et al., 2023)
IBD	P9 from *A. muciniphila* (ATCC-BAA−835)	HFD-fed mice (C57BL/6 J)	Orally 100ug/day 8 weeks	• Accelerated the Anti-inflammatory M2 macrophages ($CD11b^+CD206^+$)	(Yoon et al., 2021)
	Pasteurized *A. muciniphila* MucT (ATCC BAA−835)	Male mice (C57BL/6 J)	Orally 1.5×10^8 CFU 2 weeks	• Reduced infiltrating macrophages • Reduced $CD8^+$ cytotoxic T lymphocytes in the colon • Ameliorated colitis	(Wang et al., 2020)
CDI	Live *A. muciniphila* (ATCC-BAA−835)	Female mice (C57BL/6 J)	Orally 3×10^9 CFU 2 weeks	• Boosted intestinal barrIer function by increasing tight junction protein expression • Reduced microbiome dysbiosis • Ameliorated SCFA and bile acid metabolism	(Wu et al., 2022)
Cancer (Acute & chronic intestinal inflammation)	Live or OMVs from *A. muciniphila*	Mice	Orally 10^8 CFU or 20 mcg *A. muciniphila* OMVs / mouse 5 days	• Reduced colonic inflammation • Boosted mucus production	(Wang et al., 2023)
	Recombinant protein *Amuc_2109*	Mice	Orally 100 mcg/kg per mouse (21 days)	• Lowered disease severity • Prevented loss of body weight • Inhibited expression of inflammatory cytokines and NRLP3 activation	(Salminen et al., 2021)
Gastro-intestinal	Recombinant surface protein Amuc_2172	$Apc^{Min/+}$ *mice*	150 mcg/kg intraperitoneal injection 14 weeks	• Reduced tumor number • Heightened CTLs	(Jiang et al., 2023)
CVDs	Live *A. muciniphila* (ATCC-BAA−835)	Rats (Sprague-Dawle)	Orally 5×10^9 CFU in 200ul/rat 8 days	• Increased propionate level • Strengthened intestinal barrier • Reduced vascular calcification	(Yan et al., 2022)
	Live *A. muciniphila* (MucT/ATCC-BAA−835)	ApoE-/- mice	Orally 5×10^9 CFU 8 weeks	• Reduced atherosclerotic lesion area, inflammatory cytokines and metabolic endotoxemia • Boosted intestinal TJPs	(Li et al., 2016)
Aging	Live *A. muciniphila* ATCC BAA−835	Male aged mice (C57BL/6 J)	Orally 3×10^9 CFU 6 weeks	It improved: • Glucose sensitivity • Inflammation • Antioxidant capacity • Intestinal barrier function in aged mice	(Ma et al., 2023)

Abbreviations: LPS, lipopolysaccharide; CD11b+ , transmembrane glycoprotein; CD206 + , mannose receptor; P9, protein fraction 9; CD8 + , cluster of differentiation 8; SCFA, short-chain fatty acid; OMVs, outer membrane vesicles; NRLP3, NOD-like receptor family, pyrin domain-containing 3; CTLs, Cytotoxic T Lymphocytes; TJPs, tight junction proteins.

Mice treated with *A. muciniphila* exhibited less weight loss, longer colons, and a significant reduction in inflammatory cytokines and chemokines. Additionally, the gut microbiome interactions were markedly improved in the treated group, highlighting the potential of *A. muciniphila* in alleviating colitis.

Clinical trials have provided compelling evidence for the therapeutic potential of *A. muciniphila* in metabolic health. Dao et al. (2016) conducted a study involving 49 obese and overweight individuals who were given *A. muciniphila* supplements. The results showed significant improvements in fasting glucose levels, waist-to-hip ratio, and subcutaneous adipose tissue. In addition, participants exhibited notable enhancements in gut microbiome composition, insulin sensitivity, and overall metabolic health.

In a landmark randomized, double-blind, placebo-controlled trial,

Depommier et al. (2019) investigated the effect of *A. muciniphila* on metabolic health in overweight or obese individuals with insulin resistance. This study, which included 40 participants (32 of whom completed the trial), assessed the safety, acceptability, and efficacy of *A. muciniphila*. Participants received a daily oral capsule containing live or pasteurized *A. muciniphila* (1×10^{10} CFU) or placebo for three months. Importantly, no adverse effects were reported, confirming the safety of *A. muciniphila* supplementation. Notably, subjects who received pasteurized *A. muciniphila* experienced greater metabolic improvements than those in the placebo group. Insulin sensitivity increased by 28.62 %, while fasting insulin levels decreased by 34.08 %. Additionally, total cholesterol levels were reduced by 8.68 %. Furthermore, supplementation led to reductions in liver dysfunction and inflammation markers, although the overall composition of gut microbiota remains unchanged.

A study by Gopalakrishnan et al. (2018) analyzed oral and gut microbiome of melanoma patients receiving anti-PD-1 immunotherapy. Subgroup analysis of the fecal microbiota of patients and healthy controls demonstrated increased relative abundance of the Ruminococcaceae family in responders. Meta-analysis of responders showed that relative abundance of different bacteria and functional changes in the human gut microbiome involved anabolic pathways. In another study, where Routy et al. (2018) transferred the gut microbiota of the well responded immune checkpoint inhibitor (ICIs) cancer patients to the murine model, which helped mice to treat the cancer. *Akkermanisa muciniphila* seemed to be main immune booster in response to cancer therapy. Combined, these data have significant implications for the management of patients with melanoma and cancer using immune checkpoint inhibitors, respectively.

These findings underscore the promising role of *A. muciniphila* in managing a range of metabolic and inflammatory conditions across both animal and human models.

5. Challenges in research regarding *A. muciniphila* and future directions

Despite the promising findings from preclinical studies and early human trials, several critical knowledge gaps remain regarding the use of *A. muciniphila* as a food additive and in clinical applications as a therapeutic candidate. Two major areas requiring further investigation include large-scale human clinical trials and exploration of inter-individual variations in response to *A. muciniphila* supplementation, particularly in relation to its mechanisms of action on host physiology.

One notable limitation is the lack of extensive randomized controlled trials (RCTs) in diverse human populations. While animal studies provide compelling evidence of *A. muciniphila*'s efficacy in improving metabolic dysfunction, gut permeability, and inflammation (Ghotaslou et al., 2023), human trials remain limited. Most existing clinical studies involve small sample sizes, often fewer than 100 participants, and short follow-up durations (Becken et al., 2021). These constraints hinder the ability to generate robust, reproducible data on the bacterium's efficacy and safety across various populations.

Another critical challenge is the variability in individual responses to *A. muciniphila* supplementation. While some individuals exhibit improvements in metabolic markers or inflammation reduction, others show minimal or no response. This variability may be influenced by a range of factors, including genetics, diet, baseline gut microbiota composition, lifestyle, and overall health status. For instance, individuals with dysbiosis or reduced microbial diversity may respond differently compared to those with a more balanced microbiome. Additionally, interactions between *A. muciniphila* and other commensal gut microbes-whether synergistic or antagonistic-could influence its colonization and activity.

Genetic factors may further contribute to individual differences in response. Variations in genes associated with metabolic pathways, immune responses, or gut barrier integrity could modulate the bacterium's ability to confer health benefits (Becken et al., 2021). Identifying these genetic determinants through targeted studies will be crucial for understanding why some individuals benefit from *A. muciniphila* supplementation while others do not.

Future research should prioritize large-scale clinical trials that include diverse populations to ensure the generalizability of findings. Additionally, integrative approaches incorporating genomics, metagenomics, and personalized medicine will be essential to elucidate the factors driving individual variability. These efforts will pave the way for precision probiotic therapies, optimizing the therapeutic potential of *A. muciniphila* across different populations.

6. Potential development areas and applications of *A. muciniphila*

Previous research has demonstrated the efficacy of *A. muciniphila* in managing obesity, Type 2 diabetes, and gut barrier dysfunction. However, its potential applications in other conditions, such as CDI and anti-aging therapies, warrant further exploration. Further studies should aim to identify specific bioactive molecules produced by *A. muciniphila* that contribute to cellular regeneration and host health. For instance, the outer membrane protein Amuc_1100 has shown significant anti-inflammatory properties and the ability to preserve gut barrier integrity, even in the absence of live bacteria. Utilizing purified bacterial proteins, SCFAs such as acetate or other microbial metabolites could pave the way for disease-specific treatments targeting CDI, IBD, and aging-related conditions. These approaches would offer precise modulation of host processes without requiring the administration of live bacteria.

Another promising strategy involves combining *A. muciniphila* with other probiotics or therapeutic agents to achieve synergistic benefits. For conditions like CDI or IBD, *A. muciniphila* could be co-administrated with beneficial strains such as *Lactobacillus* or *Bifidobacterium* or paired with prebiotic compounds to enhance overall gut health. Such combination therapies could target multiple mechanisms simultaneously, including gut barrier restoration, inflammation reduction, and microbiome recolonization, thereby offering a more comprehensive and effective therapeutic approach.

7. Discussion and conclusion

The exploration of *A. muciniphila* as a therapeutic candidate has opened new avenues for leveraging gut microbiota to maintain systemic health. Research on *A. muciniphila* underscores its pivotal role in managing metabolic diseases, preserving gut integrity, mitigating inflammation, and promoting longevity. However, while current findings are promising, unresolved questions and areas requiring further investigation remain.

Substantial evidence supports the capacity of *A. muciniphila* to influence systemic health, particularly its impact on gut barrier function, immune system, and metabolic processes. Beyond metabolic disorders, *A. muciniphila* has shown therapeutic potential in conditions such as cancer, liver diseases, and *Clostridiodes difficile* infections. Notably, *A. muciniphila* has also demonstrated efficacy in slowing down the aging process. Both live and pasteurized forms of *A. muciniphila* have exhibited beneficial effects, with pasteurized forms in some cases proving even more effective, such as in enhancing insulin sensitivity and reducing inflammation. Importantly, the strain's bioactive molecules, including the Amuc_1100 surface protein, retain full activity after pasteurization, distinguishing *A. muciniphila* from many other bacterial products used in therapeutic interventions.

Despite these encouraging findings, significant gaps remain regarding the use of *A. muciniphila* as a food additive and in clinical applications as a therapeutic candidate. A critical limitation is the scarcity of extensive, large-scale, randomized controlled trails. While preclinical and small-scale human trials have yielded positive results,

most clinical research have been constrained by small sample sizes, short observation periods, and a narrow focus-often limited to individuals with obesity. These limitations prevent a comprehensive understanding of the long-term effects, safety, and efficacy of *A. muciniphila* across diverse populations.

Adding to this complexity, genomic studies using phylogenetic analyses have revealed significant evolutionary diversity within the *Akkermansia* genus. Guo et al. (2017) identified three primary *A. muciniphila* phylogroups based on core gene analysis of 39 isolates. Karcher et al. (2021) expanded this classification into four clades through comparative genomics of 23 *Akkermansia* genomes. More recently, large-scale metagenomic analyses involving over 1200 genomes identified seven phylogroups, including Amuc I–IV and *A. glycaniphila,* underscoring extensive genomic divergence among strains (Lv et al., 2022). These findings highlight the importance of strain-level resolution in evaluating the therapeutic potential of *A. muciniphila*.

To fully harness the therapeutic potential of *A. muciniphila*, further research is essential. Expanding clinical trials to include larger, more diverse cohorts and longer study durations will be crucial for establishing its safety and effectiveness in broader clinical contexts. Meanwhile, identifying specific bioactive molecules produced by *A. muciniphila* and exploring its synergistic benefits in combination with other therapeutic strategies will enable more precise modulation of host health. Addressing these knowledge gaps will pave the way for *A. muciniphila* to emerge as a viable therapeutic strategy for a wide range of health conditions.

CRediT authorship contribution statement

Waleed Khursheed: Writing – review & editing. **Bijay Gurung:** Resources. **Shaohua Wang:** Supervision, Conceptualization. **Nida Shaheen:** Writing – original draft.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability

All data required to interpret this manuscript are available within the manuscript.

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