

REVIEW

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Akkermansia muciniphila: a microbial guardian against oxidative stress–gut microbiota crosstalk and clinical prospects

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Abstract

Akkermansia muciniphila (*A. muciniphila*), a mucin-degrading commensal bacterium predominant in the gut microbiota, establishes a multifaceted antioxidant defense system through its enzymatic machinery and bioactive metabolites. The bacterium maintains mucosal homeostasis via specialized mucinolytic enzymes while secreting functionally diverse components including SCFAs, outer membrane proteins (notably Amuc_1100), and extracellular vesicles (EVs). Mechanistically, Amuc_1100 enhances SOD activity and reduces oxidative damage markers such as MDA through TLR2/NF- κ B pathway activation. SCFAs mediate systemic antioxidant responses via gut-organ axis communication, while EVs ameliorate intestinal barrier dysfunction through MAPK signaling pathway modulation. Clinically, *A. muciniphila* supplementation demonstrates therapeutic efficacy in improving insulin sensitivity in obese and type 2 diabetic patients, and shows potential in mitigating Parkinson's disease pathology by regulating α -synuclein oligomerization. Translational applications face several challenges, including strain-specific functional variations, host microenvironment dependencies, and potential risks of excessive mucin degradation. Recent advances in bioengineering approaches, particularly microencapsulation and biomimetic delivery systems, have significantly enhanced bacterial viability and targeted delivery. Future investigations should employ integrated multi-omics strategies to elucidate the intricate metabolic-immune-redox regulatory networks of *A. muciniphila*, facilitating its development as a precision therapeutic intervention.

Keywords *Akkermansia muciniphila*, Oxidative stress, Gut microbiota, Engineered probiotics

Introduction

Oxidative stress is a pathological condition resulting from an imbalance between oxidative and antioxidant systems in the body. It is characterized by excessive accumulation of reactive oxygen species (ROS) that surpasses the body's intrinsic scavenging capacity. This overabundance of ROS triggers the release of inflammatory mediators,

including cytokines and growth factors, thereby activating an inflammatory cascade. Consequently, a vicious cycle of oxidative stress and inflammation is formed, leading to chronic tissue damage, cell death, and the progression of various diseases. These diseases encompass cardiovascular disorders, inflammatory bowel disease (IBD), acute lung injury, immune system dysregulation, metabolic syndrome, and neurodegenerative diseases [1–5] (Fig. 1). Given the close interplay between inflammation and oxidative stress, disrupting this cycle by modulating the redox homeostasis of immune cells may emerge as a promising therapeutic strategy for treating inflammation-related diseases.

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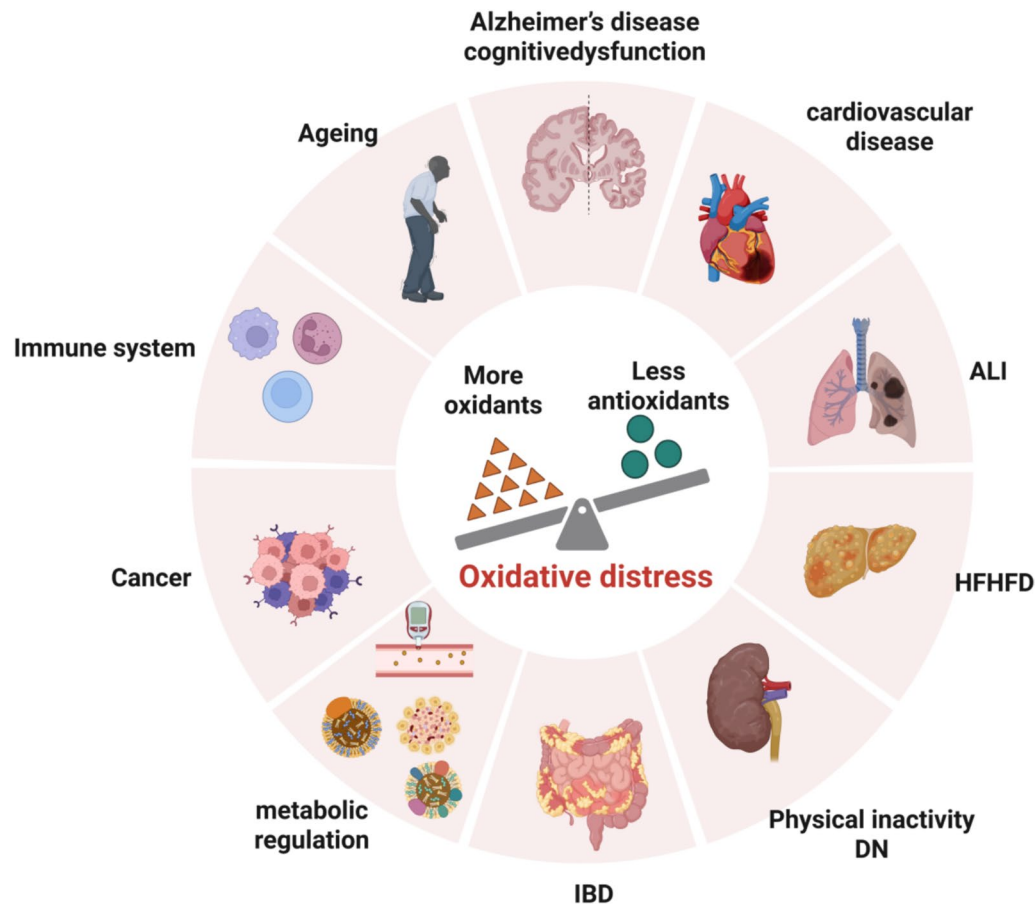


Fig. 1 Systemic damage: the multiorgan pathological effects of oxidative stress

With advancements in microbiome research, gut microbiota have been identified as pivotal regulators of host metabolism and immunity, modulating host redox homeostasis through metabolite secretion, epithelial barrier repair, and immunomodulation [6–8]. For example, specific symbiotic bacteria activate the Nrf2/ARE pathway through the secretion of metabolites such as short-chain fatty acids (SCFAs), thereby upregulating antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), to effectively scavenge excessive ROS and enhance the integrity of the intestinal epithelial barrier [9]; Additionally, microbiota-mediated metabolism of dietary components dynamically modulates the host redox network. For example, phosphatidylcholine (found in red meat and egg yolks) is metabolized by certain gut bacteria into trimethylamine (TMA), which is subsequently oxidized in the liver to pro-atherogenic trimethylamine-N-oxide (TMAO) [10]. Conversely, dietary fiber and plant polyphenols are metabolized by beneficial microbes to inhibit TMA production [11], thereby highlighting the microbiota's bidirectional role in regulating oxidative stress through the “dietary antioxidant–disease metabolite” axis. Notably,

this metabolic regulation is contingent upon the composition and functional activity of the gut microbiota, implying that microbial heterogeneity may impact the precision of intervention strategies. This review systematically analyzes the molecular mechanisms through which *A. muciniphila*, a promising next-generation probiotic, modulates oxidative stress, and explores the translational potential of microbiota-targeted antioxidant strategies, offering novel insights for disease prevention and treatment.

Akkermansia muciniphila: translating clinical findings into mechanistic probiotic applications

A. muciniphila, a mucin-degrading commensal bacterium with distinctive physiological traits, has emerged as a prime candidate for next-generation probiotics, exhibiting both potent antioxidant capacity (2.26 ± 0.99 mU/mg oxygen reduction activity) and broad-spectrum antibiotic resistance [12, 13]. Compared to conventional probiotics (e.g., *Lactobacillus*, *Bifidobacterium*, yeast, and *Bacillus*), *A. muciniphila* exhibits three distinct advantages. First, its unique mucosal colonization capacity allows persistent intestinal residence by penetrating the mucus barrier,

whereas traditional probiotics generally undergo transient gastrointestinal passage with only temporary regulatory effects [14]; Secondly, as a representative of the new generation of therapeutic probiotics, it demonstrates potent anti-inflammatory and metabolic regulatory capabilities through the expression of specific functional proteins such as Amuc_1100, which significantly exceed the mechanisms of traditional probiotics that primarily rely on vitamin synthesis and transient modulation of the gut microbiota [15]; Thirdly, its genome encodes a complete mucin-degrading enzymatic system, constituting a distinct metabolic network capable of directly participating in the regulation of mucosal homeostasis. This represents a marked contrast with strains such as *Faecalibacterium prausnitzii*, which depend on the fermentation of dietary fiber to produce short-chain fatty acids, or *Oxalobacter formigenes*, which specializes in oxalate metabolism [16]. The unique ecological niche adaptations, therapeutic functions, and metabolic characteristics of *A. muciniphila* have contributed to its notable efficacy in enhancing intestinal barrier function and managing systemic metabolic disorders. These attributes have propelled the evolution of microecological therapeutics from clinical observation to mechanistic molecular investigation.

Since the initial isolation of *A. muciniphila* at Wageningen University in 2004 [17], extensive clinical and pre-clinical studies have consistently revealed an inverse correlation between its abundance and oxidative stress-related diseases [18, 19]. Specifically, in obesity and non-alcoholic fatty liver disease models, *A. muciniphila* colonization levels exhibit significant negative correlations with hepatic oxidative damage markers including ROS and malondialdehyde (MDA) [20], while Parkinson's disease patients exhibit reduced fecal *A. muciniphila* abundance concomitant with elevated cerebrospinal fluid α -synuclein oligomers, a marker of oxidative stress-induced neurotoxicity [21]. Furthermore, both human and animal studies of metabolic disorders indicate that increased *A. muciniphila* abundance modulates energy metabolism by promoting fat oxidation and mitigating systemic oxidative stress levels [22]. This review comprehensively summarizes recent clinical cohort studies investigating *A. muciniphila*, as systematically presented in Table 1.

With the advancement of research technologies facilitating mechanistic exploration, a pivotal shift occurred in 2007 when breakthroughs in 16S rRNA fluorescence in situ hybridization and real-time quantitative PCR enabled the transition from clinical correlation studies to molecular mechanism investigations. A landmark study by Hansen's team in 2012 first demonstrated through multi-omics analysis that *A. muciniphila* could inhibit autoimmune diabetes progression by modulating gut microbiota-immune interactions [23]. In 2013, Everard et

al. [24] discovery that viable *A. muciniphila* significantly ameliorated obesity, insulin resistance, and adipose tissue inflammation in high-fat diet-fed mice, establishing the first causal relationship with metabolic disorders. In 2016, Plovier et al. [25] provided the first evidence that administration of pasteurized *A. muciniphila* demonstrated greater efficacy than its live form in ameliorating metabolic disorders in high-fat diet (HFD)-induced obese diabetic mouse models. The therapeutic potential was further confirmed in a 2019 first-in-human clinical trial showing that daily supplementation with Pasteur Institute's inactivated *A. muciniphila* (10^{10} CFU/day) for 3 months increased insulin sensitivity index by $28.62 \pm 7.02\%$ in overweight individuals [18]. On February 9, 2022, the European Commission officially authorized Pasteurized *A. muciniphila* as a novel food for entry into the EU market, specifying a maximum daily intake of 3.4×10^{10} CFU for both adults and children [26]. In 2025, a team of Chinese scholars conducted the largest randomized controlled clinical trial on *A. muciniphila* to date. This pioneering study not only bridged a critical gap in clinical translation but also demonstrated that specific live bacterial strains are markedly more effective than inactivated cells in improving metabolic parameters, challenging the conventional belief that "inactivated bacteria exert a stronger therapeutic effect." [27] (Fig. 2).

These landmark studies have provided a fundamental basis for the mechanistic dissection of *A. muciniphila*'s actions. Recent research has begun to elucidate its multidimensional antioxidant regulatory network: I. The outer membrane protein Amuc_1100 activates the PI3K-AKT signaling pathway while simultaneously modulating the Keap1-Nrf2/HO-1 pathway, thereby effectively mitigating oxidative stress [28, 29]; II. Microbially-derived SCFAs, such as butyrate, remodel the intestinal microenvironment by modulating TLR2/MyD88/NF- κ B signaling pathways, thereby enhancing the host's antioxidant defense mechanisms [30]; III. Extracellular vesicles facilitate interbacterial communication via membrane fusion while simultaneously reinforcing intestinal barrier function to alleviate oxidative damage [31, 32]; IV. Microbial metabolites and inactivated components systemically modulate multiorgan oxidative stress via gut-organ axes. These pan-disease protective effects underscore *A. muciniphila*'s central role in the regulation of systemic homeostasis. While gut microbiota reconstitution may not completely eradicate diseases, it can substantially attenuate secondary damage caused by impaired gut-brain signaling [33]. Despite remaining challenges in strain stabilization and targeted delivery technologies, the compelling preclinical evidence and multitarget mechanisms position *A. muciniphila* as a paradigm-shifting therapeutic agent that is advancing microecological interventions from symptomatic

Table 1 Clinical cohort study of *Akkermansia muciniphila*

Clinical trial registration number	Type of study	Study group	Target diseases	A. muciniphila preparations used	Application program	Key findings	References
NCT02637115	Randomized, double-blind, placebo-controlled pilot study	placebo group(n = 13); Pasteurized A.muciniphila group(n = 13); 10 ¹⁰ living A.muciniphila group(n = 14)	Overweight/obese insulin resistant volunteers	10 ¹⁰ live or pasteurized A. muciniphila	Daily oral supplementation for 3 months	Weight loss averaged about 2.27 kg; insulin sensitivity improved by 42.42%, GGT, AST, LDH↓; Promotes fatty acid β-oxidation and ketogenesis	[18, 149]
NCT03893422	Randomized, parallel group, placebo-controlled, double-blind study	placebo group(n = 26); WBF011group(n = 23); WBF010group(n = 27)	Adults with type 2 diabetes	WBF-011: Mixed in capsules containing inulin, mucinophilic Ackermania, Clostridium byssii, Clostridium butyricum, Bifidobacterium infantis, and anaerobic bacillus harzianum	Take three capsules twice a day, morning and evening within 30 min before meals for 12 weeks	Reduces total blood glucose levels and improves glycated hemoglobin; Butyric acid, ursodeoxycholic acid↑	[150, 151]
KCT0009883	Randomized, double-blind, placebo-controlled clinical trials	placebo group (n = 45); HB05P group(n = 47)	Sarcopenia	Pasteurized A. muciniphila (HB05P)	One capsule containing (1.0 × 10 ¹⁰) HB05P cells or placebo capsule (421.4 mg microcrystalline cellulose) orally daily for 12 weeks	Extensor strength ↑; serum follicle depressor levels ↑	[152]
NCT02224807	A randomized controlled trial	Low A. muciniphila group (n = 16); High A. muciniphila group (n = 16)	Early stage (0 to II) breast cancer	Study of A. muciniphila in participants' own intestines	No dedicated A. muciniphila preparation was used; gut A.muciniphila was assessed in its natural state	A. muciniphila relative abundance is negatively correlated with body fat content and positively correlated with microbiota alpha diversity	[153]

Table 1 (continued)

Clinical trial registration number	Type of study	Study group	Target diseases	A. muciniphila preparations used	Application program	Key findings	References
KCT0008680	Randomized, double-blind, parallel group, multicenter trial	placebo group (n = 73); ETB-F01 group (n = 77)	Patients with at least two of the symptoms of cough, sputum, or shortness of breath/chest tightness lasting 4–12 weeks	ETB-F01 (containing heat-inactivated A. muciniphila strain EB-AMDK19)	1 500 mg capsule of ETB-F01 (containing 5.0×10^{10} heat-inactivated A. muciniphila EB-AMDK19 cells or placebo (containing corn starch and maltodextrin) orally daily for 12 weeks	Dyspnea and cough scores ↓	[154]
NCT04797442	Randomized, double-blind, placebo-controlled phase 2 trial	placebo group and AKK-WST01 group (n = 58)	Overweight/obesity type 2 diabetes	AKK-WST01 (live strain)	3 packets daily (each containing $1-5 \times 10^{10}$ CFU) with meals for 12 weeks	Body weight, fat mass, HbA1c ↓; fat oxidation ↑; improved intestinal barrier function	[22]
ChiCTR2500095821	Randomized, double-blind, placebo-controlled trial	placebo group (PLA) (n = 30); Probiotic group (PB) (n = 50); Postbiotic group (POST) (n = 50); Healthy group (n = 30)	Overweight (BMI ≥ 24.0 kg/m ²)	PB: 1×10^{10} CFU viable A. muciniphila PRO-BIO + maltodextrin; POST: 1×10^{10} CFU pasteurized A. muciniphila PROBIO (80–90 °C, 30 min); placebo: Maltodextrin-only capsules (equal weight)	Daily oral intake of one capsule for 8 weeks	PB showed superior outcomes vs PLA/POST in: 1. Body composition 2. Lipid metabolism (TG/TC/LDL-C ↓, HDL-C stabilized); 3. Appetite regulation (GLP1/PYY/LEP ↑, IL-6 ↓) 4. Microbiota restoration (α -diversity/Akkermansia ↑)	

Table 1 (continued)

Clinical trial registration number	Type of study	Study group	Target diseases	A. muciniphila preparations used	Application program	Key findings	References
NCT01314690	Interventional study	A. muciniphila Low-abundance group(Akk LO) (n=24); A. muciniphila high Abundance group(Akk HI)(n=25)	Overweight/obesity	Study of A. muciniphila in participants' own intestines	No dedicated A. muciniphila preparation was used; Calorie restriction (CR) phase: Consume a diet rich in fiber and protein for 6 weeks; Weight stabilization (WS) phase: 6 weeks	1. Correlation with metabolic status Akk HI: Disse index↑,Total cholesterol/LDL cholesterol↓; 2. Relationship with SCFAs: serum acetate was positively correlated with A. muciniphila abundance 3. Relationship with the microbial ecosystem: Akk HI and high gene count (HGC) group had the best metabolic status	[155]
NCT04339725	Observational study	Healthy group (n=37); NAFLD patients with elevated liver enzymes (n=57)	NAFLD	Study of A. muciniphila in participants' own intestines	No dedicated A. muciniphila preparation was used	NAFLD: Firmicutes/ Bacteroidetes ratio↑, A. muciniphila↓	[156]
NCT01084967/ NCT02653430	Observational study	Obese group (n=95); healthy group (n=105); obese patients undergoing sleeve gastrectomy (n=23; pre-op, 1-month and 3-month post-op)	Obesity/ related metabolic abnormalities	Study of A. muciniphila in participants' own intestines	No dedicated A. muciniphila preparation was used	Obese group: A. muciniphila↓ Post-SG (3mo): A. muciniphila (near-control) ↑, weight↓, improved metabolites	[157]

management to etiological treatment, heralding a new era of mechanism-driven functional probiotics research and development.

Antioxidant mechanisms and functional components of *A. muciniphila*

A. muciniphila, as a keystone mucin-colonizing bacterium, critically maintains mucus layer homeostasis through its mucin-degrading enzymatic systems, SCFAs production, outer membrane proteins, and diverse bioactive metabolites [34]. Its dysregulated abundance has been consistently linked to multiple pathological conditions including inflammatory bowel diseases, metabolic disorders such as obesity and type 2 diabetes, and parasitic infections [16, 35, 36], suggesting systemic antioxidant effects mediated via immunometabolic axis modulation. This review systematically elucidates the key functional components of *A. muciniphila*, focusing on the molecular mechanisms of its outer membrane proteins, secreted proteins, and characteristic metabolites in host-microbe interactions (Table 2).

Mucin-degrading enzymatic systems in intestinal barrier homeostasis

Under physiological conditions, intestinal goblet cells maintain optimal mucus layer thickness through tightly regulated glycosylation processes and mucus secretion. This crucial physical barrier effectively segregates gut microbiota from epithelial cells, preventing direct bacterial contact and subsequent immune system activation. Under oxidative stress, however, ROS accumulation induces intestinal cellular DNA damage and mitochondrial dysfunction, impairing goblet cell viability through apoptotic pathway activation. These pathological changes result in mucus layer thinning and elevated permeability, substantially compromising barrier function and increasing intestinal epithelial vulnerability to pathogenic invasion and harmful stimuli [37].

As a specialized symbiotic bacterium colonizing the intestinal mucus layer, *A. muciniphila* plays a pivotal role in maintaining intestinal barrier integrity through its distinctive mucin metabolic network, thereby establishing a dynamic equilibrium of “controlled degradation and

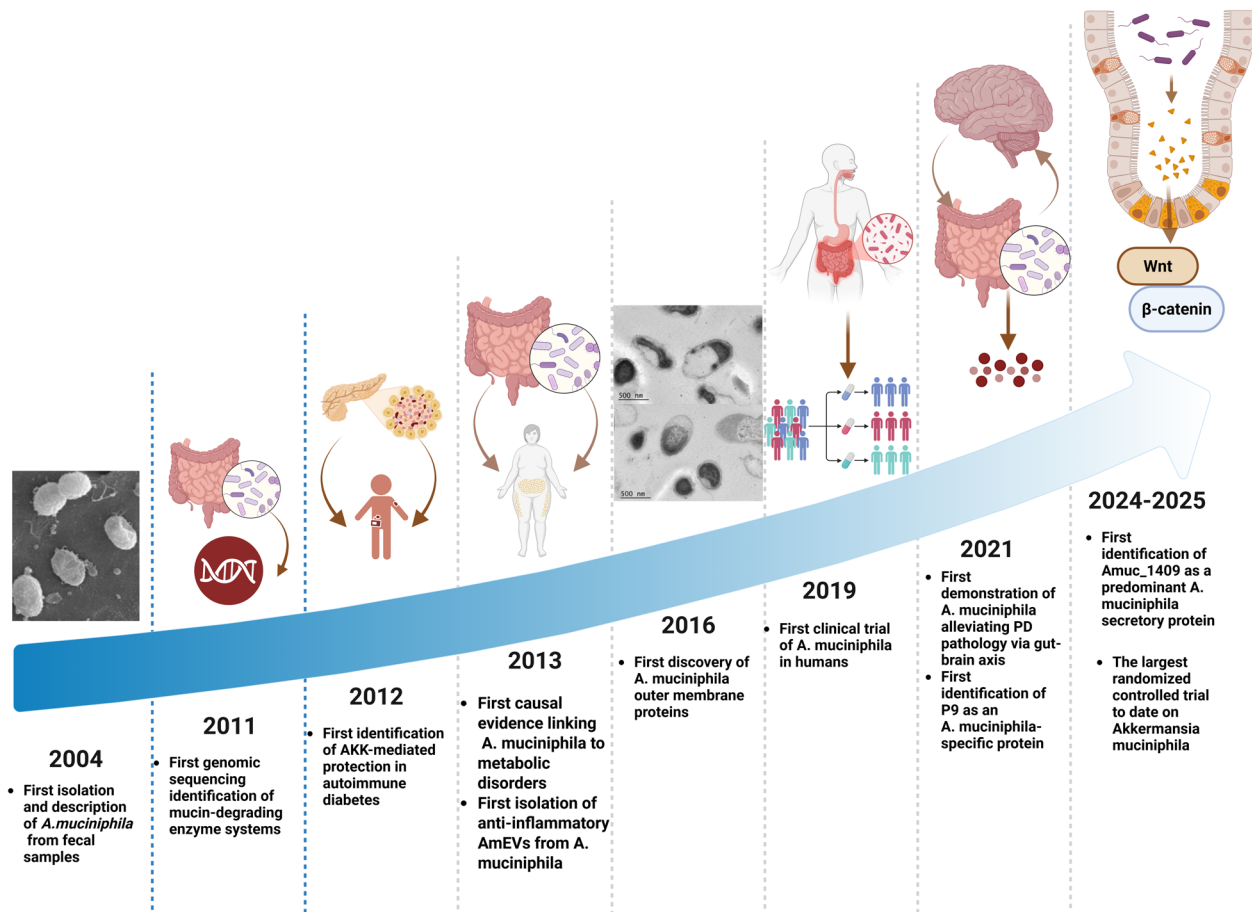


Fig. 2 Milestones in *Akkermansia muciniphila* research: a historical timeline

regeneration". Following its first genome sequencing in 2011, researchers identified its mucin-degrading enzyme system [38]. Subsequent investigations demonstrated that, in contrast to the deleterious degradation by pathogens such as *Clostridium difficile*, *A. muciniphila* establishes a dynamic equilibrium through the mechanism of "Mucinolytic Symbiosis":

I. Metabolic symbiosis—*A. muciniphila* employs sulfate esterases and glycoside hydrolases to selectively cleave mucin O-glycan chains [39], thereby releasing oligosaccharides that function as energy substrates for both itself and commensal microbes [40–42]. This process concurrently stimulates goblet cell proliferation and mucin production [43], facilitating barrier regeneration and restoration of mucus layer thickness [44–47]. For example, in high-fat diet-fed (HFD) mice, the intestinal mucus layer exhibited significant thinning, whereas *A. muciniphila* supplementation markedly restored its thickness [24]. During active Crohn's disease (CD), the intestinal mucus layer undergoes thickening, reflecting both upregulated MUC2 expression (the predominant mucin component) and increased goblet cell numbers. However, a 50% shortening of oligosaccharide

chains induces structural modifications in MUC2 that compromise mucus viscoelastic properties, ultimately impairing its protective barrier function [48]. The *A. muciniphila*-mediated "mucin degradation-stimulated mucin synthesis" cycle dynamically promotes continuous mucus layer renewal, preventing functional impairment due to prolonged stasis while maintaining mucosal barrier integrity.

II. Feedback-regulated enzyme activity—degradative enzyme activity increases with mucus layer thickness, whereas metabolic feedback inhibition suppresses enzyme gene expression when mucin availability is low, preventing excessive depletion [49, 50]; This self-regulated degradation mechanism fundamentally differs from pathogenic bacterial activity. While pathogens secrete broad-spectrum mucinases that compromise mucus layer integrity, *A. muciniphila* mediates targeted outer mucus layer degradation that specifically facilitates renewal while completely preserving the inner mucus layer's barrier function [41, 47]. This explains why, in the context of mucin degradation, different bacterial species exert distinct effects on the integrity of the intestinal barrier.

Table 2 Antioxidant mechanisms of *A. muciniphila*-derived metabolites

A. muciniphila-derived metabolites	Main Functional Ingredients	Crucial role	Targets/pathways of action	Diseases involved and applications	References
Mucin degrading enzyme system	Fucoidan; Sialidase	Participate in mucin metabolism and utilize mucin as a carbon source for growth; promote butyric acid production and maintain the ecological balance of intestinal flora	Acts on mucin O-glycans	Inflammatory bowel disease; metabolic syndrome	[29]
	Glycoside hydrolases (GH20, GH35 and other families); MUL motifs	Degradation of mucins; Improvement of lipid metabolism	Affects amino acid synthesis, lipid metabolism pathways	Inflammatory bowel disease; metabolic syndrome, cardiovascular disease	[158]
SCFAs	Butyric acid	Anti-inflammatory, antioxidant, regulates intestinal barrier function, promotes energy metabolism	Inhibition of TLR2/NF-κB pathway; activation of GPR41/43 receptor	ALI	[30]
	Butyric acid	Alleviates symptoms of <i>Campylobacter jejuni</i> -induced colitis; down-regulates inflammatory factors: IL-6↓, IL-10↑	Inhibition of PI3K-AKT and MAPK pathway	Colitis caused by <i>Campylobacter jejuni</i>	[28]
Outer membrane protein	Amuc_1100	Reduces oxidative stress in the brain and improves antioxidant capacity: SOD1, GPX, HO-1↑; MDA↓	Regulates L-arginine metabolism	Aging-related cognitive impairment	[92]
	Amuc_1100	NQO1, HO-1, SOD, Nrf2↑; MDA↓	Inhibition of TLR2/TLR4/MYD88 and NF-κB signaling pathways; activation of Nrf2 signaling pathway	Liver damage	[88]
	Amuc_1100Δ80	Plasma L-arginine ↑; SOD ↑; MDA ↓; LPS ↓; 5-HT↑	Regulates the 5-hydroxy-tryptamine system	Psychiatric disorders such as depression and anxiety disorders	[159]
	Amuc_2109	Inhibit intestinal inflammatory response, reduce oxidative stress, regulate the balance of intestinal flora, improve intestinal barrier function	Inhibition of NF-κB and NLRP3 inflammatory vesicle-associated signaling pathways	IBD	[160]
	Amuc_1409	Promotes proliferation and regeneration of intestinal stem cells; balances intestinal flora	Activation of the Wnt/β-catenin signaling pathway	Radiation enteritis; chemotherapy-associated enteritis	[100]
Secretory protein	P9 protein	Promotes GLP-1 secretion; improves glucose homeostasis in mice	Activation of the GLP-1 signaling pathway	Diabetes, metabolic syndrome	[97]
	ThrRS (threonyl-tRNA synthetase)	Monitoring and regulating immune homeostasis, triggering M2 macrophage polarization, and suppressing excessive inflammatory responses	Activation of MAPK and PI3K/AKT signaling pathways	IBD	[161]
	AmEVs	Reduce oxidative stress damage: ROS, MDA↓; CATase activity↑; inhibit inflammation: TNF-α, IL-1β, IL-6↓	Inhibition of MAPK signaling pathway	IBD	[78]
Cell membrane components	OMVs	Promotes GLP-1 levels; improves inflammation: IL-1β ↓, IL-6 ↓, IL-17a ↓, TNF-α ↓; IL -10↑	Inhibits cGAS-STING pathway; activates GLP-1 signaling pathway	Type 2 diabetes; neurological disorders	[162]
	OMVs	Inhibition of oxidative stress in the intestinal microenvironment; Modulation of mucosal immune responses; Maintenance of the intestinal physicochemical barrier	Activation of AMPK signaling pathway; membrane fusion promotes proliferation of beneficial bacteria;	IBD; colon cancer	[33]
	AmEVs	Regulates immunity; improves preeclampsia symptoms; promotes trophoblast cell proliferation, migration and invasion	Activation of EGFR—PI3K—AKT signaling pathway	Pre-eclampsia; Diseases Related to Abnormal Placental Development	[163]

Table 2 (continued)

A. muciniphila-derived metabolites	Main Functional Ingredients	Crucial role	Targets/pathways of action	Diseases involved and applications	References
Other ingredients	Cobalamin (chemistry)	Improvement of insulin resistance; Enhancement of intestinal epithelial barrier function; Reduction of inflammatory factor infiltration; Nutrient transfer between gut microbes	Regulation of methylmalonic acid metabolism, methionine synthesis pathway	Cobalamin deficiency-related diseases (e.g., megaloblastic anemia); metabolic diseases; IBD	[103]
	Self-produced carbon dioxide	Improvement of intestinal inflammation; modulation of SCFAs and intestinal flora; improvement of metabolic markers: TG↓, HDL↓	Regulating the electron transport chain /rTCA cycle	Obesity, diabetes, IBD	[164]
	peptidoglycan (PG) or murein (polymer of sugars and amino acids forming cell wall)	Promotes repair of intestinal epithelial cells and secretion of antimicrobial peptides; regulates metabolic diseases	Activation of NF-κB and AP-1 signaling pathways	Metabolic diseases; IBD	[104]

III. Substrate-selective recognition—*A. muciniphila* employs neuraminidase to desialylate core type 3 O-glycans, preferentially binding non-sialylated LacNAc disaccharides on MUC2, reflecting its specialized colonization and metabolic adaptation [41]. In addition, *A. muciniphila* colonization upregulates antimicrobial peptides (e.g., Reg3γ and Lyz1) [51], effectively inhibiting mucus layer colonization and invasion by potential pathogens. By competitively excluding other mucin-degrading bacteria, it concomitantly enhances host metabolic capacity, modulates immune responses, and mitigates pathogen-induced barrier impairment, thereby preserving mucus layer and intestinal epithelial homeostasis [52]. From the perspective of barrier function, *A. muciniphila*-mediated mucus homeostasis reinforces the physical barrier, thereby reducing systemic exposure to intestinal ROS and preventing lipopolysaccharide (LPS) leakage. Consequently, this process effectively limits oxidant accumulation at its source [53, 54].

Multidimensional antioxidant effects of metabolites

SCFAs, predominantly butyric acid representing up to 90% of total SCFAs [55], are metabolic byproducts of *A. muciniphila*-mediated mucin degradation and function as pivotal regulators of both intestinal and systemic antioxidant defense networks [56]. These microbial metabolites orchestrate oxidative stress modulation through integrated mechanisms: Within the intestinal microenvironment, butyric and propionic acids reinforce epithelial barrier integrity through histone deacetylase (HDAC) inhibition, concomitant stimulation of MUC2 mucin biosynthesis/secretion, and enhanced expression of tight junction proteins (occludin and ZO-1) [57–62]. Concurrently, butyric acid induces nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activation, potentiating endogenous antioxidant capacity via de novo glutathione

(GSH) synthesis and upregulation of antioxidant enzymes (SOD and GPx) [63, 64]. At the subcellular level, SCFAs regulate mitochondrial homeostasis via metabolic reprogramming. Butyric acid enhances β-oxidation efficiency through GPR41-dependent mechanisms and modulates mitochondrial dynamics, thereby collectively reducing ROS and nitric oxide (NO) overproduction [65]. This metabolite also induces mitophagy and inhibits NLRP3 inflammasome activation, promoting the clearance of dysfunctional mitochondria and preventing pathological ROS accumulation [66]. Concurrently, propionic acid regulates mitochondrial fission and autophagic processes via GPR41/GPR43 signaling, effectively alleviating intracellular ROS burden [67].

Notably, the antioxidant properties of SCFAs extend beyond intestinal boundaries, functioning as critical mediators in microbiota-gut-organ crosstalk. Within the gut-brain axis, acetic and butyric acids attenuate microglial overactivation while augmenting cellular antioxidant responses via the GPR109A/Nrf2/HO-1 pathway. This mechanism consequently reduces ROS production and inflammatory mediator release, thereby protecting neurons from oxidative damage [68–70]. In the gut-liver axis, SCFAs provide approximately 30% of the hepatic energy supply via the portal circulation [58], significantly attenuating ROS accumulation in both the liver and intestine of high-fat-high-fructose diet (HFHFD)-fed mice. Furthermore, SCFAs reverse lipid peroxidation and ferroptosis through metabolic regulation [71]. In the gut-kidney axis, butyrate-mediated activation of the PI3K/AKT/mTOR signaling pathway via free fatty acid receptor 2 (FFAR2) enhances GPx and SOD activities while reducing MDA levels, thereby alleviating oxidative stress in diabetic nephropathy [72]. Similarly, within the gut-lung axis, butyrate suppresses MDA activity, enhances SOD expression, and reduces inflammatory cell infiltration by modulating TLR2/MyD88/NF-κB signaling pathways,

thereby alleviating pulmonary oxidative damage [30]. On a systemic level, SCFAs regulate the UCP2-AMPK-ACC metabolic network via activation of peroxisome proliferator-activated receptor gamma (PPAR γ), which promotes fatty acid oxidation and mitigates ROS production induced by lipid accumulation [73]. Collectively, these interorgan synergistic mechanisms establish a comprehensive antioxidant defense system that extends from the intestinal lumen to peripheral tissues (Fig. 3).

Antioxidant regulatory mechanisms of other components in *A. muciniphila*

Beyond SCFAs, *A. muciniphila* synthesizes and secretes bioactive components, including surface proteins, secreted proteins, metabolites, and extracellular vesicles, which synergistically regulate oxidative stress via host-microbiome interactions [74]. These molecules penetrate the intestinal mucus layer to directly interact with epithelial and immune cell receptors, thereby modulating host signaling pathways to maintain redox homeostasis [75]. Groundbreaking research by Kang's team in 2013 was the first to isolate AmEVs from *A. muciniphila* [31], revealing

their anti-inflammatory effects in the gut. This seminal discovery redirected research focus from whole-bacterium effects toward mechanistic investigations of specific functional components (Fig. 4).

Antioxidant properties of *A. muciniphila*-derived extracellular vesicles (AmEVs)

Emerging evidence demonstrates that bacterial-derived EVs serve as multifunctional nanocarriers capable of efficiently traversing the intestinal barrier and entering the host circulatory system. These biologically active vesicles deliver diverse molecular cargo, including proteins, lipids, and nucleic acids (DNA, mRNA, and miRNA), thereby facilitating cross-kingdom communication between microbiota and host through sophisticated modulation of adjacent cellular functions [76, 77]. Notably, Am-EVs can deliver functional miRNAs to host dendritic cells (DCs), profoundly modulating their maturation status, antigen-presenting capacity, and cytokine secretion profiles while maintaining significantly lower immunogenicity compared to the parental bacterial cells.

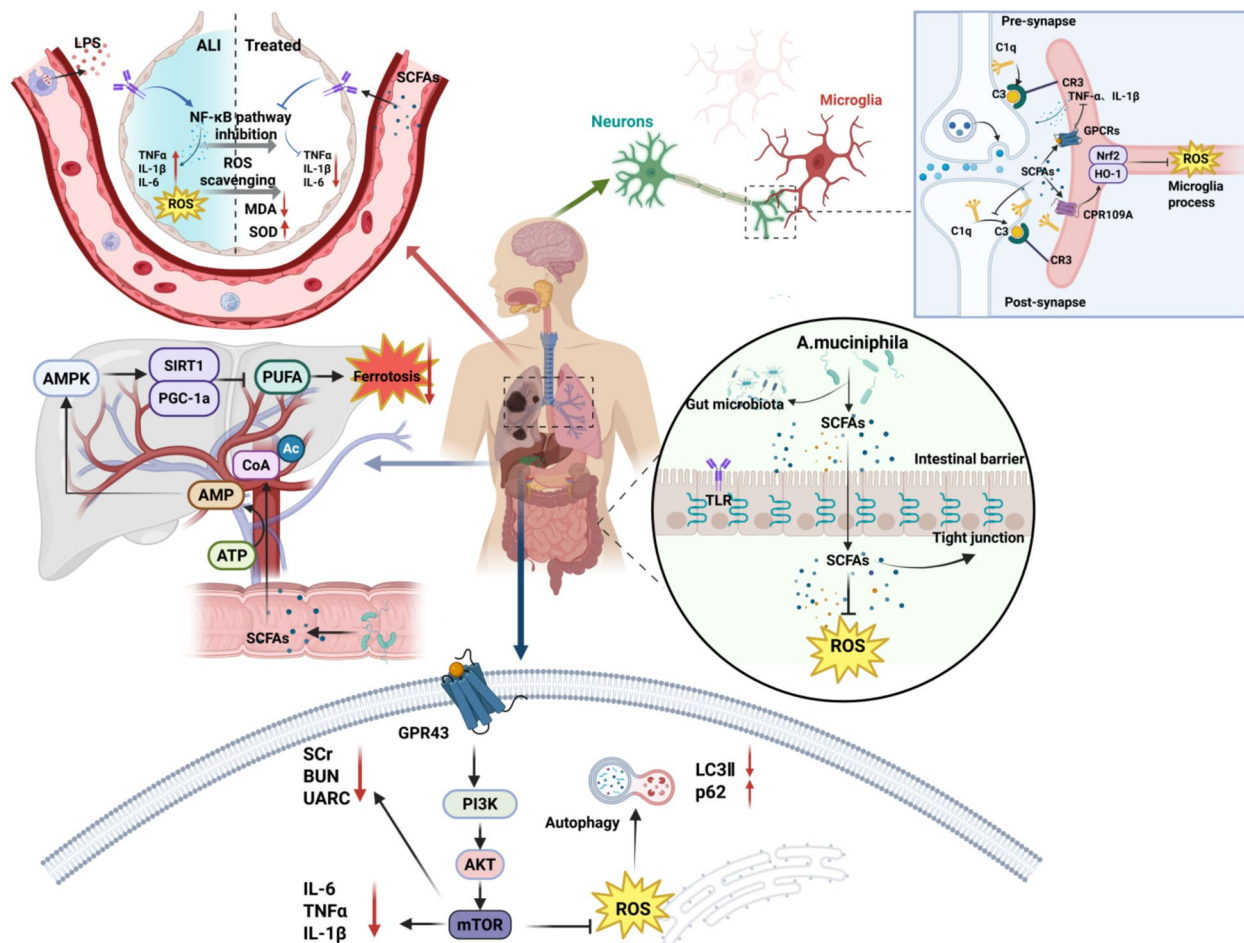


Fig. 3 SCFAs-mediated gut-organ axis in antioxidant defense

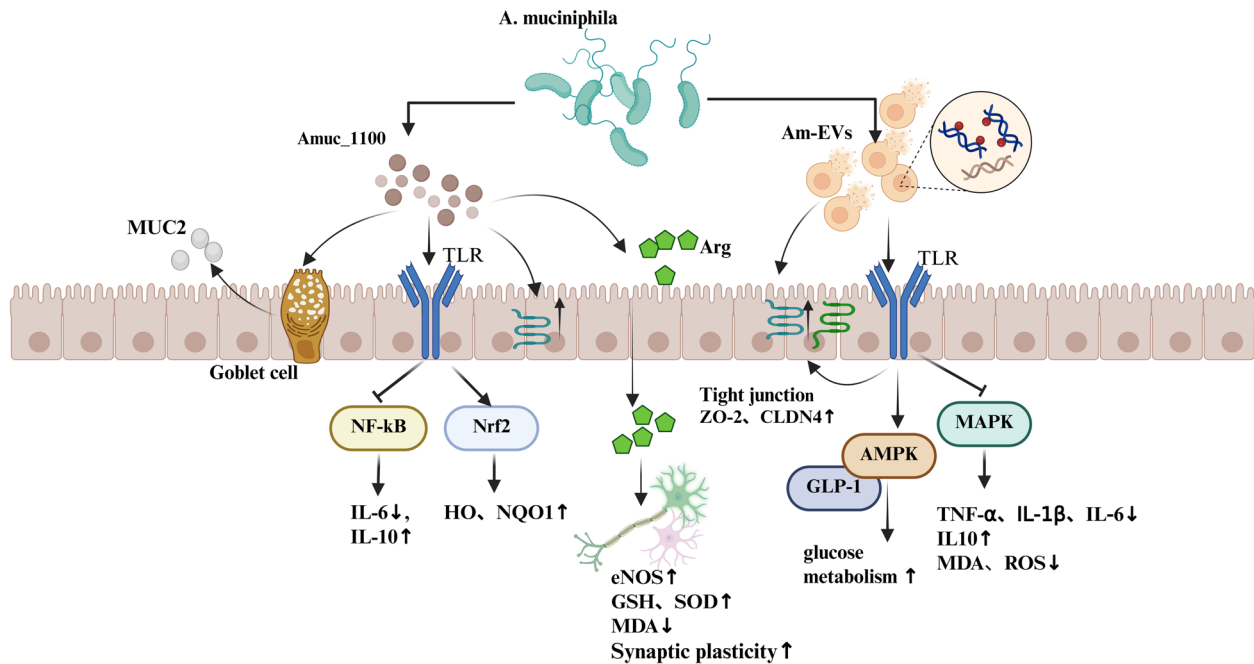


Fig. 4 Biological characteristics of Amuc_1100 and Am-EVs

Mechanism studies indicate that Am-EVs may modulate signaling pathways through interactions with specific proteins present on the surface receptors of host cells. Zhao et al. [78] revealed that 25–50 µg/mL Am-EVs in an LPS-induced Caco-2 inflammation model precisely modulated the MAPK signaling cascade through coordinated downregulation of TRIF/MyD88/p38 MAPK/FOS and upregulation of TGFBR2, leading to marked reductions in oxidative stress markers (ROS, MDA), restored catalase activity, and suppressed pro-inflammatory cytokine (TNF-α/IL-1β/IL-6) expression. This pioneering work first established the vesicle-mediated antioxidant defense mechanism whereby Am-EVs reprogram the oxidative stress-inflammation network to protect intestinal barrier integrity. Further research has revealed that Am-EVs exhibit multifaceted regulatory capacities, simultaneously enhancing glucose metabolism and energy expenditure through activation of both GLP-1 and AMPK signaling pathways while concurrently mitigating local inflammation via TLR2/4-mediated suppression of pro-inflammatory cytokines and reinforcing intestinal barrier function through upregulated expression of tight junction proteins ZO-2 and CLDN4 [79].

Structural analyses demonstrate that Am-EVs comprise both outer membrane (OM) and inner membrane (IM) components along with core structural molecules such as D-glucose and L-galactose, which collectively determine their structural and functional specificity while playing pivotal roles in mediating biological effects on host cells.

Functional characterization of Amuc_1100 in *A. muciniphila*

Since the pioneering systematic characterization of *A. muciniphila*'s outer membrane proteome through integrated genomic and proteomic approaches in 2016 [80], the high-abundance outer membrane protein Amuc_1100 has emerged as a key functional component with multiple therapeutic advantages [81]. Accumulating evidence from multiple studies demonstrates that Amuc_1100 not only retains the core biological functions of the bacterium but also possesses several superior characteristics [82–84]. Notably, it is capable of maintaining its active conformation even at the pasteurization temperature of 70 °C [25], and this significant finding has prompted a series of in-depth investigations. Multiple animal models and clinical trials have demonstrated that *A. muciniphila* subjected to pasteurization under specific conditions not only maintains the beneficial properties associated with live bacteria, but also exhibits significantly enhanced therapeutic effects in reducing inflammation, repairing the intestinal barrier, inhibiting liver fibrosis, and exerting anti-tumor activity, without compromising the ecological balance of the gut microbiota [18, 25, 85–87]. In-depth mechanistic studies demonstrate that pasteurization treatment moderately disrupts bacterial cellular integrity, thereby facilitating the complete exposure and rapid release of key outer membrane proteins, including Amuc_1100. Significantly, Amuc_1100 functions as a core effector molecule and exerts significant therapeutic effects, offering a robust molecular foundation for the pronounced efficacy

of inactivated *A. muciniphila* observed in preclinical investigations.

Further research has demonstrated that Amuc_1100 exhibits notable oxygen tolerance and functional stability within the complex intestinal microenvironment, with its antioxidant activity primarily mediated through the regulation of the NRF2 signaling pathway. This protein effectively maintains a balance between oxidative products and antioxidant enzymes. It significantly mitigates liver oxidative stress induced by *Salmonella typhimurium* by suppressing the upregulation of NRF2 protein and its downstream target, HO-1, while also modulating the mRNA expression of the NQO1 gene [88].

It is noteworthy that Amuc_1100 exhibits multiple biological functions. On one hand, it specifically activates the TLR2/NF- κ B signaling pathway [89], upregulates the expression of tight junction proteins, thereby effectively reducing intestinal permeability [25, 90, 91]. On the other hand, Amuc_1100 can release L-arginine under the influence of intestinal fluid digestion, thereby activating its synthesis and metabolic pathways, enhancing synaptic plasticity, and reversing age-related cognitive dysfunction. Additionally, Amuc_1100 can upregulate the expression of endothelial nitric oxide synthase (eNOS/Nos3), promoting the conversion of L-arginine to nitric oxide. These processes are associated with a significant increase in the activity of key antioxidant enzymes such as SOD and glutathione peroxidase (GSH-PX), as well as a marked reduction in the oxidative stress marker MDA. Consequently, Amuc_1100 effectively repairs intestinal-brain axis dysfunction mediated by oxidative stress, including improvements in critical pathological alterations such as synaptic dysfunction [92].

Metabolic and antioxidant effects of *A. muciniphila*-secreted P9 protein

The year 2021 marked the initial identification of P9 as a secretory protein from *A. muciniphila*, which modulates host metabolic processes via multiple pathways [93]. Although its direct effects on oxidative stress regulation have yet to be fully elucidated, emerging evidence indicates that P9 may indirectly affect redox homeostasis through its metabolic activities. P9 protein specifically binds to intercellular adhesion molecule-2 (ICAM-2), activating macrophage IL-6 signaling and significantly increasing uncoupling protein-1 (UCP-1) expression in interscapular brown adipose tissue (BAT) [94, 95]. The elevated UCP-1 levels enhance thermogenesis while reducing lipid accumulation in BAT. Importantly, UCP-1 has been demonstrated to effectively inhibit mitochondrial ROS overproduction [96], upporting its potential role in antioxidant defense. In addition, P9 induces GCG gene expression in intestinal L cells and elevates glucagon-like peptide-1 (GLP-1) levels via

a non-cAMP-dependent pathway [93]. Furthermore, P9 binds to ICAM-2, acting as a GPCR-like signaling molecule to mediate GLP-1 secretion from L cells [97]. Studies have shown that GLP-1 receptor agonists can reduce oxidative stress by activating the GSK3 β /Nrf2 pathway [98], as well as activate the PI3K/AKT axis, inhibit NF- κ B activity, and suppress the release of pro-inflammatory cytokines, which may indirectly alleviate oxidative stress-induced damage [99]. While direct evidence supporting P9 targeting oxidative stress regulatory molecules is still lacking, the current findings indicate its potential to indirectly alleviate oxidative stress associated with metabolic disorders via coordinated UCP-1-dependent thermogenic activation and GLP-1-mediated metabolic modulation. Future studies should systematically elucidate the downstream signaling cascades initiated by P9-ICAM-2 interactions and their functional crosstalk with cellular redox networks.

Potential antioxidant effects of Amuc_1409

In 2024, researchers employed nanoflow liquid chromatography-tandem mass spectrometry (nLC-MS/MS) to analyze the secreted proteome of *A. muciniphila*, identifying 2216 unique peptides corresponding to 325 proteins. Predictive analysis revealed 60 putative signal peptide-containing proteins, among which Amuc_1409 was further characterized. Experimental validation demonstrated that Amuc_1409 interacts with E-cadherin, leading to dissociation of the E-cadherin/ β -catenin complex and subsequent activation of the Wnt/ β -catenin signaling pathway. This mechanism regulates intestinal stem cell proliferation, regeneration, and differentiation, as confirmed in both in vitro organoid and in vivo aging models. Notably, Amuc_1409 exhibits a unique mode of action in modulating intestinal stem cell function, representing the first reported bacterial secreted protein capable of enhancing intestinal stem cell-mediated regeneration [100]. Oxidative stress is widely recognized for its ability to disrupt cellular proliferation and differentiation processes [101]. Evidence demonstrates that impaired Wnt/ β -catenin signaling not only exacerbates lipid peroxidation but also increases cellular susceptibility to ferroptosis [102]. Although the precise relationship between Amuc_1409 and oxidative stress regulation requires further investigation, its established role in activating Wnt/ β -catenin signaling implies a potential capacity to alleviate oxidative stress-induced impairments in intestinal cells. This hypothesized mechanism may contribute to maintaining normal cellular physiology and preventing dysfunction associated with oxidative stress.

Notably, beyond the aforementioned components, *A. muciniphila*-derived cobalamin (a vitamin B₁₂ analog) enhances intestinal epithelial barrier function and ameliorates insulin resistance by modulating methylmalonic

acid metabolism and the methionine synthesis pathway [103]. Additionally, its peptidoglycan component stimulates goblet cell-derived mucin MUC2 synthesis via NOD2 receptor activation, reinforcing the physicochemical barrier against enteric pathogens [104]. Collectively, these findings demonstrate that *A. muciniphila* exerts a central role in intestinal barrier maintenance, energy metabolism homeostasis, and oxidative stress regulation through multi-component, multi-target mechanisms. Importantly, this work elucidates how inactivated *A. muciniphila* retains biological activity at the molecular level, providing a mechanistic foundation for its clinical development as a next-generation probiotic.

Synergistic antioxidant network

Recent studies have progressively unveiled the pivotal role of *A. muciniphila* in intestinal microecological regulation. This bacterium contributes to the establishment of host antioxidant defense networks through multifaceted mechanisms, including intestinal barrier remodeling, immune homeostasis modulation, and metabolic pathway regulation. Intriguingly, *A. muciniphila* not only autonomously activates antioxidant signaling pathways but also forms a metabolic network with commensal bacteria such as *Bifidobacterium* and *Lactobacillus*, creating synergistic antioxidant effects. This cross-species cooperation offers novel ecological insights for combating

oxidative stress. Current research focuses on synthetic biology approaches to enhance its antioxidant potential. Engineering strategies aimed at improving bacterial colonization capacity, environmental tolerance, and targeted delivery systems have demonstrated significant improvements in ROS scavenging efficiency by modified strains, providing a scientific basis for developing precision antioxidant microbial therapeutics (Fig. 5).

Host-dependent regulation of *A. muciniphila* colonization

The gastrointestinal colonization dynamics of *A. muciniphila* exhibit distinct spatiotemporal patterns that are fundamentally associated with its mucinolytic activity. This bacterium's abundance directly correlates with intestinal mucus layer development, showing a well-defined age-dependent trajectory: emerging during infancy (first year of life), progressively accumulating through maturation, peaking in adulthood, and markedly declining during senescence [105]. *A. muciniphila* colonization prevalence in southern Chinese populations (51.74%) is significantly lower than European counterparts (74.70%), yet reaches 69.23% among southern Chinese elderly (>60 years) [106]. This distinct epidemiological pattern suggests potential geographic variation in host-microbe interactions.

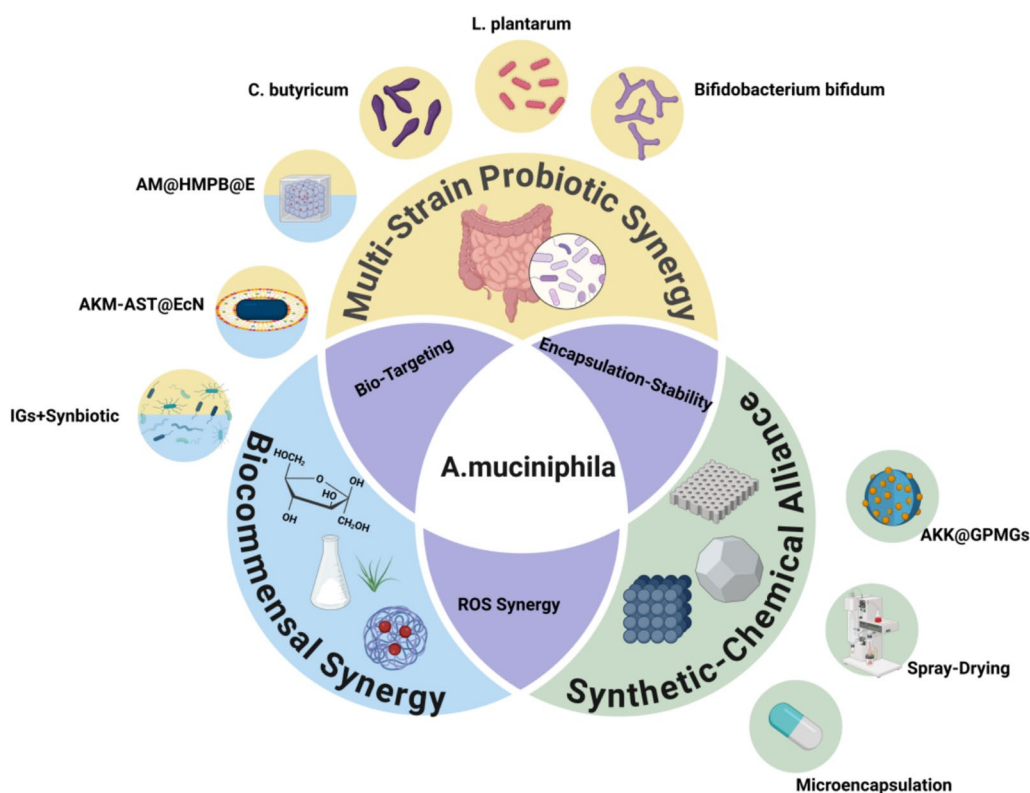


Fig. 5 Therapeutic potential of tri-modal synergy: combining multi-strain probiotics, synthetic-chemical and biocommensal alliance

Dietary interventions significantly modulate *A. muciniphila* abundance in the gut. In 2013, Everard et al. observed that an 8-week HFD (60% fat) reduced *A. muciniphila* levels by 100-fold in mice [24]. Similarly, In 2016, Neyrinck et al. demonstrated that acute alcohol administration (30% w/v, 6 g/kg) decreased its relative abundance from 9.3 to 3.8%, concurrent with elevated inflammatory and oxidative stress markers [107]. Conversely, dietary heme iron, a predominant red meat component, substantially increased *A. muciniphila* colonization [108]. Most remarkably, combined polyphenol supplementation from black tea, red wine, and cranberry extracts restructured the gut microbiota composition, elevating *A. muciniphila* abundance from 2 to >30% (OTU-based) and from 6.2 to 49.1% [109, 110].

Pharmacological agents differentially modulate *A. muciniphila* intestinal colonization. Omeprazole treatment reduces *A. muciniphila* abundance in C57BL/6 J mice, whereas metformin increases its population through goblet cell-mediated mucin secretion [111], consequently improving glucose tolerance in high-fat diet-fed mice. These findings collectively suggest that targeted manipulation of *A. muciniphila* colonization via dietary or pharmacological approaches could enhance metabolic health [112].

Functional interactions between *A. muciniphila* and the symbiotic microbiota

Given the inherent limitations of single-strain probiotics—such as their ecological niche specificity, limited functional diversity, and the complex dynamics of the gut ecosystem—researchers have increasingly turned to the development of multi-strain consortia with complementary functionalities, which offer a more effective strategy for regulating the intestinal microecology [113, 114].

A. muciniphila orchestrates intestinal ecosystem regulation through multidimensional host-microbe interactions. When administered synergistically with *Bifidobacterium bifidum*, this bacterial combination significantly attenuates hepatic lipid peroxidation in non-alcoholic fatty liver disease (NAFLD) models through coordinated modulation of the hepatic FXR/intestinal FXR signaling axis, leading to CYP7A1 suppression and subsequent remodeling of enterohepatic bile acid dynamics. 16S rRNA gene sequencing analyses demonstrate that this dual-strain intervention selectively reduces Proteobacteria abundance while promoting the expansion of *Lactobacillus* and *Parabacteroides* populations—microbial restructuring that correlates strongly with both improved glucose/lipid metabolism profiles and elevated anti-inflammatory IL-10 levels, thereby establishing a clear mechanistic link between microbiota-metabolite crosstalk and NAFLD pathogenesis [115]. In a dextran sulfate sodium (DSS)-induced IBD model, *A. muciniphila*

and *Clostridium butyricum* co-administration enhances microbial diversity, strengthens barrier integrity, and decreases myeloperoxidase (MPO) and malondialdehyde (MDA) activity, alleviating DSS-induced oxidative damage [116]. SLE studies show *A. muciniphila* and *Lactobacillus plantarum* jointly remodel immunity by reducing IL-17/IL-6, elevating IL-10, inhibiting Th17 differentiation, and restoring claudin-7 polarity, while promoting *Roseburia* proliferation and TCA cycle activation to enhance immunometabolic crosstalk [117].

A. muciniphila exhibits potent antagonistic properties when combined with *Bacteroides ovatus* and *Bifidobacterium breve*, forming structurally dense biofilms that secrete lactate to directly suppress *Clostridioides difficile* growth and toxin production [118]. This consortium additionally inhibits *Salmonella enterica* serovar Typhimurium proliferation and mitigates colonic mucosal damage through enhanced differentiation and expansion of regulatory T cells (Tregs) [119, 120]. Through competitive niche occupation in the intestinal mucus layer, *A. muciniphila* restricts ecological availability for other mucin-degrading bacteria, as demonstrated in both enterotoxigenic *Escherichia coli* (ETEC)-challenged porcine/murine models and antibiotic-induced dysbiosis systems, where it effectively outcompetes pathogenic species [121]. These collective findings establish that *A. muciniphila*-based microbial synergies mediate broad-spectrum antioxidant effects across disease models via three integrated mechanisms: gut microbiota restructuring, metabolic pathway regulation, and immune-oxidative network modulation.

Enhanced therapeutic efficacy of engineered *A. muciniphila*

As a promising next-generation probiotic candidate, *A. muciniphila* faces critical challenges for food and pharmaceutical applications due to its oxygen sensitivity and limited gastrointestinal tract tolerance [122]. To achieve therapeutic efficacy, maintaining viable cell counts at the recommended dosage (10^9 CFU) during both aerobic storage and gastrointestinal delivery remains essential [123]. Extensive research has explored physical encapsulation approaches employing synthetic materials and chemical surface modifications to improve microbial oxygen tolerance and gastrointestinal survival [124–129]. In a key study addressing bacterial viability preservation, Joana et al. [130] established that physical encapsulation using 10% skimmed milk as a matrix, followed by spray drying at 150/65 °C, enabled microencapsulated *A. muciniphila* to maintain viability at 10^7 CFU/g after 28 days of aerobic storage at 4 °C, with less than 1 log reduction. This approach substantially enhanced bacterial survival in simulated gastrointestinal conditions, demonstrating the potential of spray drying technology

Table 3 Strain-specific physiological properties of *Akkermansia* species

Strain	Isolation source	Growth temperature/PH	Phylogroup	Mucin substrates	Number of coding genes	Key gene	Function/Mechanism	References
ATCC BAA-835	Human faeces	20–40°C (optimum, 37°C); 5.5–8.0 (optimum 6.5)	Aml	Mucin, fucose, GlcNAc, GalNAc, mannose	2176	Amuc_1100; SCFA-synthetic genes (acetate/propionate); 125 strain-specific genes (unknown function)	Immunomodulation: Induces Treg/IL-10; suppresses inflammation; Metabolic regulation: SCFAs → GPR43 activation; anti-inflammatory Microbiota repair: Diversity restoration; promotes anti-inflammatory taxa	[82, 165]
Marseille-P5162	Human faeces	20–40°C (optimum, 37°C); 5.5–8.0 (optimum 6.5)	Aml	Not characterized	2648	Not characterized	Participate in mucus metabolism; maintain intestinal flora balance	[166]
Amuc_GP25	Human faeces	20–40°C (optimum, 37°C); 5.5–8.0 (optimum 6.5)	AmlI	Not characterized	Not characterized	Differential CAZyme-encoding profiles vs Aml	Glucose metabolism: Glu tolerance↑ (< Aml); TC↓; no TG change; Gut barrier: Tight junctions↑; no endotoxemia improvement;	[167]
Marseille-P6666	Human faeces	15–40 °C (optimum 5–30 °C)	AmlI	Mucin as sole carbon source	2793 (2726 protein-coding, 9 rRNA, 57 tRNA, 1 tmRNA)	More genes in cell wall/membrane biogenesis, energy production/conversion, and carbohydrate transport/metabolism vs BAA-835 T	Adapted to microaerophilic mucus layer; produces anti-inflammatory acetate/propionate; enhances gut colonization	[166]
Akk0196	Human faeces	Not characterized	AmlII	Not characterized	2705 (Core genome: 2,539; Pan-genome: 2,767)	125 strain-specific genes (unknown function)	uncultivated strain	[168]
WON2089T	Human faeces	25–45°C (optimum 30–37°C); 5.5–9.5 (optimum 6.5–8.0)	AmlIV	Mucin, GlcNAc, GalNAc, mannose	2544	Capable of acid production from D-mannitol	Engages in mucus metabolism; sustains intestinal homeostasis	[169]
A.muciniphila 139	Mouse feces	Not characterized	Not characterized	uses mucin as its sole carbon and nitrogen source	Not characterized	Amuc_1100; 278 strain-specific genes (unknown function)	Anti-inflammatory: IL-8↓ (in vitro); Improved colitis parameters (in vivo; < BAA-835); Microbiota restoration: Slower and less extensive than ATCC strain Immunomodulation: No significant regulatory Treg; No increased SCFAs production	[140]
PROBIO	Human faeces	20–40°C; 5.8–7.2; Resistant to 0.5% oxygen	Not characterized	Grown anaerobically in mucin-based medium	2309(+ 151)	Amuc_1100 + new gene amuX (Efficiency + 40%)	Modulates hepatic function and lipid metabolism; Regulates appetite and inflammation; improves mood and sleep; Adjusts gut microbiota composition	[27]

Table 4 Akkermansia clade characteristics

Phylogenetic Clade	Aml	AmlI	AmlII	AmlIII	AmlIV
Quantity	Most prevalent clade (Highest human colonization rate)	Subdominant clade		Rare	Rare
Genomic features	Contains complete assimilatory sulfate reduction (ASR) genes for mucin utilization; lacks vitamin B12 biosynthesis genes	Contains unique Rhs repeat protein genes (associated with interbacterial competition); lacks partial key ASR genes		Minimal genome; deficient in ASR cluster; no cysteine synthesis	Maximized genome; missing ASR cluster; cannot synthesize cysteine or B12
Metabolic capacity	Lacks fucosidase genes (GH29 and GH95)	mucin utilization capacity < Aml; Can synthesize vitamin B12		Can synthesize vitamin B12	Rich in fucosidase genes (GH29 and GH95)
Immunostimulatory potency	Weak, EV-independent immune activation; TLR4 activated at low bacterial load, TLR2 requires high load; overall < AmlI & AmlIV	TLR2/TLR4 activation > Aml		Stronger	TLR2/TLR4 activation ≈ AmlI
Competitive fitness	Dominates in untreated mice; replaced by AmlI/AmlIV post-antibiotics; Easily replaced by other Clades	Unidirectionally inhibits Aml growth via EVs		Stronger	Demonstrates strong competitive fitness in antibiotic-treated mice
Primary distribution	Human and mouse	human		Narrowly distributed, only detected in a few individuals	Predominantly distributed in Western populations
Mucinolytic activity	Strong (ASR gene-dependent, fast-growing)	Weak (slow-growing), requires mucin-derived galactose or depends on other bacteria for H ₂ S		Stronger	Weak but unique (possesses fucosidase, degrades terminally fucosylated mucin), slowest-growing
Oxygen tolerance	Varied tolerance among subtypes: Amla: Intermediate Amlb: Sensitive	Highest tolerance		Stronger	Highest sensitivity
Colonization dynamics	Rapid initial colonization (advantage in mucin utilization), but susceptible to later displacement by AmlI	Reduced fitness (partial ASR gene deletion, slower initial colonization than Aml)		Understudied	Rapidly becomes dominant in microbiota-disrupted mouse models

for *A. muciniphila* microencapsulation applications. In the context of delivery system optimization, Zhang et al. [131] developed an encapsulation strategy based on gelatin porous microgels (AKK@GPMGs). This approach significantly enhanced the gastric acid tolerance of *A. muciniphila* by 30.49-fold through multilayer encapsulation, improved intestinal colonization efficiency by 83.46-fold, increased the mucus layer thickness by 5.63-fold, and promoted goblet cell proliferation by 3.93-fold. Additionally, it reduced intestinal permeability by 5.60-fold and enhanced ROS scavenging ability by 26.47-fold. These findings confirm that *A. muciniphila* exhibits both mechanoprotective and functional-enhancing properties.

Recent advances in strain engineering and innovative transformation approaches have driven growing interest in biomaterials-based bacterial functionalization strategies [127]. Researchers developed AKM-AST@EcN nanocoated engineered bacteria by coating *Escherichia coli* Nissle 1917 (EcN) with *Akkermansia muciniphila* membrane (AKM) and astaxanthin (AST), demonstrating ABTS and DPPH radical scavenging efficiencies of $34.64\% \pm 1.54\%$ and $41.68\% \pm 3.59\%$, respectively. When engineered to express immunomodulatory proteins (Amuc_1409 and Amuc_1100), these bacteria exhibited synergistic antioxidant, anti-inflammatory, and

microbiota-modulating effects in DSS-induced colitis mice [132]. In the field of precise targeted delivery, the bionanosystem AM@HMPB@E demonstrates precise colon lesion targeting capability through the integration of Prussian blue nanozyme (HMPB), entinostat, and AKM, leveraging their combined electrostatic adsorption and bioadhesive properties. The unique core-shell structure effectively protects the active ingredients from gastric acid degradation while simultaneously enabling precise synergistic effects including ROS scavenging, intestinal epithelial barrier repair, and apoptosis inhibition [133]. Notably, significant breakthroughs have been achieved in the development of engineered multi-strain synergistic approaches. Du et al. [134] demonstrated that inulin hydrogels (IGs) encapsulating a multi-strain probiotic bacteria (MSPs: *Clostridium butyricum*, *Bifidobacterium adolescentis*, and *Akkermansia muciniphila*) formed an effective synbiotic system. This system physically embeds the bacterial strains, thereby protecting the gut microbiota from gastrointestinal environmental damage. The synbiotic system significantly mitigated radiation-induced intestinal injury in an insulin-based model, enhanced intestinal barrier function, reduced levels of inflammatory cytokines, and increased anti-inflammatory mediators such as SCFAs and IL-10. These

findings confirm that the synergistic effects of multiple bacterial strains can disrupt the pathological cycle of oxidative stress, immune imbalance, and dysbiosis in a radiation injury model. These innovative approaches, integrating materials science with synthetic biology principles, have accelerated the translation of probiotic therapeutics from fundamental protective agents to clinically applicable diagnostic and treatment modalities. While further breakthroughs remain necessary—particularly in standardizing preparation protocols and evaluating long-term efficacy—this work establishes a crucial theoretical framework for developing clinical-grade, multifunctional probiotic combinations with enhanced targeting capabilities.

Future and outlook

While numerous studies have demonstrated the antioxidant potential of *A. muciniphila* in various oxidative stress-associated disorders [16, 43, 135], its clinical translation faces significant challenges stemming from context-dependent functional variability across host ecosystems. Emerging evidence indicates that *A. muciniphila* may, under specific conditions, increase intestinal infection susceptibility through virulence factor upregulation [12, 136, 137]. For example, in IL-10-deficient mouse models, *A. muciniphila* overproliferation leads to excessive mucus layer degradation, compromising intestinal epithelial barrier integrity and promoting bacterial translocation. These effects subsequently trigger hyperactive innate immune responses via MyD88/TLR4-dependent signaling pathways, ultimately aggravating colitis progression [138]. Wang et al. [139] demonstrated that impaired ILC3 function leads to abnormal galactosylation of colonic mucins, thereby establishing a microenvironment conducive to the excessive proliferation of the commensal bacterium *A. muciniphila* within the mucus layer. The resultant bacterial overgrowth produces succinic acid, which enhances the virulence of enteropathogenic *Escherichia coli* (e.g., promoting Tir and Ler gene expression) and increases epithelial invasiveness. These findings indicate that the biological effects of *A. muciniphila* are largely influenced by the host microenvironment.

Strain-level heterogeneity constitutes a significant translational barrier for *A. muciniphila* therapeutic development. Zhai et al. [140] revealed functional divergence between *Akkermansia muciniphila* strains ATCC BAA-835 and 139. While both strains suppressed TNF- α -induced IL-8 secretion in vitro, only BAA-835 significantly ameliorated disease parameters (spleen weight, inflammation index, and histological scores) in DSS-induced colitis. This strain-specific efficacy correlates with BAA-835's 125 unique genes, which encode critical regulators of Treg differentiation, SCFA biosynthesis, and GPR43 signaling—functional modules absent or impaired

in strain 139's 278 unique gene repertoires. Although all strains belong to the genus *Akkermansia*, notable physiological heterogeneity exists among different *Akkermansia* strains. These strain-specific variations directly influence their metabolic functions, immune regulatory properties, and adaptability to ecological niches (Table 3).

Recent research has thoroughly demonstrated that the *Akkermansia* population exhibits substantial (Table 4) [141–143]. In Hong et al. [141] conducted systematic phylogenetic analyses that classified this bacterium into four distinct clades (AmI–AmIV), demonstrating that inter-strain competition is mediated through secretion of specific EVs. While the AmI clade exhibits superior initial colonization capacity, the AmII clade can effectively suppress AmI growth via EV-mediated inhibition. This inter-lineage antagonism carries important clinical implications: supplementation with AmIV strains proves ineffective in hosts pre-colonized with AmI due to competitive exclusion, whereas remarkable therapeutic effects are observed in AmI-free individuals. These findings were experimentally validated using fecal supernatants (SF) from EB-AMDK39 (AmII) donors, which specifically inhibited EB-AMDK19 (AmI) growth. Further investigations revealed that the AmII clade potently activates innate immune responses through TLR2/TLR4 signaling pathways, inducing specific effector molecules including Reg3 γ . Metabolomic profiling identified substantial metabolic divergence among clades: the AmI clade lacks vitamin B12 biosynthesis genes, while AmII and AmIV are deficient in assimilatory sulfate reduction genes [142, 143]. The pronounced metabolic and functional heterogeneity among *A. muciniphila* lineages suggests that targeted modulation of specific lineages may significantly enhance therapeutic efficacy and optimize clinical outcomes, thereby overcoming the current challenge of “ineffective bacterial supplementation.”

In addition, this bacterium exhibits a distinct dose-dependent dual effect: when present at moderate levels, it can significantly enhance the anti-tumor immune response through the induction of M1-type macrophage polarization and activation of the NLRP3 inflammasome, thereby suppressing colorectal cancer (CRC) progression [144–146]; however, in cases of over-proliferation, it promotes CRC development due to excessive mucin degradation [147].

The therapeutic efficacy of *A. muciniphila* is critically determined by host-microbe-environment interactions, with its probiotic effects being precisely regulated through an integrated interplay of host genetic factors, strain-dependent characteristics, and the ecological dynamics of commensal microbiota [148].

Given the dynamic potential of this bacterium to transition from a commensal to a pathogenic phenotype under varying pathophysiological conditions, establishing a

rigorous evaluation framework becomes paramount before considering its clinical translation. This necessitates, first and foremost, a comprehensive characterization of the host's genetic background and intestinal microecological composition to identify potential risk factors that may influence bacterial behavior [54]. Equally critical is the precise determination of the strain's interaction threshold with intestinal mucin to achieve controlled “protective degradation,” wherein the mucin-degrading activity must be carefully balanced against its capacity to preserve immune homeostasis. Such equilibrium is indispensable for preventing compromised intestinal barrier function resulting from excessive mucin breakdown, thereby ensuring both efficacy and safety in therapeutic applications. At the technology transfer level, the development of targeted delivery platforms leveraging biomimetic materials or synthetic biology must prioritize two fundamental challenges: improving bacterial colonization stability within the complex intestinal microenvironment and resolving functional heterogeneity across strains. Addressing these limitations necessitates the establishment of a standardized strain evaluation system, encompassing comprehensive functional profiling and optimized therapeutic dosing strategies. Importantly, current multicenter clinical trials have yet to systematically evaluate the relationship between *A. muciniphila* and oxidative stress markers—a critical knowledge gap that future studies must resolve by delineating the bacterium's multidimensional regulatory network spanning metabolism, immunity, and redox homeostasis. Advancements in these foundational areas will be pivotal in translating *A. muciniphila*-based research into precision therapeutic interventions.

Acknowledgements

We thank BioRender (biorender.com) for providing the tools to create scientific figures.

Author contribution

Wen-Yu Ye: Data Curation, Writing and Original Draft; Yan Cai: Conceptualization, Supervision, Writing - Review and Editing. All authors have read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 21 May 2025 / Accepted: 11 September 2025

Published online: 24 October 2025

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