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Akkermansia muciniphila: The role as a probiotic bacterium for the prevention and treatment of metabolic syndrome.

Akkermansia muciniphila: Su papel como bacteria probiótica para la prevención y tratamiento de síndrome metabólico

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Abstract:

Metabolic syndrome (MetS) is a complex health condition characterized by multiple metabolic abnormalities, commonly observed in the Mexican population and worldwide. It is often addressed by treating individual components rather than a comprehensive approach. This review explores the mechanisms and effects of probiotic bacteria as natural therapeutic alternatives for the prevention and management of MetS. The gut microbiota plays a crucial role in human health; alterations in its composition and abundance are strongly associated with various diseases, including obesity, inflammatory disorders, type 2 diabetes mellitus, certain cancers, and neurodegenerative diseases. Among these microorganisms, *Akkermansia muciniphila* has shown particular promise. It enhances intestinal mucosal thickness and produces short-chain fatty acids, contributing significantly to the host's metabolic and inflammatory regulation. *Akkermansia muciniphila* emerges as a promising probiotic for preventing and treating metabolic disorders, particularly metabolic syndrome. Its supplementation, combined with a low-calorie diet and functional foods, may promote its growth and activity in the large intestine, offering a potential strategy for improving metabolic health.

Keywords:

Akkermansia muciniphila, gut microbiota, metabolic syndrome, insulin resistance, obesity, type 2 diabetes mellitus

Resumen:

El síndrome metabólico (SMet) es una condición de salud compleja caracterizada por múltiples alteraciones metabólicas, comúnmente observadas en la población mexicana y a nivel mundial. A menudo, su tratamiento se enfoca en abordar componentes individuales en lugar de adoptar un enfoque integral. Esta revisión explora los mecanismos y efectos de las bacterias probióticas como alternativas terapéuticas naturales para la prevención y el manejo del SMet. La microbiota intestinal desempeña un papel crucial en la salud humana, y las alteraciones en su composición y abundancia están fuertemente asociadas con diversas enfermedades, incluyendo la obesidad, los trastornos inflamatorios, la diabetes mellitus tipo 2, ciertos tipos de cáncer y las enfermedades neurodegenerativas. Entre estos microorganismos, *Akkermansia muciniphila* ha demostrado un potencial particular. Esta bacteria aumenta el grosor de la mucosa intestinal y produce ácidos grasos de cadena corta, que contribuyen significativamente a la regulación metabólica e inflamatoria del huésped. *Akkermansia muciniphila* se presenta como un probiótico prometedor para la prevención y el tratamiento de trastornos metabólicos, en especial el síndrome metabólico. Su suplementación, combinada con una dieta baja en calorías y alimentos funcionales, puede favorecer su crecimiento y actividad en el intestino grueso, ofreciendo una estrategia potencial para mejorar la salud metabólica.

***Palabras Clave**:*

Akkermansia muciniphila, microbiota intestinal, síndrome metabólico, resistencia a la insulina, obesidad, diabetes mellitus tipo 2

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INTRODUCTION

Metabolic syndrome (MetS) is a clinical disorder, a chronic and progressive pathophysiological condition, representing a group of risk factors (mainly obesity, insulin resistance, hypertension and dyslipidemia) that form a complex syndrome defined by a unifying pathophysiology and associated with an increased risk for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and other related disorders.[1-4] The main manifestations of MetS are insulin resistance, abdominal obesity, hypertension, atherogenic dyslipidemia (elevated blood levels of triglycerides and LDL-cholesterol, and low levels of HDL-cholesterol), high fasting serum glucose concentrations, endothelial dysfunction, and a hypercoagulable state.[5]

The WHO has classified MetS as a global epidemic, since its prevalence is estimated at 20-25% of the world's population.[6] Worldwide prevalence of MetS ranges from <10% to 84%, depending on the region, urban-rural environment, sex, age, race, ethnicity, and the definition used (Table 1).[7-12] In 2018, it was reported that 36.5 million adults in Mexico had metabolic syndrome. Of these, 2 million were at high risk of developing type 2 diabetes mellitus in the next 10 years, and 2.5 million had cardiovascular disease.[13] Nowadays, OECD countries spend 8.4% of their total health budget on obesity-related disease treatments. This figure is roughly equivalent to US$311 billion or US$209 per capita per year. Obesity is responsible for 70% of all treatment costs related to diabetes and 23% related to cardiovascular diseases.[14] MetS is a complex disorder with a high socioeconomic cost and is considered a public health problem, as it constitutes a real epidemic.[6]

Table 1. *Criteria determined for metabolic syndrome according to the World Health Organization (WHO) and the International Diabetes Federation (IDF).* [15]

Criteria	IDF	WHO
Triglycerides ≥ 150 mg/dL	x	x
HDL-cholesterol Men: <40 mg /dL Women: <50 mg/dL	x	x
Blood pressure >130/80 mmHg	x	x
Insulin resistance		x
Fasting glucose >100 mg/dL	x	
Abdominal obesity	x	
High BMI		x
Microalbuminuria		x
Risk factors and diagnosis	Abdominal obesity	More than 2 factors

The role of the gut microbiota in human health is crucial, and it is believed that alterations in its abundance and composition are related to multiple diseases. Numerous studies have shown a strong association between obesity, inflammatory diseases, T2DM, different types of cancer, neurodegenerative diseases, and certain microorganisms, like *Akkermasia muciniphila*, a promising natural probiotic, inhabitant of the intestinal microbiota.[16-18] There is a clear need to find treatments that help treat metabolic disorders effectively, including treatments with probiotics that promise multiple benefits, so this article aims to focus on the potential role of *Akkermansia muciniphila* as an innovative therapeutic tool in managing the metabolic syndrome. Unlike previous reviews, this work analyses not only the metabolic and anti-inflammatory benefits of this probiotic bacterium and the feasibility of incorporating it into functional foods as a practical and accessible strategy to improve intestinal and metabolic health in high-risk populations. In addition, it explores recent studies evaluating its effectiveness in animal models and human clinical trials, identifying gaps in the literature and areas of opportunity for future research. The article is based on a literature search in databases such as PubMed, SciELO, ScienceDirect, and Springer using terms from medical subject headings (MeSH) and keywords such as (*Akkermansia muciniphila*) AND (metabolic syndrome), (*Akkermansia muciniphila*) AND (insulin resistance) AND (Obesity), (*Akkermansia muciniphila*) AND (Type 2 Diabetes Mellitus) without restriction of initial year until 2024 in English, Spanish, and French languages.

OVERVIEW OF METABOLIC SYNDROME

Metabolic syndrome (MetS) is a public health problem involving genetic predisposition, environmental factors, and gut microbiota dysbiosis. Characterized by central obesity, dyslipidemias, insulin resistance, hypertension, and low-grade inflammation.[19] Studies have shown that MetS pathophysiology is related to chronic inflammatory conditions and oxidative stress, disrupting redox signalling and cellular damage, and in turn, plays a fundamental role in the development of metabolic comorbidities such as hyperlipidemia, high blood pressure, and increased glucose intolerance.[20]

Additionally, metabolic syndrome negatively affects cognitive performance and brain structure, increasing the risk of cognitive decline due to Diabetic Encephalopathy, Alzheimer's type diseases, Parkinson's disease, vascular dementias, and other neurodegenerative pathologies.[21] Reviews on brain images in adults linked MetS as a risk factor for ischemic stroke. Regarding risk factors, insulin resistance reciprocally leads to inflammation, as inflammation leads to insulin resistance since both conditions reduce cerebral vascular reactivity. On the other hand, a study called Protein Over Feeding Effect on Body Weight analysed magnetic resonance images of older adults and found associations between overweight/obesity (measured by BMI) with alterations in the volume of grey and white matter in the brain and cerebellum, morphological damage related to the

risk of developing severe neurocognitive disorders.[22] As a result, every patient diagnosed with MetS is at risk of developing cognitive impairment, worsening the disease, and complicating the treatment. The above is even more affected because in the syndrome, there is an alteration in the composition of the intestinal microbiota, influenced by diet, age, lifestyle, and the presence of inflammatory processes, and there is a close correlation between the intestinal microbiota and the brain. While the exact mechanisms are not entirely understood, intestinal dysbiosis may be a key factor linking certain neurological disorders and metabolic diseases. Both conditions can elevate the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Regarding this, several studies have shown that intestinal microbiota repair interventions can reverse the risk for MetS and its complications. Dietary changes and probiotic supplementation could positively influence the clinical conditions.[23] Probiotics are beneficial microorganisms that regulate the gut microbiota and enhance host immunity.[24] They derive from fermented foods. The primary type is lactic acid. However, traditional probiotics have quality problems, such as contamination and insufficient live bacteria. Among the observed gut microbiota, *Akkermansia muciniphila* is a promising probiotic broadly used in different models of multiple diseases for more than a decade.[25]

It has been identified as a bacterium that colonizes the gut microbiota. It is one of the most abundant bacteria in the human gut microbiota. However, it is not sufficient for people suffering from metabolic syndrome.[26] In contrast, the effects of metformin or bariatric surgery, two treatments aimed respectively at regulating blood sugar and combating obesity, are associated with an increase in the abundance of this bacterium.[27-29]

METABOLIC SYNDROME AND ITS RELATIONSHIP TO THE GUT MICROBIOTA

The pathophysiology of metabolic syndrome (MetS) involves alterations in glycolipid metabolism, proinflammatory and prothrombotic states. Insulin resistance (IR) links all of them, as increased free fatty acids –often associated with being overweight- favor this condition. This state causes cells to disorderly utilize glucose and results in the dysregulation of hepatic glucose production. Lipid metabolism also presents the consequences of IR, which lead to the characteristic alterations of MetS: hypertriglyceridemia and HDL hypocholesterolemia. Hypertension relates to different mechanisms due to alterations in the insulin pathway and the regulation. of the vegetative nervous system. In addition to the impact on the development of atherosclerosis, recently, MetS and IR have been linked to other diseases, such as fatty liver disease.[30] The factors that contribute to the development of metabolic syndrome are the result of complex intrinsic host factors and extrinsic factors.[31] Various bacteria inhabit our gut, but the difference between beneficial and harmful bacteria is unclear. Many factors, such as age, genotype, diet, nutrition, and environmental components regulate our gut microbiota.[32,33] Some of the most frequent factors that damage our microbiome are pharmaceuticals and personal care products, especially antibiotics, and pollutants, including pesticides and insecticides.[34,35] While genetic traits remain constant over time, the gut microbiome enables us to influence how the body processes external signals, potentially reducing the risk of metabolic syndrome.[31]

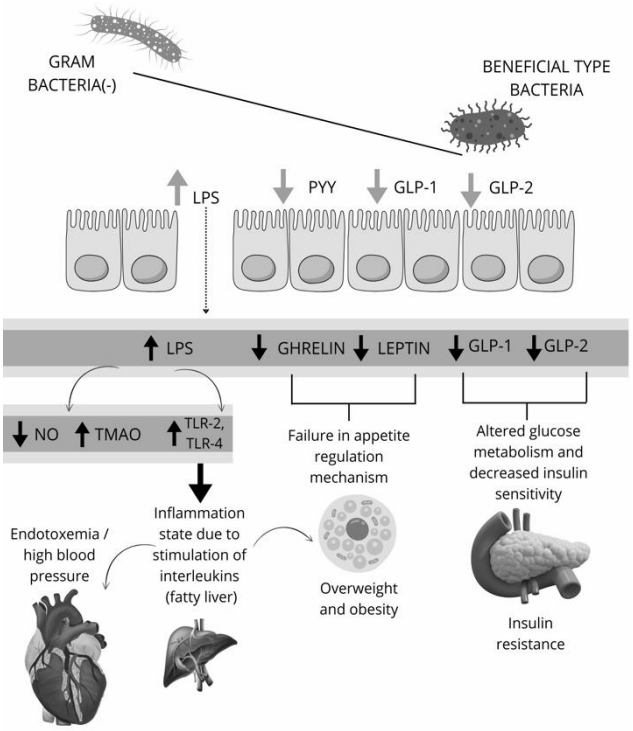

***Figure 1**. Gut microbiota and its link to metabolic alterations that make up MetS. (GLP: glucagon-like peptide; LPS: lipopolysaccharide; NO: nitric oxide; PYY: peptide YY; TLR: Toll-like receptors; TMAO: trimethylamine N-oxide).[36]*

Figure 1 shows the chain reactions generated by intestinal dysbiosis.[36] We can see how the imbalance between gram-negative bacteria and beneficial bacteria leads to a decrease in the production of neuropeptides and incretins. A state of intestinal permeability will allow the passage of LPS, which, once in the bloodstream, will stimulate the increase in TMAO levels, which leads to endotoxemia; similarly, the stimulating effect on TLRs will lead to the development of an inflammatory state that, together with the decrease in neuropeptides, will lead to obesity and IR.[36] Likely, gut microbiota dysbiosis is responsible for several metabolic disorders, including inflammatory diseases, autoimmune diseases, cancers, mental disorders, and diabetes.[37] In the case of obesity and diabetes mellitus, metabolic endotoxemia with breakdown of intestinal barrier integrity has been reported. The sequence of events is characterized by an increase in polysaccharide (LPS) levels from the death of gram-negative bacteria, the CD14/TLR4 receptor of macrophages recognizing them, and subsequent synthesis and release of proinflammatory cytokines TNF-α, IL-

1 and IL-6 into the bloodstream, leading to a state of chronic inflammation, obesity and insulin resistance. It is relevant to recognize the modifiable factors that alter the composition and diversity of the microbiota, as their timely restoration leads to balancing the different metabolic processes involved in the genesis and progression of the disease.[38]

In a study presented, it was possible to observe how these factors influence the complications of metabolic syndrome until death from metabolic syndrome. During the study years, there were 10,734 participants diagnosed with metabolic syndrome. The mean age of the population with metabolic syndrome was 59 years, and women represented a slightly higher proportion than men (5,570 cases versus 5,164 cases). However, men with metabolic syndrome showed a higher mortality risk than women (1,182 cases versus 1,033 cases). Almost half of the population with metabolic syndrome were non-Hispanic whites (4,940 cases), and less than 40% of them had a college degree or higher. More than 30% of the population with metabolic syndrome were overweight (3,573 cases), and almost 57% were obese (6,051 cases). At the time of the interview, more than half of the study population was still drinking (5,982 cases), and almost 20% of them were still smoking (2,015 cases). The prevalence of comorbidities was 12.19% (1,309 cases) for cancer, 20.48% (2,198 cases) for CKD, and 14.48% (1,554 cases) for CVD, respectively. With a median follow-up of 100 months, 2,215 deaths were observed, with 360 for diabetes mortality and 615 for cardiovascular mortality. Non-survivors had the following characteristics: male, non-Hispanic white, single marital status, older age, lower daily energy intake, lower educational level, lower BMI, and history of comorbidities.[39]

AKKERMANSIA MUCINIPHILA: CHARACTERISTICS AND MECHANISMS OF ACTION

The name *Akkermansia* honors the Dutch microbiologist Antoon Akkermans, to acknowledge his contribution to microbial ecology. *Muciniphila* (the species) means "*mucus-loving*", as this bacterium feeds almost exclusively on the mucus that lines the intestine.[40]

For more than ten years, *Akkermansia muciniphila* has been recognized as a bacterium colonizing the gut microbiota. It is relevant because it constitutes 1-4% of the gut microbiota and has metabolism-related activities. It is a commensal Gram-negative bacterium belonging to the phylum *Verrucomicrobia*, whose energy source is the mucin of the intestinal epithelium: it degrades it for nutrition and releases monosaccharides, amino acids and short-chain fatty acids into the environment.[41-42]

Akkermansia muciniphila produces short-chain fatty acids (SCFAs) that may play a significant role in the health and inflammatory status of the host. *Akkermansia muciniphila* produces SCFAs, acetate, butyrate, and propionate; these metabolites can promote the differentiation of naive T cells into regulatory T cells (Tregs) or facilitate their migration to the intestine, where they play a crucial role in maintaining host health and regulating inflammation.[43] Acetate is a substrate for lipid synthesis and cholesterol metabolism, influencing energy balance and adipose tissue regulation.[44] Propionate contributes to hepatic gluconeogenesis and is key in appetite regulation, thereby regulating food intake, enhancing insulin sensitivity, and leading to metabolic homeostasis.[44-46] Butyrate, in turn, serves as a primary energy source for colonocytes, enhancing intestinal barrier integrity, reducing intestinal permeability, and modulating inflammatory responses by inhibiting pro-inflammatory cytokine production.[47] These SCFAs collectively improve insulin sensitivity, lipid metabolism, and energy homeostasis, highlighting their potential synergy with *Akkermansia muciniphila* supplementation.[48]

This bacterium also appears to be associated with increased intestinal mucosal thickness, which improves intestinal barrier function. In addition, other studies have revealed its anti-inflammatory role in the intestinal environment. On the other hand, different studies have demonstrated the beneficial effects of *Akkermansia muciniphila,* such as a protective role against pathogens, antitumor properties, inflammation reduction, improvement of intestinal permeability and enhancement of the immune response. All this could explain why the presence of *Akkermansia muciniphila* is associated with a healthy gut.[41] Most of the *Akkermansia muciniphila* genome contains coding genes involved in metabolic processing, including protease, sialidase, and sugar hydrolase.[49] As a producer of SCFAs such as acetate, butyrate, and propionate, *Akkermansia muciniphila* influences the host's metabolism and homeostasis by altering the activity of several transcription factors.[42,50,51]

BENEFITS OF *AKKERMANSIA MUCINIPHILA* IN METABOLIC DISORDERS

Akkermansia muciniphila has several relevant roles in host metabolic functions, such as effects on energy intake, enhancing insulin function, participating in lipid metabolism, which controls the production of glucagon-like peptide-2 (GLP-2), which regulates the expression of genes involved in fat synthesis, which is involved in the process of triglyceride synthesis and improving intestinal epithelial tight junction function and glucose tolerance.[51-56] On the other hand, obesity, fatty liver disease, and diabetes are common metabolic syndromes, and numerous studies have found a strong association between altered gut microbiota, especially *Akkermansia muciniphila*, and these metabolic syndromes.[57]

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.[58,59] The gut microbiota significantly influences the development and training of essential components in the host's innate and adaptive immune systems. In addition to their role in regulating infection and the spread of commensal organisms, microbiome-immune interactions are involved in multiple diseases.[59] Despite the increasing clarity of the relationship between the gut microbiota and human health problems, specifically regarding the influence on the immune system, there is still a notable

deficiency in the understanding of the precise molecular factors that control and adjust immune balance, as well as the mechanisms by which they operate.[57]

On the other hand, it is essential to note that some active components, such as oligosaccharides, polysaccharides, and polyphenols have been identified for acting as possible prebiotics, helping to improve health. While *Akkermansia muciniphila* is present in the microbiota and helps enrich the intestinal barrier, providing probiotic benefits. In this regard, researchers have found that oligosaccharides, including xylooligosaccharides, chitosan oligosaccharides, and resistant starch, mitigate the deterioration of the intestinal mucosal barrier and alleviate metabolic abnormalities, potentially through the stimulation of *Akkermansia* growth.[60-64] Furthermore, inulin and polysaccharides from flaxseed and pumpkin exerted anti-obesity, anti-diabetes, and anti-hyperlipidemia effects, along with upregulating *Akkermansia muciniphila* levels.[65-67] Polyphenol, another common natural compound found in numerous foods, also exhibits beneficial effects. Polyphenols extracted from apple, cranberry, pomegranate, and green tea have shown efficacy in preventing obesity and other metabolic syndromes, accompanied by an increase in the relative abundance of *Akkermansia*. Incorporating appropriate dietary supplements can be considered a safe and effective strategy to promote *Akkermansia muciniphila.*[68-71]

EFFECTS OF SUPPLEMENTATION WITH *AKKERMANSIA MUCINIPHILA*

A study in mice showed that a low presence of *Akkermansia muciniphila* in the intestinal barrier due to alterations in high-fat diets negatively interferes with the functioning of the gut microbiota, and physiological and homeostatic functions during obesity and T2DM. Furthermore, human studies have shown that with lower amounts of this bacterium, subjects were less likely to have positive responses to hypocaloric diets in the treatment of obesity in terms of improvement of inflammatory markers, insulin resistance and glycemia.[53] However, the bacterium has many benefits in nutritional status as it demonstrated that calorie restrictive diets supplemented with pomegranate extract, resveratrol, polydextrose, EpiCor or sodium butyrate, or a high FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet increase the concentration of *Akkermansia muciniphila*.[72] In addition, consuming foods such as nopal, chia seeds, and soy protein demonstrated their capacity to modify the composition of the gut microbiota, increasing the percentage of this bacterium.[73]

Similarly, in a clinical trial conducted on 32 overweight/obese insulin resistant subjects, supplemented with daily doses of live and pasteurized *Akkermansia muciniphila* for 3 months, it was found that the subjects tolerated the *Akkermansia muciniphila* supplementation well and that it was safe and improved metabolic parameters such as insulin sensitivity, reduction of insulin requirement, and plasma total cholesterol. In addition, body weight decreased, compared to those supplemented with placebo, and waist circumference and fat mass also reduced, compared to the initial values. In this study, the gut microbiota was negatively affected during the supplementation months. On the other hand, *Akkermansia muciniphila* treatment achieved a significant reduction in WBC (white blood cells) counts, which are elevated in obesity and linked with glucose intolerance and the risk of developing T2DM.[74] Another study also showed that *Akkermansia muciniphila* ameliorated metabolic disorders in diet-induced obese mice. Treatment with the bacterium normalized diet-induced metabolic endotoxemia, adiposity, and the adipose tissue marker CD11c.[75] *Akkermansia muciniphila* treatment reduced body weight and improved body composition (i.e., fat mass to lean mass ratio) without changes in food intake. They demonstrated that treatment with *Akkermansia muciniphila* completely reversed diet-induced fasting hyperglycemia through a mechanism associated with a 40% reduction in hepatic glucose-6-phosphatase expression, suggesting a reduction in gluconeogenesis. Notably, the insulin resistance index decreased similarly after treatment with *Akkermansia muciniphila*. These results suggest a key role for *Akkermansia muciniphila* in intestinal barrier function, metabolic inflammation, and fat storage.[53] Also, the ability to incorporate the bacteria into foods already on the market, improving their bioavailability, is promising for significantly increasing the gut microbiota, as was done in the study in which the probiotic *Akkermansia muciniphila* was incorporated into a dairy matrix containing Portuguese whey cheese and Greek-style yogurt in a ratio of 3.5:1, respectively. The probiotic spreadable cheese showed high microbiological quality, low total phenolic content, and interesting biological activities, including antidiabetic (98.10% inhibition of α-glucosidase) and antihypertensive (49.18% inhibition of angiotensin-converting enzyme).[75] Furthermore, prebiotic feeding strongly increases the presence of *Akkermansia muciniphila* and improves metabolic disorders. All trials in which animals and humans took *Akkermansia muciniphila* showed that it reduces body weight and fat mass gain, inflammation, and cholesterol levels; improves insulin sensitivity, and restores intestinal barrier function.[53,74]

Similarly, *Akkermansia muciniphila* produces a specific protein called Amuc_1100, which is involved in immunomodulatory aspects, improves glucose tolerance, and decreases body weight and fat mass gain in mice fed a high-fat diet compared to untreated mice. Therefore, an adequate amount of *Akkermansia muciniphila* in the gut microbiota would stimulate the presence of these proteins that can promote the health of people with obesity and MetS.[76]

On the other hand, scientific interest in *Akkermansia muciniphila* arises from evidence highlighting that its abundance in the gut correlates with host health, while its alterations are associated with several dysfunctions.[25,77,78] However, an excessive enrichment in *Akkermansia muciniphila*, in specific intestinal microenvironments, may

exacerbate local inflammation caused by damage to the epithelial barrier.[79-81] For example, increasing *Akkermansia* in a *Salmonella typhimurium* infection condition or a condition of intestinal diseases might not have expected beneficial effects.[81,82] Furthermore, a cautionary note on its wide use comes from the neurological field, since in some pathological contexts, including Parkinson's disease and multiple sclerosis, the gut microbiota exhibits a characteristic signature of *Akkermansia muciniphila* abundance.[83]

CONCLUSIONS

Akkermansia muciniphila is a promising probiotic for preventing and treating metabolic disorders, especially metabolic syndrome, due to its positive effects on insulin sensitivity, blood pressure, obesity, and fat reduction. Despite extensive research, opportunities remain for randomized controlled trials and exploratory studies to address existing gaps.

Future research should focus on improving its incorporation into functional foods, while evaluating stability, bioavailability, and interactions with bioactive compounds. Additionally, studies should examine its impact on metabolic health, considering factors such as fermentation, storage, and consumer acceptance.

Due to the variability in metabolic syndrome symptoms, *A. muciniphila* supplementation could improve the intestinal barrier and reduce inflammation, especially when combined with low-calorie diets and functional foods. Further studies are needed to explore ways to maintain its intestinal levels and to conduct human trials assessing its efficacy in food applications. Developing functional formulations that integrate *A. muciniphila* as part of nutritional strategies for at-risk populations is crucial. Research should also explore combining this probiotic with specific diets and bioactive compounds to maximize its benefits and establish its role in managing metabolic syndrome.

Finally, the effects of *A. muciniphila* may vary depending on individual medical histories, particularly in case of neurological or metabolic dysfunctions. These variations could impact the potential benefits, highlighting the need for further research to determine which populations may benefit the most while minimizing potential risks.

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