VIRULENCE
2024, VOL. 15, NO. 1, 2375555
https://doi.org/10.1080/21505594.2024.2375555

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REVIEW

Akkermansia muciniphila: A promising probiotic against inflammation and metabolic disorders

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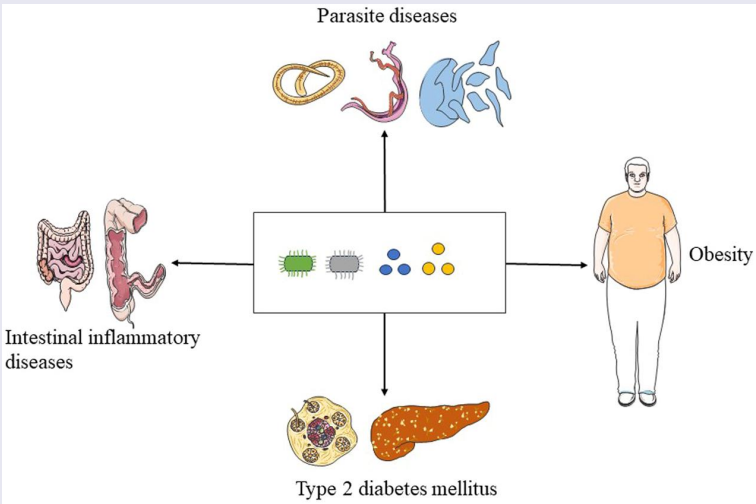
ABSTRACT

Metabolic disease is a worldwide epidemic that has become a public health problem. Gut microbiota is considered to be one of the important factors that maintain human health by regulating host metabolism. As an abundant bacterium in the host gut, *A. muciniphila* regulates metabolic and immune functions, and protects gut health. Multiple studies have indicated that alterations in the abundance of *A. muciniphila* are associated with various diseases, including intestinal inflammatory diseases, obesity, type 2 diabetes mellitus, and even parasitic diseases. Beneficial effects were observed not only in live *A. muciniphila*, but also in pasteurized *A. muciniphila, A. muciniphila*-derived extracellular vesicles, outer membrane, and secreted proteins. Although numerous studies have only proven the simple correlation between multiple diseases and *A. muciniphila*, an increasing number of studies in animal models and preclinical models have demonstrated that the beneficial impacts shifted from correlations to in-depth mechanisms. In this review, we provide a comprehensive view of the beneficial effects of *A. muciniphila* on different diseases and summarize the potential mechanisms of action of *A. muciniphila* in the treatment of diseases. We provide a comprehensive understanding of *A. muciniphila* for improving host health and discuss the perspectives of *A. muciniphila* in the future studies.



ARTICLE HISTORY
Received 25 February 2024
Revised 13 June 2024
Accepted 28 June 2024

KEYWORDS
Gut microbiota; *Akkermansia muciniphila*; metabolic diseases; host health; mechanisms

Introduction

The gut microbiota comprises a diverse and dynamic population of microbial species, including bacteria, fungi, viruses, and protists. The role of the gut microbiota in human health is crucial; consequently, alterations in the abundance and composition of the gut microbiota are thought to be related to multiple diseases. Numerous studies have demonstrated a strong association between

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21505594.2024.2375555

certain microorganisms and diseases such as obesity, inflammatory diseases, type 2 diabetes mellitus (T2DM), cancer, and neurodegenerative diseases [1,2]. Therefore, increasing attention has been paid to the treatment of metabolic diseases with the gut microbiota using different approaches, including probiotics, prebiotics, and fecal microbiota transplantation [3,4]. Probiotics are beneficial microorganisms that play a crucial role in regulating gut microbiota and enhancing host immunity [5]. Traditional probiotics are often derived from fermented foods, with lactic acid as the main type. However, traditional probiotics suffer from quality issues such as contamination and an insufficient number of live bacteria. Among the gut microbiota observed, *A. muciniphila* a promising probiotic that has been widely used in different models of multiple diseases in recent years.

A. muciniphila is an abundant symbiotic bacterium in the intestinal tract that efficiently utilizes mucin as its sole source of carbon, nitrogen, and energy, thereby providing energy for epithelial cells [6]. Since its discovery, *A. muciniphila* has gradually gained attention and is now considered a promising next-generation probiotic. It has been suggested that changes in the levels of *A. muciniphila* are involved in various diseases, such as obesity, inflammatory diseases, diabetes mellitus, and parasitic diseases [2,7–10]. Moreover, some researchers have reported that the outer membrane proteins of *A. muciniphila* (Amuc_1100) and *Akkermansia muciniphila*-derived extracellular vesicles (AmEVs) play a role in regulating and improving intestine function [11–13].

Although there are many reviews about *A. muciniphila*, the summary of its regulation on disease mechanisms is still not sufficiently comprehensive and in-depth. In this review, we provide a comprehensive understanding of *A. muciniphila* in improving host health and discuss perspectives of *A. muciniphila* in the future study. We also elaborated the correlation between *A. muciniphila* and host immunity, which has been less discussed in other review articles. Additionally, we have summarized the relationship between *A. muciniphila* and pathogen infection, which has been scarcely reported in other review articles. Furthermore, the primary mechanisms underlying the beneficial effects of *A. muciniphila* on various diseases are discussed. Finally, we summarized the literature on the relationship between *A. muciniphila* and diseases reported in the past three years. By reviewing the numerous literatures, we summarize the important progress of *A. muciniphila* in improving host health and discuss the perspectives of *A. muciniphila* in future studies. This review provides insights into the roles of *A. muciniphila* as a probiotic in different diseases, thereby offering a blueprint to facilitate clinical therapeutic application.

Method

The authors conducted a systematic review of literature to evaluate the relationship between *A. muciniphila* and metabolic disease, intestinal inflammatory diseases and pathogen infection. The studies in this review were searched from the following data sources: Web of Science, PubMed and Medline with the period September 2004- June 2024. In the literature search process, we did not use any restrictions or filters. The references from chosen studies were manually scanned to identify additional related studies [14,15]. Furthermore, in order to create a high-sensitivity strategy, the search terms "*Akkermansia muciniphila*", "inflammatory bowel disease", "obesity", "type 2 diabetes mellitus", and "parasite" were utilized as both free-text and topic headings. The data obtained from these studies were author, publication year, study types, sample types, analysis method, disease model, dietary intervention and control, and result characteristics.

Major properties of *A. muciniphila*

A. muciniphila is an oval-shaped, non-motile bacterium that was first isolated and described in 2004 [16–18]. Most studies have focused on the type strain *A. muciniphila* MucT (ATCC BAA-835). *A. muciniphila* belongs to the Verrucomicrobia phylum and is representative of the *Verrucomicrobiota* in gastrointestinal samples that can be cultured [19]. Moreover, *A. muciniphila* was originally classified as a strict gram-negative anaerobic bacterium that is widely distributed in the human and animal intestines, with the largest number in the cecum. However, some studies have reported that *A. muciniphila* can tolerate a small amount of oxygen, and more than 90% of *A. muciniphila* can survive when exposed to air for one hour [17,18]. The whole genomes of *A. muciniphila* MucT and *Akkermansia glycaniphila* Pyt^{T} were sequenced, and the results showed that numerous enzymes encoded by genes of *A. muciniphila* can degrade oligosaccharide chains, such as glycosidase, sulfatase, and sialidase [20,21]. These enzymes release glycans to promote the growth of mucin-degrading bacteria and affect the abundance of gut microbiota [22].

A. muciniphila is found in breast milk and in different parts of the digestive tract, such as the small intestine, large intestine, pancreas, and biliary system [19]. In healthy adults, the number of bacteria in feces ranges from 10^9 to 10^{10} CFU/g, and the amount of *A. muciniphila* is approximately 10^6 to 10^8 CFU/g, accounting for 1% to 4% of the total number of bacteria in the intestinal tract [23]. Interestingly, *A. muciniphila* was

found in the human intestine in early life, and its abundance reached adult levels within one year [23,24]. *A. muciniphila* mainly resides in the mucus layer of the intestines and has a significant impact on enhancing the intestinal barrier, producing mucus, and maintaining mucus layer thickness [25]. It has been suggested that *A. muciniphila* degrades mucin to produce monosaccharides, oligosaccharides, and chain fatty acids, which can serve as energy sources for the host, as well as other bacteria [26,27]. A recent systematic literature review concluded that *A. muciniphila* grows most efficiently in an environment containing mucin, which is continuously produced by goblet cells present in gastrointestinal tissue [27]. Therefore, the colonization of *A. muciniphila* does not rely solely on diet and possesses distinct advantages for survival. Moreover, several studies have found that *A. muciniphila* can survive in the digestive systems of humans and mice treated with antibiotics, indicating its resistance to antibiotics [28,29].

The connection between *A. muciniphila* and host immunity

The host and its gut microbiota co-evolve into a strongly mutualistic relationship, where the gut microbiota plays an essential role in preserving host homeostasis [30,31]. The gut microbiota has a crucial impact on the training and development of key components of the innate and adaptive immune systems in the host. In addition to their role in regulating infection and the spread of commensal organisms, microbiome-immune interactions are involved in multiple diseases [31]. Despite the increasing clarity of the relationship between gut microbiota and human health issues, specifically with regard to the influence on the immune system, there is still a notable deficiency in understanding the precise molecular factors that control and adjust immune balance, as well as the mechanisms by which they operate [32].

The occurrence of intestinal IgG antibody responses is believed to be limited to instances of mucosal barrier disruption or as a reaction to enteric pathogens and specific pathogens that invade the intestinal barrier [33]. It has been shown that T cells are significantly activated when gut microbiota is present, utilizing the anti-IgG2b and IgG3 independent pathways, which primarily rely on the presence of toll-like receptor (TLR) [34,35]. Ansaldo et al. reported that *A. muciniphila* triggers the production of IgG1 antibodies and elicits T-cell responses specific to the antigen in mice [36]. Moreover, in a gnotobiotic environment, T cell reactions specifically to *A. muciniphila* are limited to T follicular helper cells and do not prompt other T helper responses or movement toward the lamina propria. Kuczma et al. reported that microbial antigens from *A. muciniphila* could induce anergy and promote the transformation of naive $CD4^{+}CD44$ Foxp3 − T (Tn) cells to the Treg lineage [37].

Finding showed that NF-κB in intestinal epithelial cells (IECs) can be activated by *A. muciniphila* without the involvement of TLRs and NOD receptors [38]. However, activation of Toll-like receptor 2 (TLR2) and its downstream NF-κB pathway is initiated by Amuc_1100 [39]. By modulating TLR2-activated γδT17 cells and macrophage polarization, *A. muciniphila* effectively prevented nonalcoholic steatohepatitis in mice [40]. It was reported that threonyl-tRNA synthetase (AmTARS) by *A. muciniphila* induces the polarization of M2 macrophages and manages the generation of IL-10 through its distinct, evolutionarily acquired regions, which enable specific interactions with TLR2 [30]. Activation of the MAPK and PI3K/AKT signaling pathways through this interaction results in the convergence of cAMP response element-binding protein (CREB), thereby facilitating the efficient production of IL-10 and inhibiting the central inflammatory mediator NF-kB. *A. muciniphila* performs immune functions, and there are undoubtedly additional mechanisms involved in the interactions between the host and *A. muciniphila* that remain unexplored.

Correlation between *A. muciniphila* and diseases

With regard to *A. muciniphila*, increasing attention has been paid to the treatment of multiple diseases using it as a prebiotic. Changes in the abundance of *A. muciniphila* have been found to be associated with metabolic disorders, such as T2DM, obesity, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases [41–45]. Among these disorders, the connection between *A. muciniphila* and obesity has been extensively studied. Furthermore, apart from the alteration in the levels of *A. muciniphila* associated with metabolic disorders, the positive impacts of *A. muciniphila* have also been demonstrated in relation to immune-related conditions, such as ulcerative colitis (UC) and Crohn's disease (CD) [46–48]. In addition to these health issues, the correlation between *A. muciniphila* and neurological diseases as well as cancer has also been studied [49,50]. Interestingly, in recent years, numerous studies have indicated that the levels of *A. muciniphila* was change after parasite infection [51–54], suggesting a promising approach to treat parasitic diseases.

The production and secretion of the intestinal mucus layer are carried out by goblet cells, and then cover on the IECs [55]. *A. muciniphila* exists in the mucus layer and can degrade intestinal mucus to produce crucial metabolites short-chain fatty acids (SCFAs). The relationship between intestinal diseases and *A. muciniphila* depends on healthy mucus layer and mucosal immune response. It has been suggested that *A. muciniphila* can ameliorate metabolic disorders by reestablishing the thickness of mucus layer and expressing antimicrobial peptides in mice [41]. The mechanism by which *A. muciniphila* increase the thickness of mucus layer remains unclear. The possible mechanism is as follow: on one hand, *A. muciniphila* produces numerous SCFAs by degrading mucins, which serve as a valuable source of energy for epithelial cells involved in the synthesis and secretion of mucins; on the other hand, the degradation of mucins can stimulate goblet cells to generate more new mucins, and the mucins can also promote the development of *A. muciniphila*; a positive feedback loop is generated, and the virtuous cycle can constantly updates the mucus layer, which provides a protective effect on intestinal epithelial cells.

The disturbance of gut balance in metabolic disorders is strongly connected to the function of the intestinal immune system [56]. The intestine serves as a physical barrier to keep harmful substances from entering the body. It was found that *A. muciniphila* can enhance gut barrier function by restoring the thickness of mucus layer in mice and increasing the intestinal expression of the antimicrobial peptide Reg3g, both of which are altered during obesity and metabolic disorders [41]. Moreover, it was demonstrated that extracellular vesicles from *A. muciniphila* reproduce some of the positive effects of the bacteria and can also decrease gut permeability by controlling tight junctions in mice. In addition to the alterations in gut permeability associated with metabolic disorders, studies have also shown the positive impact of *A. muciniphila* on gut barrier function during intestinal inflammation [57]. Numerous studies have demonstrated that *A. muciniphila* protect the host from diseases by enhancing the integrity of the intestinal barrier and modulating the immune system through various mechanisms such as thickening the mucus layer, improving epithelial connectivity, and altering mucus composition [7]. Several beneficial effects of *A. muciniphila* have been observed, along with a notably increased efficacy when utilizing pasteurized *A. muciniphila*. Therefore, more research is needed to explore the beneficial effect of *A. muciniphila* and pasteurized *A. muciniphila* in the different diseases.

Potential function of A. muciniphila *in intestinal inflammatory diseases*

The pathogenesis of inflammatory bowel disease (IBD) is not fully understood, but it is a chronic relapsing immune-mediated disease [58,59]. Metabolic and gastrointestinal disorders are often caused by disruption of intestinal homeostasis and intestinal barrier integrity [60]. The gut microbiota strongly influences the intestinal barrier function and intestinal homeostasis. The dextran sulfate sodium (DSS)-induced colitis model has been extensively used to investigate the interaction between gut microbiota and IBD. There are also some studies using Trinitro-benzenesulfonic acid (TNBS)-induced colitis model to evaluate the beneficial effect of *A. muciniphila* on colitis [61]. Although the probiotic properties of *A. muciniphila* have been widely recognized in metabolic diseases, its therapeutic potential in intestinal inflammatory diseases remains controversial [62]. *A. muciniphila* is increasingly being used as a probiotic to treat IBD in animal and preclinical models [46,63–65]. Several studies have demonstrated that *A. muciniphila* and its compounds exert protective effects against intestinal inflammatory diseases in different models [66–69]. *A. muciniphila* is believed to be able to regenerate the mucus layer and maintain gut integrity [70]. It has been suggested that the levels of *A. muciniphila* was significantly lower in patients with ulcerative colitis compared with healthy subjects [71–73]. Bian et al. reported the protective effects of *A. muciniphila* in DSS-induced colitis mouse models and provided an explanation for the underlying mechanisms. Several potential mechanisms have been proposed, including (1) colonic mucosal barrier damage has been improved (2) regulation of the inflammatory response, (3) rebuilding of the gut microbiota (4) modulation of metabolic function [74]. According to Qu et al., the abundance of *A. muciniphila* was lower in the feces of patients with ulcerative colitis (UC) than in healthy individuals. The symptoms of DSS-induced acute colitis were significantly ameliorated by supplementation *A. muciniphila* [63,65]. Supplementation with *A. muciniphila* resulted in a decrease in inflammatory cell infiltration and an increase in the number of goblet cells, as well as the expression of MUC2 and MUC3. Moreover, NLRP3 in the colon tissues of individuals with UC was significantly upregulated, and NLRP3 was upregulated by supplementation *A. muciniphila*, suggesting that the positive effect *A. muciniphila* against acute colitis may depend on the activation of NLRP3. Wang et al. found that *A. muciniphila* or membrane proteins (Amuc_1100) derived from *A. muciniphila* can improve DSS-induced colitis in mice by regulating

$CD8^+$ T cells [75]. Histological damage in the proximal colon improved, and proinflammatory cytokines, including IFN-γ, IL-1β, and TNF-α, were significantly downregulated. Moreover, tumor formation was delayed and tumor number and size were decreased by supplementation with *A. muciniphila* or Amuc_1100. Furthermore, some components and secretions are also associated with the occurrence of intestinal inflammation [76]. The composition of AmEVs from *A. muciniphila* was significantly reduced in the feces with DSS-induced IBD. DSS-induced IBD phenotypes were alleviated by oral administration of AmEVs, including body weight loss, colon length reduction, and inflammatory cell infiltration in the colon wall.

However, some studies have suggested that *A. muciniphila* can potentially contribute to the development of intestinal inflammatory [77–80]. It was found that the levels of *A. muciniphila* were increased in DSS-induced IBD mice, and its relative levels were positively correlated with the severity of histopathological damage and inflammation in the colon. In addition to the DSS-induced colitis model, *A. muciniphila* promoted the progression of intestinal inflammation in other mouse models. Ganesh et al. reported that the symptoms of colitis were aggravated by oral administration *A. muciniphila* in mice infected with *Salmonella typhimurium* [80]. Seregin et al. found that the severity of colitis in IL10 −/− mice was increased by oral administration *A. muciniphila* [81]. Another study conducted by Baxter et al. reported that mice with colorectal cancer (CRC) received fecal microbiota from CRC patients exhibited a direct relationship between the presence of *A. muciniphila* and an elevated tumor burden [82]. Although these studies suggested that *A. muciniphila* may act as an opportunistic pathogen and contribute to the development of colitis, the reasons and mechanisms for its pathogenic effects remain unclear. However, most studies have demonstrated that *A. muciniphila* has beneficial effects on intestinal diseases. Finally, we summarized the research on the correlation between *A. muciniphila* and IBD in the last three years, as shown in Table 1.

Currently, the positive mechanism of *A. muciniphila* on intestinal inflammatory diseases can be explained roughly from the following three aspects (Figure 1): (1) enhance the physical barrier of intestinal mucosal barrier; The physical barrier consists of epithelial cells that are connected by tight junctions and is safeguarded by mucous layer [83]; The integrity of the intestinal mucosal barrier can be maintained by *A. muciniphila*, which can improve the production of tight junction proteins and reduce intestinal permeability; Supplement with *A. muciniphila* can enhance the amount of goblet cells and the secretion of mucins, thereby normalize the thickness of the mucus layer [25,84]; Moreover, *A. muciniphila* can effectively enhance the amount of Paneth cells to restore the secretion of antimicrobial peptides to normal levels, thus playing a protective role in the intestinal mucosa [85]. (2) enhance the immune barrier of intestinal mucosal barrier; *A. muciniphila* can promote the differentiation of initial $CD4^+$ T cells into peripheral Treg cells and downregulate the expression of proinflammatory cytokines [86]; *A. muciniphila* enhance the activation of AMPK signaling pathway while inhibiting the NF-κB signaling pathway by stimulating TLR2, maintain the balance of intestinal mucosal immune function [87]; Furthermore, pasteurized *A. muciniphila* or Amuc_1100 show the ability to reduce the infiltrating macrophages and cytotoxic T lymphocytes [75]. (3) Stable colonization of *A. muciniphila* results in the proliferation of neighboring bacteria and alters their gene expression [67]; *A. muciniphila* can specifically degrade mucins and oligosaccharides to produce metabolite SCFAs, such as propionate and butyrate [59]; SCFAs have the ability to enhance the differentiation of Treg cells and alter gut microbiota composition; butyrate is considered to alleviate intestinal diseases by inhibiting histone deacetylase and activating G protein-coupled receptors (GPR) to enhance protective immunity and improve the intestinal barrier [88,89]; Moreover, butyrate can also enhance the defense function of the intestinal mucosa by upregulating the expression of tight junction proteins and intestinal mucosal epithelial mucus [90]. Consequently, as a probiotic for intestinal inflammatory diseases, *A. muciniphila* maintains the balance of gut microbiota by regulating inflammatory factors and protects the integrity of the intestinal mucosal barrier structure and function at different levels to reduce intestinal damage caused by intestinal inflammatory diseases.

The function of A. muciniphila *in obesity*

In recent years, obesity and its associated metabolic disorders have gradually become one of the world's most serious health problem [91]. Obesity is associated with gut dysbiosis, which refers to an imbalance between energy intake and expenditure, which promotes the proliferation of pathogenic bacteria. Currently, it is widely accepted that the gut microbiota has a significant impact on whole-body metabolism by affecting the energy balance [92–96]. It has been suggested that the gut microbiota plays a crucial role in the

Table 1. Overview of the correlation between *A. muciniphila* and IBD in the past three years.

Study types	Model	Subject	Sample types	Analysis method	Result characteristics	Reference
Animal	DSS-induced colitis	7-weeks old C57BL/6J mice	Feces	16S rRNA	Stable colonization of live *A. muciniphila* is essential for its anti-inflammatory function.	Wang et al. 2023 [67]
Animal	DSS-induced colitis	6-weeks old male C57BL/6J mice	Colon contents	16S rRNA	*A. muciniphila* alleviates the symptoms of colitis in mice.	Xue et al. 2023 [68]
Animal	DSS-induced colitis	CREBH-KO mice	Ileum and colon tissues	qRT-PCR	*A. muciniphila* ameliorates intestinal inflammatory in DSS-induced colitis mice.	Wade et al. 2023 [66]
Animal	TNBS-induced IBD	6-8 weeks old male BALB/c mice	Feces	16S rRNA	The abundance of *A. muciniphila* was decreased in the TNBS-treated mice.	Chang et al. 2022 [46]
Animal and human	DSS-induced colitis and UC	TLR4-knockout C57BL/6 mice and UC patients	Feces	16S rRNA	The abundance of *A. muciniphila* was negatively to colitis risk.	Liu et al. 2022 [47]
Human	UC and Crohn's diseases	UC and Crohn patients	Feces and blood	RT-PCR	Relative abundance of *A. muciniphila* was significantly lower in IBD.	Sezgin et al. 2022 [73]
Human	UC and IBS	UC and IBS patients	Feces	qPCR	The level of *A. muciniphila* reduced in patients with UC from HPRs.	Dorofeyev et al. 2022 [72]
Animal	TNBS-induced IBD	6–8 weeks old male BALB/c mice	Feces	16S rRNA	The abundance of *A. muciniphila* was degraded in the TNBS-treated mice but elevated in the PAW-drinking mice.	Chang et al. 2022 [46]
Animal	DSS-induced colitis	5-6 weeks old male C57BL/6 mice	Feces	16S rRNA	Amuc_2109 secreted by *A. muciniphila* reshaped the intestinal microbiota.	Qian et al. 2022 [69]
Animal and human	DSS-induced colitis and UC	6-weeks old male C57BL/6 mice and UC patients	Feces	16S rRNA	The level of *A. muciniphila* was decreased UC patients and *A. muciniphila* showed the protective effect in colitis.	Qu et al. 2021[63]
Animal	DSS-induced colitis	C57BL/6 mice	Feces	16S rRNA	*A. muciniphila* showed a positive effect on UC.	Liu et al. 2021 [65]
Animal	DSS-induced colitis	6-weeks old male Wistar/ST rats	Feces	16S metagenomics	Antibacterial (OPS-2071) increased the occupancy of *A. muciniphila* in the DSS-treated rats.	Nakashima et al. 2021 [120]
Animal	DSS-induced UC	6-8 weeks old male C57BL/6 mice	Feces	16S rRNA	The level of *A. muciniphila* was increased after metformin treatment.	Ke et al. 2021 [118]
Animal	DSS-induced colitis	GPR43-knockout mice	Feces	16S rRNA	The level of *A. muciniphila* was increased after lithium carbonate treatment.	Huang et al. 2021 [177]

Note: ulcerative colitis (UC), colitis-associated colorectal cancer (CAC), irritable bowel syndrome (IBS), colorectal cancer (CRC), highly polluted with PM2.5 (HPRs), 2,4,6-trinitrobenzene sulphonic acid (TNBS), Plasmon-activated water (PAW).

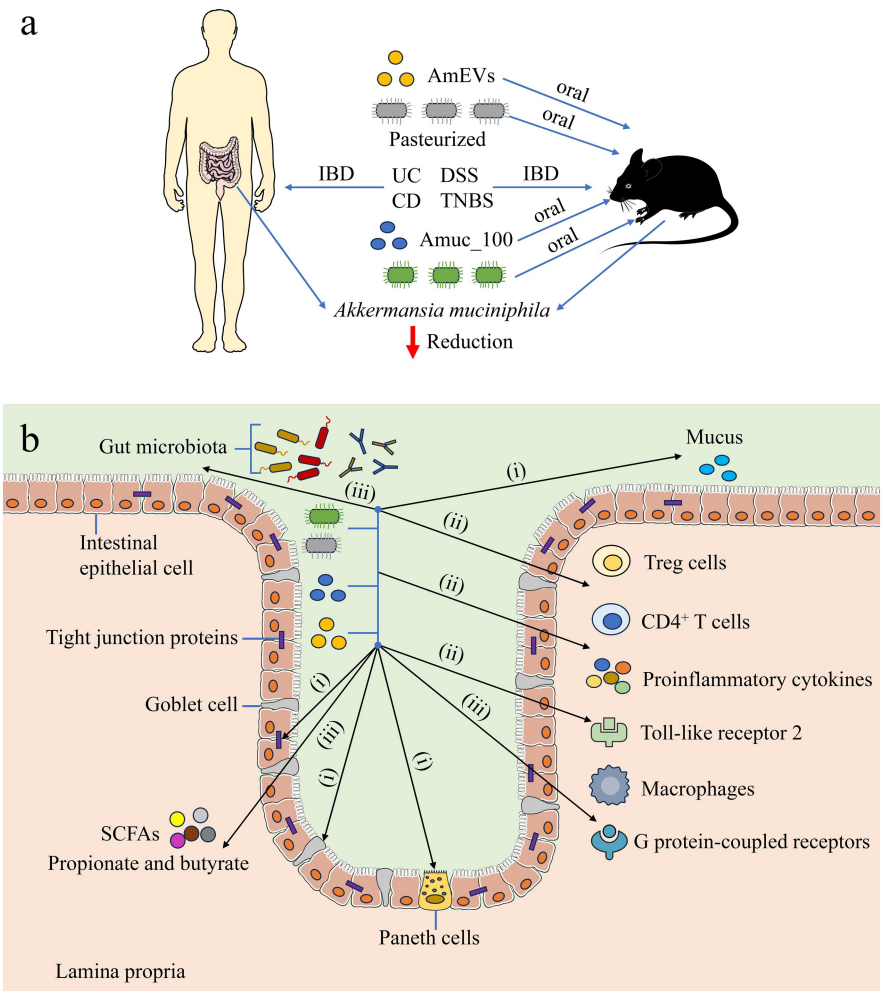

Figure 1. The role of *A. muciniphila* in intestinal inflammatory diseases. (a) The correlation between *A. muciniphila* and IBD in human and mice (b)The possible mechanisms of *A. muciniphila* regulating intestinal inflammatory diseases in host: (i) *A. muciniphila* improves the physical barrier of intestinal mucosal barrier (ii) *A. muciniphila* improves the immune barrier of intestinal mucosal barrier (iii) Stable colonization of *A. muciniphila* results in the proliferation of neighboring bacterium and alters their gene expression. IBD: inflammatory bowel disease, UC: ulcerative colitis AmEVs: *Akkermansia muciniphila*-derived extracellular vesicles, CD: Crohn's disease, DSS: dextran sulfate sodium, TNBS: 2,4,6- trinitrobenzene sulfonic acid, SCFAs: short-chain fatty acids.

development of obesity-related disorders [97–100]. Thus, the novel therapy of administering probiotics or increasing beneficial bacteria through drugs or food has received significant attention for treating obesity [101–105]. Recently, *A. muciniphila* was introduced as a promising probiotic to regulate energy homeostasis [106,107]. Several studies have suggested that *A. muciniphila* is a promising candidate for preventing or treating metabolic disorders associated with obesity [41,108–111].

High-fat diet (HFD) is the most significant cause of obesity and the most studied environmental factor in obesity. HFD can reduce the expression of intestinal tight junction proteins and increase intestinal permeability, thereby increasing the entry of endotoxins produced by intestinal gram-negative bacteria into the blood circulation, leading to metabolic endotoxemia and a long-term inflammatory response, which is crucial for the occurrence and development of obesity. The levels of *A. muciniphila* have been suggested to be negatively associated with obesity [112]. Vitro studies have found that *A. muciniphila* attaches to the intestinal epithelium and enhances the integrity of the enterocyte monolayer, indicating its potential to reinforce the integrity of the intestinal barrier in people with obesity [60,113]. It was found that metabolic toxicity effects in HFD-fed mice could be counteracted by administration of live *A. muciniphila*; notably, the beneficial effect was only observed when live *A. muciniphila* was used [85]. In another study, supplementation with *A. muciniphila* was found to reduce the levels of lipopolysaccharide (LPS) in the plasma by enhancing intestinal barrier function, thus reversing obesity and glucose metabolism disorders in HFD-fed mice.

However, it is important to note that heat-inactivated *A. muciniphila* does not exhibit the same protective effect [41]. Interestingly, pasteurized *A. muciniphila* enhances its ability to alleviate fat mass development, insulin resistance, and dyslipidemia in HFD-fed mice [11]. Yang et al. found that obesity was correlated with an increased risk of neurodevelopmental disorders during the early stages of life [114]. HFD in early life can impair learning and memory dependent on the hypothalamus in mice, affecting neurodevelopment and cognitive function, whereas the levels of *A. muciniphila* were significantly reduced. Additionally, Ashrafian et al. investigated the positive effects of live and pasteurized *A. muciniphila* and its EVs on HFD-induced obesity [115]. Pasteurized *A. muciniphila* and EVs exhibited significant beneficial effects on obesity characterized by a reduction in body weight, blood biochemical parameters, and food intake. The development of fatty liver in HFD-fed mice was prevented by *A. muciniphila* through the modulation of lipid metabolism and inflammation. Furthermore, administration of *A. muciniphila* prevented the intestinal barrier disruption, inflammation, and gut dysbiosis in HFD-fed mice by restoring the microbial population balance. Similar to animal experiments, the levels of *A. muciniphila* were also reduced in overweight or obese people. Depommier et al. conducted a study to explore how pasteurized *A. muciniphila* affects overall energy metabolism while feeding on a high-fat diet [116]. These findings demonstrated that the increase in body weight and fat mass caused by a high-fat diet was alleviated, and food energy efficiency was decreased by supplementation with *A. muciniphila*. Remely et al. recruited 33 obese individuals receiving a dietary intervention and detected the fecal microbiota by real-time quantitative PCR using the 16S rRNA method [117]. The result revealed that there was a notable decline in the levels of *A. muciniphila* after weight reduction. A study on diet intervention for obesity and diabetes showed that the levels of *A. muciniphila* were negatively associated with fasting blood glucose, waist-to-hip ratio, and adipocyte diameter in overweight and obese individuals [26]. Moreover, participants with high *A. muciniphila* levels exhibited a healthier metabolic state. Despite the positive effects of *A. muciniphila* demonstrated in animal models, the impact of *A. muciniphila* on humans has yet to be defined, and its applicability in clinical settings needs to be evaluated [118–120]. Finally, we summarized the research on the relationship between *A. muciniphila* and obesity in the last three years, as shown in Table 2.

Currently, a complete understanding of how *A. muciniphila* regulates obesity is lacking. The possible mechanism by *A. muciniphila* affects obesity can be explained roughly by the following aspects (Figure 2): (1) *A. muciniphila* can enhance thermogenesis and the secretion of glucagon-like peptide-1 (GLP-1) while diminishing the expression of proteins associated with adipose cell differentiation and the gene expression of glucose and fructose transporters in the jejunum. (2) *A. muciniphila* can increase the levels of endocannabinoids in the ileum, which have functions in controlling inflammation, intestinal barrier, and intestinal peptide secretion. (3) *A. muciniphila* can reduce plasma lipopolysaccharide levels by enhancing the intestinal barrier function, thereby reversing obesity and glucose metabolism disorders. (4) *A. muciniphila* can reduce the energy efficiency of food, total cholesterol in plasma, and the expression of carbohydrate transport proteins and increase energy excretion in feces. The results from the above literature indicated that *A. muciniphila* may be a crucial factor in obesity-related diseases, and these results also provided a basis for the development of *A. muciniphila* to prevent or treat obesity.

The role of A. muciniphila *in type 2 diabetes mellitus*

According to a report from the WHO, T2DM is a chronic metabolic disease, and its global incidence rate is continuously increasing [121]. According to a report by the International Diabetes Federation, the global prevalence of diabetes in 2019 was 9.3%, with T2DM accounting for 90%. Therefore, it is important to strengthen the prevention of diabetes and explore effective treatment measures. A growing number of studies have demonstrated that gut microbiota is closely associated with the pathological processes of T2DM [122–124]. Gut dysbiosis is involved in glucose metabolism, impairment of intestinal barrier function, and induction of chronic low-grade inflammation, leading to disorders in SCFA. It has been suggested that *A. muciniphila* as a potential probiotic can improve the symptoms of T2DM by enhancing intestinal barrier function, inhibiting chronic inflammation and regulating body metabolism. Analysis of the gut microbiota in T2DM patients revealed that the abundance of *Verrucomicrobia* is less or even completely absent, suggesting a reduced or even total absence of *A. muciniphila* [125–129]. Thus, *A. muciniphila* has the potential to be used as a therapeutic target for the prevention and treatment of T2DM. The decreased abundance of *A. muciniphila* can be detected before the onset of T2DM, which is helpful for early diagnosis and intervention of T2DM.

Table 2. Summary the research on the role of *A. muciniphila* in obesity and diabetes mellitus in the past three years.

Type of study	Diseases condition	Sample type	Analysis method	Result characteristics	Reference
Animal	HFD induced obesity	Feces	16S rRNA	The abundance of *A. muciniphila* in mice treated with D3 increased about 100 times, compared with the HFD mice.	Li et al. 2023 [97]
Human	Obesity	Feces	16S rRNA	The abundance of *A. muciniphila* in the treatment group was increased.	Cao et al. 2023 [101]
Animal	Obesity	Feces	16S rRNA	The abundance of *A. muciniphila* was increased in mice fed milk and the FMT group from the mice fed milk.	Okamura et al. 2023 [102]
Animal	HFD induced obesity	Feces	16S rRNA	The level of *A. muciniphila* was elevated in obese mice after administration of *E. cristatum*.	Wang et al. 2023 [105]
Animal	HFD induced obesity	Feces, feces contents	16S rRNA	The level of *A. muciniphila* was increased after IX treatment in obese mice.	Watanabe et al. 2023 [94]
Animal	HFD induced obesity	Feces	16S rRNA	The mice challenged with HFD and treated with VCM had large amounts of *A. muciniphila* in their ileum and cecum.	Sonomoto et al. 2023 [95]
Animal	Diet-induced obesity	Feces	16S rRNA	*A. muciniphila* showed significant improvement in body weight, total fat weight.	Kumar et al. 2022 [106]
Animal	HFHS-induced obesity	Feces	16S rRNA qPCR	The level of *A. muciniphila* was significantly increased in obese mice treated with AG and GSE.	Watanabe et al. 2022 [99]
Animal	HFD induced obesity	Feces	16S rRNA RT-qPCR	*A. muciniphila* controls weight gain and increases the Firmicutes/Bacteroidetes (F/B) ratio.	Lin et al. 2022 [171]
Animal	HFD induced obesity	Feces	16S rRNA	*A. muciniphila* were significantly increased after a combined supplement of three probiotic strains.	Liao et al. 2022 [103]
Animal	HFD induced obesity	Feces	16S rRNA	The abundance of *A. muciniphila* was increased in HFD mice after EPA treatment.	Pal et al. 2022 [184]
Animal	HFD induced obesity	Feces	16S rRNA	Supplemented with *A. muciniphila* prevented HFD-induced body weight gain, fat mass gain.	Acharya et al. 2022 [107]
Animal	HFD induced obesity	Feces	16S rRNA	The relative abundance of resident *A. muciniphila* was increased in HFD mice after PMGs treatment.	Pruss et al. 2021 [100]
Human	Obesity	Feces	Metagenomic sequencing	After weight loss, the abundance of *A. muciniphila* was significantly increased.	Alili et al. 2021 [98]
Animal	HFD induced obesity	Feces	16S rRNA RT-PCR	*A. muciniphila* could avoid HFD induced dysbiosis by decreasing obesity-related pathobiont bacteria and increasing health-related gut microbiota.	Ashrafian et al. 2021 [115]
Animal	HFD induced obesity	Feces	16S rRNA	With LA5 administration, *A. muciniphila* in the colon were more than 2,000 folds higher than the regular diet mice.	Ondee et al. 2021 [104]
Animal	HFD induced obesity	Feces	16S rRNA	Supplementation with betaine increase the level of *A. muciniphila* in HFD mice.	Du et al. 2021 [96]
Human	Obesity	Feces	Metagenomic sequencing	*A. muciniphila* was significantly enriched in lean individuals, and its abundance increased during dieting.	Jie et al. 2021 [92]
Animal	HFD induced obesity	Intestinal tissues	RT-PCR	Live and pasteurized forms of *A. muciniphila* improved the HFD-induced obesity and metabolic dysregulation in mice.	Choi et al. 2021 [111]
Human	Obesity	Feces	16S rRNA	The abundance of *A. muciniphila* was enhanced in the postop group.	Shi et al. 2021 [93]
Animal	T2DM	Intestines sample	16S rRNA	Intestinal health of TA zebrafish was improved with pasteurized *A. muciniphila*.	Qu et al. 2023 [133]
Animal	T2DM	Feces	16S rRNA RT-qPCR	Metformin led to a significant increase in the abundance of *A. muciniphila* in mice.	Ye et al. 2023 [132]
Animal	Diabetes	Feces	16S rRNA	Compared to the control group, treatment with *A. muciniphila* significantly increased serum insulin and GLP-1 level.	Wang et al. 2023 [131]
Human	T2DM	Feces	qPCR	In T2D patients with high HOMA-IR and BMI, there was a low abundance of *A. muciniphila*.	Pai et al. 2022 [128]
Human	T2DM	Feces	qPCR	The abundance of *A. muciniphila* was decreased in patients with type1 and increased in type2 diabetes.	Demirci et al. 2022 [127]
Human	T2DM	Feces	Metagenomic sequencing	The abundance of *A. muciniphila* significantly decreases in lean individuals with T2D than without T2D.	Zhang et al. 2021 [135]
Human	Diabetes	Feces	RT-PCR	Compared with control group, *A. muciniphila* was significantly lower in diabetic.	Tabasi et al. 2021 [129]
Animal	T2DM	Colonic contents	16S rRNA	The DFs significantly improved the relative abundance of *A. muciniphila* on diabetic mice.	Li et al. 2021 [124]

Note: Faecal microbiota transplantation (FMT), Eicosapentaenoic acid (EPA), *Lactobacillus acidophilus* 5 (LA5), Capsanthin (CAP), High-fat diet (HFD), high-fat, high-sucrose (HFHS), Zebrafish with combined T2DM and Alzheimer's disease (TA zebrafish), *Scutellaria baicalensis* (SB), arctigenin (AG), burdock sprout extract (GSE), vancomycin (VCM), *Eurotium cristatum* (*E. cristatum*), Isoxanthohumol (IX), porcine mucin glycans (PMGs), dietary fibers (DFs).

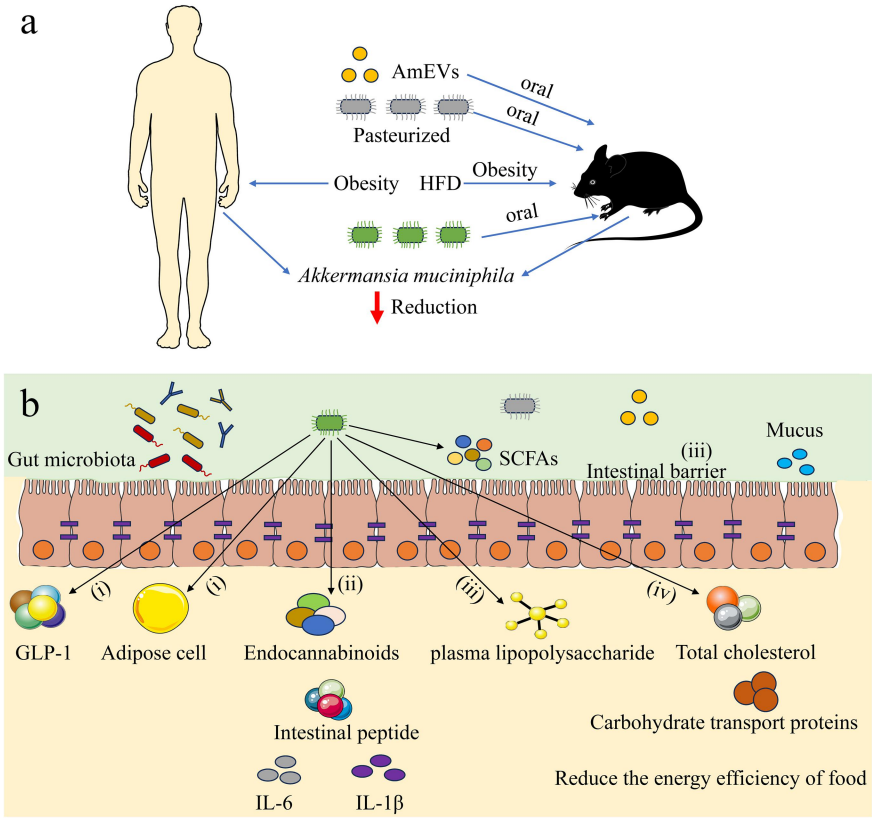

Figure 2. The role of *A. muciniphila* in obesity. (a) The correlation between *A. muciniphila* and obesity (b) The possible mechanisms of *A. muciniphila* regulating obesity in host: (i) *A. muciniphila* improves thermogenesis and the secretion of GLP-1 (ii) *A. muciniphila* regulates the intestinal barrier and inflammatory response (iii) *A. muciniphila* regulates the levels of plasma lipopolysaccharide (iv) *A. muciniphila* improves energy metabolism in obese hosts. HFD: High-fat diet, GLP-1: glucagon-like peptide-1.

In recent years, several epidemiological and animal studies have indicated that *A. muciniphila* plays a vital role in the regulation of T2DM [130–132]. Hanninen et al. found that a high incidence of diabetes was associated with a lack of *A. muciniphila* [130]. Moreover, the incidence of diabetes was reduced by administration *A. muciniphila*. Qu et al. reported that pasteurized *A. muciniphila* provides therapeutic and preventive effects against diabetes in a zebrafish model [133]. Zebrafish with diabetes mellitus showed significant improvement in blood glucose, body mass index, and diabetes indices after administration of pasteurized *A. muciniphila*. Niu et al. explored the molecular mechanism of pasteurized *A. muciniphila* in improving T2DM symptoms. The results revealed that pasteurized *A. muciniphila* improved symptoms of T2DM by increasing the production GLP-1, with pasteurized *A. muciniphila* total proteins (PP) playing a crucial role in this process [134]. A study reported that metagenomic and targeted metabolomics were used to analyze the abundance of *A. muciniphila* in 182 subjects who were lean and had abdominally obesity, with and without recently diagnosed T2DM [135]. The abundance of *A. muciniphila* was significantly lower in lean individuals with T2DM than in those without T2DM. However, it did not exhibit the same decline when comparing obese people with and without T2DM. Furthermore, supplementing mice with *A.muciniphila* is sufficient to safeguard them from high sucrose-induced glucose intolerance. The protective effect was achieved by reducing the levels of 3β-chenodeoxycholic acid (βCDCA), insulin secretion, and fibroblast growth factor 15/19 (FGF15/19). Shin et al. found that the glycemic profile of HFD-fed mice improved significantly after metformin treatment [136]. The abundance of *A. muciniphila* in mouse intestines was significantly increased, suggesting that metformin intake could promote an increase in the levels of *A. muciniphila* in the intestine. Moreover, the glucose tolerance of HFD-fed mice was significantly improved by the oral administration *A. muciniphila* without metformin, indicating that *A. muciniphila* might potentially contribute to improving T2DM. Finally, we summarized the research on the correlation between *A. muciniphila* and T2DM in the last three years, as shown in Table 2.

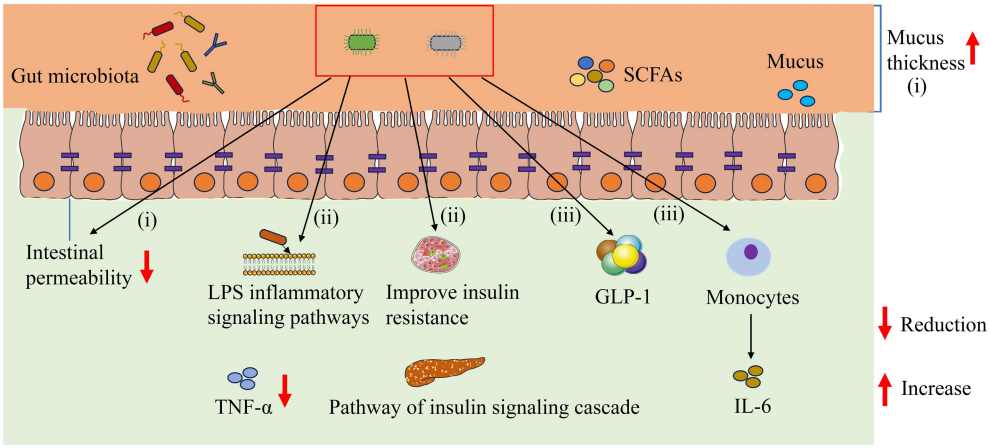

Figure 3. The possible mechanisms of *A. muciniphila* regulating T2DM in host: (i) *A. muciniphila* improves intestinal barrier function and intestinal permeability (ii) *A. muciniphila* regulates LPS inflammatory signaling pathway, metabolic endotoxemia and local inflammatory (iii) *A. muciniphila* improves the secretion of GLP-1and regulates insulin resistance. LPS: Lipopolysaccharide.

At present, there is still a lack of a comprehensive understanding of how *A. muciniphila* regulates T2DM. The potential mechanism of *A. muciniphila* in T2DM can be roughly explained by the following aspects (Figure 3): (1) The impairment of intestinal barrier function and the increase in intestinal permeability are critical factors for T2DM; *A. muciniphila* and its products can increase the thickness of the mucus layer and reduce the permeability of the intestinal mucosal barrier. (2) *A. muciniphila* can inactivate LPS inflammatory signaling pathways and improve metabolic endotoxemia and local inflammation. *A muciniphila* can also reduce the levels of the inflammatory factor TNF-α, intervene in the insulin-signaling cascade, and improve insulin resistance. (3) *A muciniphila* can promote the secretion of GLP-1, improve glycemic tolerance, and reduce insulin resistance in the body. Moreover, *A muciniphila* can induce monocytes to express high levels of IL-6, stimulating the secretion of GLP-1, thus reducing the risk of insulin resistance. The literature suggests that *A. muciniphila* could potentially play a significant role inT2DM. Additionally, these findings offer a foundation for the development of strategies involving *A. muciniphila* in the prevention and treatment of T2DM.

The correlation between A. muciniphila *and pathogen infection*

Parasitic diseases are a common public health problem that pose a threat to human health, especially in developing countries where they are prevalent. The human intestinal tract can harbor various parasites and a large number of symbiotic bacteria, and organisms living in the same environment can undergo important interactions. Parasite infection can potentially influence the species diversity and community structure of the host gut microbiota. In contrast, some components of the gut microbiota can also prevent parasites from colonizing the intestines or inhibit their persistence during parasite infection. Kupritz et al. conducted a comparative analysis of 23 studies on changes in the diversity of gut microbiota in populations infected and non-infected with parasites [137]. They found that the intra-diversity (alpha diversity) and the inter-individual diversity (beta diversity) of the gut microbiota were significantly altered in these populations after parasite infection. Jenkins et al. investigated the effect of soil-transmitted gastrointestinal nematode infection on the composition of the host gut microbiota [138]. These findings indicated that the alpha diversity and richness of infected subjects did not differ significantly from those of uninfected subjects. However, there was a significant increase in the beta diversity. Furthermore, Jin et al. evaluated the effects of butyrate and probiotics on *Trichinella spiralis* (*T. spiralis*) infection as well as their effect on mucus levels [139]. They found that the presence of butyrate and butyrate-producing bacteria significantly reduced helminth burden and promoted mucus production.

Several studies have demonstrated that the levels of *A. muciniphila* was increased after parasite infection, suggesting its potential role in preventing parasite infection [53,140,141]. Compared with uninfected mice, the levels of *A. muciniphila* were significantly increased in the colonic and intestinal contents of mice 28 and 50 days after *Schistosoma mansoni* infection [53]. Moreover, Zhao et al. found that compared to uninfected mice, the levels of *A. muciniphila* were significantly increased in the intestinal contents of mice

42 days after *Schistosoma japonicum* infection [140]. After treatment with koumiss, mice infected with *Toxoplasma gondii* exhibited changes in their gut microbiota composition, including an increase in the relative abundance of *A. muciniphila* [142]. Xie et al. demonstrated that the levels of *A. muciniphila* in wild-type mice infected with *Plasmodium berghei* ANKA were approximately threefold higher than those in uninfected mice [52]. However, Smith et al. discovered a negative relationship between *Plasmodium* burden and the abundance of five specific Operational Taxonomic Units (OTUs), including *A. muciniphila* [143]. Jin et al. reported that β-glucan (BG) can trigger *T. spiralis* expulsion through the mucus layer without relying on type 2 immunity, but relies on the gut microbiota in mice [51,144]. The dominant bacteria *A. muciniphila* showed significant expansion in *T. spiralis*-infected mice with BG. Xie et al. found that compared with the control group, the levels of *A. muciniphila* in WT and *Mif*$^{-/-}$ C57BL/6 mice was increased after *T. spiralis* infection [145].

Although several studies have identified *A. muciniphila* as a potential biomarker after different parasite infections, suggesting its possible crucial role in fighting parasite infection, there are very few reports on the application of *A. muciniphila* for treating or preventing parasitic diseases. Jin et al. found that pasteurized *A. muciniphila* exhibited stronger effects on host defense against *T. spiralis* infection by enhancing mucus production [51]. The absence of TLR2 completely eliminated the ability of pasteurized *A. muciniphila* to expel worms. Moreover, they also found that butyrate, one of the main metabolites of *A. muciniphila* has anthelmintic effects on *T. spiralis*. Although research has confirmed that *A. muciniphila* can improve the function of the mucus layer during *T. spiralis* infection, the mechanism by which *A. muciniphila* improves the function of the mucus layer and exerts its deworming effect remains unclear.

Additionally, numerous studies have demonstrated that changes in the levels of *A. muciniphila* are associated with viral diseases [146–149]. Vaibhav et al. found that the gut microbiota of mice was significantly disrupted by SARS-CoV-2 variants, such as USA-WA1/2020, Delta, and Omicron [149]. Unexpectedly, although the Omicron variant resulted in milder symptoms in mice, it disrupted the gut microbiota and caused a significant decrease in *A. muciniphila*. Another study showed that the abundance of *A. muciniphila* in patients infected with high SARS-CoV-2 viral load was higher than that in patients infected with low SARS-CoV-2 viral load [150]. Xie et al. analyzed stool and serum samples obtained from patients with severe fever with thrombocytopenia syndrome virus (SFTS) using 16S ribosomal RNA-sequencing and untargeted metabolomics [151]. The results indicated that *A. muciniphila* exhibited an increase in relative abundance over the course of infection, but its abundance was decreased in deceased patients. According to a study conducted by Chen et al., the levels of *A. muciniphila* were significantly lower in seroconverters (SC) before HIV-1 infection than in negative controls [147]. Kim et al. reported that compared with hepatitis B virus (HBV)-negative mice, HBV-positive mice exhibited a notable increase in alpha diversity and abundance of *A. muciniphila* in the analysis of gut microbiota in fecal microbiota transplantation (FMT) mice [146]. Additionally, some studies have confirmed a strong connection between the pathogenicity of influenza and the gut microbiota. Hu et al found that the presence of *A. muciniphila* was positively correlated with H7N9 infection [148]. Weight loss and mortality resulting from H7N9 infection in mice can be significantly reduced by the administration of pasteurized *A. muciniphila*. Additionally, administering live or pasteurized *A. muciniphila* has been shown to reduce the titers of pulmonary viral and the levels of IL-1β and IL-6, while increasing the levels of IFN-β, IFN-γ, and IL-10 in mice infected with H7N9. The results indicated that the anti-influenza effects of *A. muciniphila* are a result of its anti-inflammatory and immunoregulatory properties.

The relationship between A. muciniphila *and other diseases*

A. muciniphila plays a crucial role in the occurrence, development, and regulation of other diseases. It is well known that cancer has always been one of the most dreaded diseases and a significant contributor to human death worldwide. Studies have found that the reduction in *A. muciniphila* levels is correlated with the occurrence and progression of many malignancies, and *A. muciniphila* in tumors has a positive effect on the response to chemotherapy agents and immune checkpoint inhibitors [152]. Moreover, nasopharyngeal carcinoma patients were found to have a significant reduction in *A. muciniphila*, compared to healthy subjects [153]. Shi et al. reported that combining IL-2 and *A. muciniphila* exhibited a higher level of antitumor efficacy in the tumor tissues of colorectal cancer patients than monotherapy [154]. Activation of the TLR2 signaling pathway partially contributes to the antitumor immune response triggered by *A. muciniphila*, which is primarily elicited by its outer membrane protein. Luo et al. found that Am-EVs can alleviate the tumor burden of prostate cancer in a murine model

and that macrophages treated with Am-EVs can inhibit the proliferation and invasion of prostate cells [155]. In vitro, Am-EVs elevated the numbers of $GZMB^+CD8^+$ and IFN-γ^+CD8^+ T cells, as well as M1-like macrophages. Activated $CD8^+$ T cells have the ability to enter tumor tissue and attach to tumor cell surface ligands using the T-cell receptor, ultimately causing cell death by releasing IFN-γ, granzyme, TNF-α, or perforin. Moreover, M1 macrophages typically exhibit tumoricidal activity through the production of inflammatory cytokines and the activation of the immune response. These studies suggested that supplementation with *A. muciniphila* can enhance the effectiveness of immunotherapy in patients with cancer, offering new perspectives for tumor prevention and treatment.

Multiple sclerosis (MS) is a chronic demyelinating disease with inflammatory and autoimmune characteristics, and experimental autoimmune encephalomyelitis (EAE) is an ideal animal model [156]. The gut microbiota, which plays a crucial role in regulating immune responses and brain function, is increasingly believed to be a significant environmental factor in the development of MS [157,158]. The levels of *A. muciniphila* in subjects with MS were higher than those in the healthy subjects. In the analysis of the gut microbiota in 71 patients with MS and 71 healthy controls, it was found that MS patients exhibited a significant increase in the amount of *A. muciniphila*, and *A. muciniphila* had the ability to enhance the differentiation of Th1 lymphocytes in vitro [159]. Moreover, the International Multiple Sclerosis Microbiome Study (iMSMS) found a significantly increased proportion of *A. muciniphila* in MS patients through an analysis of the gut microbiota of 576 MS patients and 1152 healthy subjects [158]. A study has found that MicroRNAs-30d from the feces of MS patients can increase the levels of *A. muciniphila* in the intestine by regulating the expression of β-galactosidase, thereby promoting the secretion of Treg cell cytokines to suppress MS-like symptoms in mice. These results indicated that microbial manipulation and dietary intervention might potentially be employed as preventive and therapeutic approaches for MS.

In recent years, the concept of the "microbiota-gut-brain axis" has been proposed in some studies, indicating a close correlation between gut microbiota and neural system function [160–163]. Studies have shown that there is a mutual regulatory effect between the gut microbiota and central nervous system. On one hand, the gut microbiota directly or indirectly affects the central nervous system through metabolic molecules; On the other hand, central descending signals also influence the intestinal microbial ecology by controlling intestinal secretion, motility, immunity, and endocrine functions. In a study conducted by Wang et al., there was a notable decline in the levels of Bifidobacterium and *A. muciniphila* in the feces of children diagnosed with autism spectrum disorder (ASD) compared with healthy controls [164]. Qu et al. evaluated the effects of *A. muciniphila* on Alzheimer's disease (AD) in a murine model with different diets [165]. The results indicated that *A. muciniphila* has the potential to postpone pathological alterations in the brain and alleviate damage to spatial learning and memory in mouse models of AD.

The correlation between *A. muciniphila* and diseases, such as amyotrophic lateral sclerosis (ALS) and alcoholic liver disease has also been reported, suggesting that *A. muciniphila* may be associated with more diseases [166,167]. Furthermore, *A. muciniphila* may have complex regulatory mechanisms in the host, and the correlation between *A. muciniphila* and more diseases in the host remains to be discovered and explored.

Future perspectives and challenges

There are numerous studies on the relationship between *A. muciniphila* and different diseases, and most of them have reached similar conclusions. Although a few studies have reported the negative effects of *A. muciniphila*, most studies have consistently demonstrated that the levels of *A. muciniphila* are reduced in metabolic disorders. Current research has focused on directly supplementing *A. muciniphila* to increase its abundance and utilize its probiotic characteristics. However, *A. muciniphila* is an anaerobic bacterium with high requirements for both the culture environment and growth medium components, which hinders its clinical application. The study conducted by Machado et al. discovered that the sensitivity of *A. muciniphila* to anaerobic environments and pH values was much lower than that reported by Derrien et al. [168]. Plovier et al. successfully developed a synthetic medium for high-yield cultivation of *A. muciniphila* that does not include any substances that cannot be administered to humans, thus overcoming a significant hurdle in the clinical use of *A. muciniphila* [11]. Moreover, the storage, transportation, and administration conditions of *A. muciniphila* have strict requirements. Research has found that live *A. muciniphila* must use cryoprotectants during the administration process, and its biological activity may be lost if environmental conditions cannot meet its characteristics [169]. Marcial-Coba et al. developed an approach for encapsulating *A. muciniphila* in a xanthan and gellan gum matrix and embedding the microencapsulated

bacteria in dark chocolate to enhance their survival rate in vitro [169,170]. Lin et al. constructed microcapsules containing *A. muciniphila*, which showed high viability and stability in an aerobic environment [171].

Contradictory research findings have shown that *A. muciniphila* may play a role in exacerbating diseases [81,172]. Although it has been reported that *A. muciniphila* has a beneficial role in preventing intestinal inflammation, it could also have negative effects when harmful bacteria damage the intestinal mucosal barrier [173,174]. In mice colonized with a simplified human gut microbiota (SIHUMI) to mimic the human intestinal microbiota, *A. muciniphila* did not have a therapeutic effect and instead worsened the intestinal inflammation caused by *Salmonella typhimurium* (*S. typhimurium*) [80]. It is important to mention that the gut microbiota of mice was not significantly altered by the presence of *A. muciniphila* by itself. However, when both *A. muciniphila* and *S. typhimurium* were present in SIHUMI mice simultaneously, it would worsen the gut inflammation. It is logical to conclude that in the specific case of existing pathogenic bacterium, *A. muciniphila* could potentially turn into a harmful bacterium that negatively impacts the host [59]. Consistently, Ayres et al. classified that disruptions in intestinal homeostasis can cause beneficial microbes to transform into potentially harmful species, resulting in negative effects on the host [175]. Additionally, although *A. muciniphila* is widely recognized as a beneficial commensal, multiple recent studies have linked it to different types of cancers [176–178]. Howe et al. reported that the level of *A. muciniphila* in the stool samples of CRC patients has been found to be four times greater than in healthy subjects. Moreover, the colonization of *A. muciniphila* worsens tumor development in the intestines of Apc $^{min/+}$ mice [176]. Huang et al. found that the level of *A. muciniphila* was notably elevated in the first three weeks in cancer-bearing mice, indicating its involvement in the early phase of cancer establishment [177]. The above studies suggested that gut commensals like *A. muciniphila* could promote the development of some diseases. More research is needed to explore under what conditions *A. muciniphila* promotes the development of diseases.

Currently, there is no clear definition of the toxicological characteristics of *A. muciniphila*, such as dose-response. However, the relevant research on the dosage of *A. muciniphila* is limited. Studies have shown that *A. muciniphila* must be present in sufficient quantities to exert its probiotic properties [179]. A suitable amount of *A. muciniphila* added to food and the impact of long-term consumption on intestinal homeostasis need to be determined urgently. Although many studies have shown that oral *A. muciniphila* is safe, further clinical trials are required to confirm its effectiveness and safety. Moreover, Oral administration of exogenous probiotics cannot establish long-term colonization in the patient's body, which has become a major challenge in the development of *A. muciniphila* formulations.

Although extensive research has been conducted on the effects of *A. muciniphila* on metabolic diseases, some studies have focused on its effects of *A. muciniphila* on parasitic diseases [51,140,141]. Most experiments are aimed at investigating the impact of parasite infection on the gut microbiota, thereby screening potential biomarkers. Numerous studies have indicated that *A. muciniphila* is a potential biomarker after parasite infection [51,52,140]. These findings indicated that combining *A. muciniphila* with a drug or parasite vaccine will provide new ideas for the treatment or prevention of parasitic diseases in the future. However, there is very limited research on the use of *A. muciniphila* for treating or preventing parasitic diseases. Until now, there have been no studies that have thoroughly investigated the involvement of *A. muciniphila* in helminth infections [144]. More research is needed to evaluate the protective function of *A. muciniphila* and its associated molecules against infection with helminths. Moreover, the underlying molecular mechanisms of *A. muciniphila* in the regulation of helminth infection needs to be further explored in the future.

Numerous studies have verified the changes in *A. muciniphila* in animal models and individuals with metabolic diseases, along with its therapeutic benefits and the effectiveness of interventions to enhance its abundance. Nevertheless, the majority of animal studies involving *A. muciniphila* supplementation have been conducted using *A. muciniphila* cultivated under conditions containing mucin [3]. The presence of contaminants in animal-derived mucin may reduce the positive impact of *A. muciniphila* in relieving metabolic diseases. Additionally, most studies have explored the positive effects of *A. muciniphila* in animal models, and further research on the role of *A. muciniphila* in human diseases is needed. Although the mechanism of the positive effects of *A. muciniphila* on diseases is not yet fully understood, *A. muciniphila* has broad development prospects as a highly regarded next-generation probiotic. Perraudeau et al. studied the beneficial effects of a probiotic formulation containing *A. muciniphila* on T2DM, and the safety of this product has been proven through clinical trials, indicating significant potential for the development of *A. muciniphila* [180].

Researchers have conducted therapeutic trials of *A. muciniphila* owning to its beneficial effects, which were demonstrated in cohort studies of various human and animal models [181]. Clinical studies have found that 53.7% of Chinese people with IBD experienced improvements in clinical indicators through the use of washed microbiota transplantation (WMT), which is different from FMT, which involves a higher frequency of *A. muciniphila* [181,182]. In Belgium, a human clinical experiment was conducted to investigate the relationship between *A. muciniphila* and metabolic diseases [183]. Although the index of body weight, fat mass, or hip circumference in overweight/obese insulin-resistant subjects was not reduced after oral administration of *A. muciniphila*, the index of insulin sensitivity, lower insulinemia, and lower plasma cholesterol were enhanced. Furthermore, research conducted on individuals with type 2 diabetes from the United States provided further evidence supporting the secure utilization of a probiotic mixture containing *A. muciniphila* to enhance the management of postprandial glucose levels [27]. As the mechanism of *A. muciniphila* function in host health is becoming increasingly clear, the clinical application of *A. muciniphila* has broad prospects.

Conclusion

In summary, it has been demonstrated that *A. muciniphila* acts an active role in promoting host health and maintaining the integrity of the intestinal barrier. Alterations in *A. muciniphila* levels can be regarded as an indicator of disease development. In this review, we have summarized the findings of various studies that focused on alterations in the levels of *A. muciniphila* and its influence on different diseases, such as IBD, obesity, T2DM, and parasitic diseases. Moreover, metabolites and enzymes derived from *A. muciniphila*, such as Amuc_1100, AmEVs and SCFAs, show promising potential for the treatment of obesity, IBD, and T2DM. Intervention studies on *A.muciniphila* are mostly restricted to animal experiments; thus, further research should focus on its safety and effectiveness in the treatment or prevention of diseases. More importantly, the function and mechanism of action of *A.muciniphila* in different diseases are still poorly understood, and further research is needed for its application in clinical diseases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Cultivating Project for Young Scholar at Hubei University of Medicine [2021QDJZR012] and the National Natural Science Foundation of China [82002160].

Data availability statement

Data sharing not applicable-no new data generated.

Author contributions

Daoxiu Xu and Yanqing Zhao: conception and design. Daoxiu Xu, Yanqing Zhao and Huijun Yang: drafting the manuscript. Biao Xu, Sirui Zhang and Wenkun Xue: analysis and interpretation of the data. Peng Wu, Shuguo Yang and Bin Tang: revising it critically for intellectual content. Bin Tang and Daoxiu Xu: final approval of the version to be published. All authors have read and approved the final manuscript.

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