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Review Article

Akkermansia muciniphila: A Promising Next Generation Probiotic

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Abstract

An important mucin-degrading member of the phylum Verrucomicrobia, *Akkermansia muciniphila*(AKK) has become a promising next-generation probiotic with important host health implications. AKK, which is mostly found in the intestinal mucus layer, regulates gut barrier integrity, immunological responses, and metabolic activities to help maintain gut homeostasis. Recent research has explored its potential to contribute to the improvement of various diseases conditions such as obesity, type 2 diabetes, nonalcoholic fatty liver disease, cardiovascular illnesses, and neurodegenerative diseases. Its extracellular vesicles and outer membrane proteins affect T-cell responses, systemic inflammation, and even neurotrophic signaling, which is involved in mood and cognitive function. Its action seems context-dependent, though, as both positive and negative effects have been noted in various neurological conditions including multiple sclerosis and Parkinson's disease. Significant strain-level diversity is shown by genomic analysis, indicating functional heterogeneity that could be the cause of these disparate results. Current research on AKK's diverse functions in health and illness is discussed in this review, highlighting the directions for further studies to further explore its probiotic potential.

Keywords

next generation probiotic, gut barrier integrity, immune modulation, therapeutic potential, extracellular vesicles

Introduction

Human microbiota,which is also called the *hidden organ* includes a variety of microorganisms dominated by bacterial community. Microbiota coexists and coevolves in various sites of human body mainly gut, skin and oral cavity. It contributes genetic information, surpassing 150 times that of the entire human genome (Hou *et al.*, 2022). It plays an important role in host's health status through physiological metabolic and immune

modulations such as food fermentation, protection against the pathogens, vitamins production and immune response stimulation (Fujimura *et al.*, 2010).

Gastrointestinal tract has a diverse microbial ecology where two bacterial phyla *Bacteroidetes* and *Firmicutes* predominate, while *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* are typically present in lower abundance (Lozupone *et al.*, 2012). Among the gut microbiota, *Akkermansia* is notable for its mucin-degrading capacity, involvement in metabolic homeostasis, and potential as a therapeutic agent in metabolic disorders.

Akkermansia muciniphila (referred as AKK hereafter) has been consistently associated with host health, and its reduced abundance is linked to a range of pathological conditions in both murine models and humans. Although the precise molecular signaling pathways through which this probiotic confers benefits to the host are still being explored actively, its preventive and therapeutic potential in conditions such as obesity, aging, diabetes and various other metabolic syndromes is well established (Hasnain *et al.*, 2024). Importantly, AKK plays a central role in preserving gut barrier integrity and modulating immune responses, thereby limiting chronic low-grade inflammation-a key contributor to the pathogenesis of numerous diseases (Aja *et al.*, 2025).

This mini-review aims to provide a concise overview of the current understanding of AKK as a next-generation probiotic, with a focus on its roles in metabolic regulation, immune modulation, and gut barrier function. We explore emerging evidence linking AKK to various health conditions, including metabolic disorders, inflammation, and neurodegeneration. Additionally, we highlight the underlying mechanisms by which this bacterium may exert its beneficial effects, discuss and identify key concerning areas that warrant further investigation.

Taxonomy, Genomics and Physiology

AKK is a Gram-negative, oval-shaped, non-motile oxygen-tolerant anaerobe which was first discovered in 2004 in human fecal samples. It belongs to phylum *Verrucomicrobia* and was the 1st cultivated member of *Akkermansia* genus (Aja *et al.*, 2025). While it's most abundant in colon, mucus layer of small intestine is also inhabited by AKK (Hasnain *et al.*, 2024). First genome of AKK was sequenced in 2011. With a total size of 2.7 Mb, 11% of its large secretome (61 proteins) were involved in mucus degradation along with 43% other proteins with no known function which might also play role in mucin modification/processing (van Passel *et al.*, 2011). In addition, its genome analysis revealed the presence of two CRISPR loci and many phage-derived sequences highlighting the vital role of viral infections in their evolution. Analysis of various other AKK isolates have demonstrated the possibility of horizonal gene transfer since the CRISPR genes are located close to predicted phage genes (Becken *et al.*, 2021; van Passel *et al.*, 2011). While a type-strain, MucT (ATCC BAA-835) remains most extensively studied, pangenome analysis of 234 isolates revealed the presence of significant genomic diversity in AKK strains based on which these can be categorized into separate clades and subspecies with diverse attributes (Mueller *et al.*, 2024).

Since it colonizes intestinal mucosa, its energy harvesting and synthesis pathways are based on mucin degradation and processing. It thrives by degrading mucin, its main energy and nitrogen source. It metabolizes mucin-derived monosaccharides such as fucose, galactose and *N*-acetylgalactosamine, with enhanced growth observed when mucin is co-metabolized with these sugars (Ottman *et al.*, 2017). Although it can ferment some non-mucin sugars like fructose and human milk oligosaccharides, it does not efficiently utilize sugars like maltose, melibiose or trehalose, despite genomic indications of potential metabolism (Aja *et al.*, 2025; Ottman *et al.*, 2017). Notably, threonine is the only essential amino acid AKK cannot produce, likely due to its abundance in mucin, reflecting its adaptation to the mucosal niche (Ottman *et al.*, 2017; Schrager 1970).

Role in Gut Health

Intestinal tight junctions and mucus are important in keeping the damage from digestive secretions and

pathogens. AKK is involved in improving the intestinal barrier integrity through **i)** enhancement of mucus-producing goblet cells and regulating their autophagy process, **ii)** intestinal stems cell stimulation and differentiation to intestinal epithelial cells and Paneth/ goblet cells, **iii)** upregulation of tight junction proteins e.g. Occludin, Claudin-3, ZO-1 directly or through its extra extracellular vesicles (EVs) mainly via inhibition of NF-κB pathway and yet-to-establish mechanisms (Mo *et al.*, 2024). In addition, AKK improves the *leaky gut* situation through suppressing the production of inflammatory cytokines like TNF-α and IL-8. Short-chain fatty acids (SCFAs), and proteins like Amuc_1100 and P9 stimulate L cells to secrete glucagon-like peptide-1 (GLP-1) which improves barrier function and reduces inflammation (Mo *et al.*, 2024; Yoon *et al.*, 2021). AKK and its out-membrane protein i.e. Amuc_1100 have been shown to induce CD8+ cytotoxic T lymphocytes activity and Treg differentiation thereby inhibiting colitis-associated colorectal cancer (Wang *et al.*, 2020). Two other membrane proteins from AKK, namely Amuc_2172 and Amuc_2173 further reprogram tumor immune microenvironments in intestinal tumors (Jiang *et al.*, 2023; Mo *et al*, 2024). Further, through TLR2/NLRP3 signaling, AKK shifts macrophages toward M1 phenotype in anti-cancer immunity (Fan *et al.*, 2021).

Implications in Metabolic Disorders and Cardiovascular Health

Recent research has found changes in the abundance of AKK to be associated with various metabolic disorders like obesity, type 2 diabetes mellitus (T2D), nonalcoholic fatty liver disease and cardiovascular diseases (Everard *et al.*, 2013; Shi *et al.*, 2021; Zhang *et al.*, 2021).

Obesity and its associated disorders have become a serious health issue. The role of gut microbiota in metabolism and energy harvesting process is well established and gut dysbiosis has been linked to imbalance in energy intake and expenditure leading to obesity and related disorders. Recent research has suggested that AKK is a promising candidate for preventing or ameliorating obesity and associated diseases (Hasnain *et al.*, 2024). Live and pasteurized AKK and its EVs plays a protective role against obesity primarily by enhancing gut barrier integrity and modulating host metabolism. In high-fat diet (HFD)-induced models, it reduces intestinal permeability, lowers plasma lipopolysaccharide (LPS) levels, and mitigates systemic inflammation (Ashrafian *et al.*, 2021; Depommier *et al.*, 2020). Mechanistically, AKK promotes thermogenesis, increases GLP-1 secretion, elevates endocannabinoid levels, and downregulates genes involved in adipogenesis and carbohydrate transport. These actions collectively reduce fat accumulation, improve insulin sensitivity, and decrease energy efficiency. While animal studies demonstrate consistent anti-obesity effects with live, pasteurized, or EVs derived from AKK, clinical evidence in humans remains limited and warrants further investigation (Zhao *et al.*, 2024).

T2D is a heterogeneous metabolic disorder characterized by hyperglycemia, insulin resistance, obesity, and low-grade inflammation, with a rapidly increasing global prevalence. If left uncontrolled, T2D leads to severe complications such as diabetic nephropathy, cardiomyopathy, retinopathy, and cognitive impairment, significantly contributing to mortality (Gregg *et al.*, 2014). AKK exerts multifaceted beneficial effects in T2D through several interconnected mechanisms. It modulates host glucose metabolism by enhancing GLP-1 secretion via microbial metabolites such as propionate and direct interaction of outer membrane protein P9 with intercellular adhesion molecule (ICAM)-2, which together stimulate insulin release and improve glycemic control (Li *et al.*, 2023; Psichas *et al.*, 2015; Yoon *et al.*, 2021). The bacterium also activates the phosphatidylinositol 3-kinase (PI3K)-Akt pathway and promotes lipid oxidation through upregulation of the liver kinase B1 (LKB1)-AMPK signaling axis, thereby mitigating hepatic steatosis (Huang *et al* 2018; Jiafeng *et al*; 2022; Rao *et al.*, 2021). Furthermore, it influences bile acid metabolism by modulating farnesoid X receptor signaling and fibroblast growth

factor 15/19 (FGF15/19) pathways, contributing to improved lipid and glucose homeostasis (Li *et al.*, 2023). AKK strengthens the gut barrier by increasing mucin (Muc2) production, tight junction protein expression (e.g., ZO-1, occludin), and stimulating Wnt signaling in intestinal stem cells, which collectively reduce metabolic endotoxemia by limiting LPS translocation (Guo *et al.*, 2022; Li *et al.*, 2023). Additionally, AKK contributes to microbiota homeostasis by enhancing microbial diversity and rebalancing the *Firmicutes/Bacteroidetes* ratio, which is often disrupted in T2D. Its beneficial effects are not limited to live bacteria; components such as pasteurized cells, outer membrane protein Amuc_1100, and extracellular vesicles also retain immunomodulatory and metabolic regulatory properties, supporting its potential as a next-generation probiotic for T2D.

AKK supports cardiovascular health by reducing endothelial inflammation through downregulation of TNF-α, MCP-1, and ICAM-1, thereby inhibiting macrophage adhesion and atherosclerotic plaque formation (Gofron *et al.*, 2024; Li *et al.*, 2016). It lowers systemic inflammatory markers such as CRP and TNF receptor II without altering lipid or glucose levels, reducing atherosclerosis severity (Gofron *et al.*, 2024). The bacterium also produces propionate, which inhibits arterial calcification, and reduces TMAO synthesis, thereby protecting against atrial fibrillation and cardiomyocyte pyroptosis. These benefits are primarily observed with live bacterial supplementation. Additionally, AKK improves gut barrier function and lipid metabolism, contributing to weight reduction and blood pressure control, indirectly mitigating cardiovascular risk (Gofron *et al.*, 2024; Luo *et al.*, 2022; Yan *et al.*, 2022). Table 1 enlists recent research regarding the ameliorative potential of AKK in different disease conditions.

AKK and Neurological Disorders

In neuropsychiatric conditions, AKK modulates host physiology through multifaceted mechanisms involving metabolic, immunological, and gut-brain signaling pathways. Its outer membrane protein Amuc_1100 and secreted protein P9 influence serotonin biosynthesis and brain-derived neurotrophic factor (BDNF) signaling, critical in depression and anxiety-like behaviors (Lei *et al.*, 2023). Amuc_1100 acts via TLR2 to promote 5-HT production and upregulate BDNF, while P9 enhances GLP-1 secretion with downstream neuroprotective effects (Holst *et al.*, 2011; Wang *et al.*, 2021). In Parkinson's disease (PD) and Alzheimer's disease (AD), studies consistently report elevated levels of AKK in patient microbiota, but with mixed implications. While some studies suggest AKK may help reduce inflammation, others associate its increased abundance with damage to the gut lining and higher levels of endotoxins in the blood (Lei *et al.*, 2023). Therefore, further research is necessary to clarify the dual role of AKK in PD and determine whether its increased abundance is protective or contributes to disease pathology. In PD and multiple sclerosis (MS), both human and mouse studies show elevated AKK abundance correlating with either beneficial modulation of T-cell responses or exacerbation of inflammation, depending on context and strain (Takewaki *et al.*, 2020). The production of SCFAs, particularly butyrate, by AKK or its microbial consortia, is linked to anti-inflammatory effects, enhanced synaptic plasticity, and modulation of the enteric and central nervous systems (Lei *et al.*, 2023; Yang *et al.*, 2019). Hence, clinical and animal studies across conditions like depression, AD, and stroke reveal alterations in AKK levels, often tied to behavioral and cognitive outcomes. These findings suggest a complex, context-dependent role for AKK in neurological disorders, balancing mucosal health and immune regulation with potential pathogenic effects in dysregulated states (Lei *et al.*, 2023).

Conclusions

AKK is gaining attention as a strong candidate for next-generation probiotics because of its important role in supporting gut and metabolic health. It helps maintain the gut barrier, supports the immune system, and produces useful compounds like SCFAs, which are linked

Table 1. Application of AKK in various disease conditions

Type of disorder	Type of model	Main observation	Reference
Depression	CRS mouse model	↓Depression-like behavior; ↑BDNF, ↑dopamine, regulation of gut microbiota and metabolic pathways	Ding *et al.*, 2021
	Antibiotic-treated mouse model	↓Depression-like behavior, ↑BDNF and 5-HT, modulated gut-brain axis, normalized HPA axis	Sun *et al.*, 2023
	Murine alcohol + LPS model	↓ Depression-like symptoms, ↑occludin, BDNF, and 5-HT; ↓LPS, TNF-α, IL-1α, and IL-6	Guo *et al.*, 2022
Alzheimer's disease (AD)	APP/PS1 transgenic mouse model	↓Aβ plaques and levels; Improved cognition and gut barrier integrity	Ou *et al.*, 2020
Cardiovascular disease	Atherosclerosis (ApoE$^{-/-}$ mice)	↓Atherosclerotic lesions; Improved lipid profiles, and restored gut microbial balance	Xiao *et al.*, 2024
	Abdominal aortic aneurysm (mice)	↓ Aneurysm development, restored microbiota diversity, ↓systemic inflammation	He *et al.*, 2022
Metabolic disease	HFD-fed rats	Protected β-cells from apoptosis, promoted differentiation, ↑ gut barrier function	Yan *et al.*, 2024
Obesity & T2D	Meta-analysis of animal studies	↓ Body weight by 10.4%, fasting glucose by 21.2%; ↑ insulin by 26.9%, improved glucose tolerance	Liu *et al.*, 2024
Colorectal cancer	Mouse tumorigenesis model	Amuc_2172 inhibits tumorigenesis by upregulating HSP70 and enhancing CD8+ T cell activity	Jiang *et al.*, 2023
Sepsis	Mouse sepsis model	Arg-Lys-His tripeptide from AKK reduces inflammation via TLR4 inhibition	Xie and Prasad, 2020
Metabolic syndrome/gut barrier integrity	Mouse gut permeability model	AKK-EVs promote gut barrier integrity	Chelakkot *et al.*, 2018
Type 2 diabetes	Clinical trial (probiotic formulation)	↓Postprandial glucose levels; ↑ insulin sensitivity and metabolic markers	Perraudeau *et al.*, 2020
Age-related muscle decline	Clinical trial (pasteurized AKK HB05)	↑Muscle strength, function, and physical performance	Kang *et al.*, 2024
Chronic respiratory symptoms	Clinical trial (ETB-F01, heat-killed AKK)	Improved respiratory symptoms and lung function	Lee *et al.*, 2024
Obesity and diabetes	HFD mouse model	↓ Body weight gain, fat mass, insulin resistance, lowered plasma leptin and triglycerides; ↑glucose tolerance, gut barrier integrity	Plovier *et al.*, 2017
Obesity, insulin resistance	Randomized, double-blind, placebo-controlled pilot study	↑ Insulin sensitivity; ↓plasma total cholesterol, fat mass, plasma LPS, creatine kinase	Depommier *et al.*, 2019

to benefits in conditions such as obesity, type 2 diabetes, and inflammatory bowel disease. Different strains of AKK have shown differences in how they function, suggesting that their health effects may depend on the specific strain used. While animal studies have shown encouraging results, more research in humans is needed to confirm these findings. Future studies should focus on testing the safety of using live AKK, understanding how different strains work, and exploring how it interacts with diet and other gut microbes. There is also potential in combining

AKK with other gut-based treatments to manage complex health problems. With more evidence, this microbe could become a valuable tool in future treatments for metabolic and gut-related diseases. Preclinical data substantially supports its therapeutic promise, however, there are still a limited number of human studies. Therefore, further research is needed into strain-specific effects, administration methods, and long-term safety.

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