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Review

The Role of *Akkermansia muciniphila* in Human Health: A Clinical Review

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Abstract

Akkermansia muciniphila—a mucus-resident commensal—has emerged as a promising target at the interface of metabolism, barrier function, and immunity. Observational human studies link higher intestinal abundance of *A. muciniphila* with healthier adiposity and glycemic profiles, while preclinical experiments demonstrate causal benefits on adiposity, insulin resistance, gut-barrier integrity, and inflammatory tone. These effects are attributed to mucus-layer reinforcement, reduced intestinal permeability and endotoxemia, production of short-chain fatty acids, and host signaling by defined bacterial components. In a randomized proof-of-concept trial in overweight/obese insulin-resistant adults, pasteurized *A. muciniphila* was safe and well tolerated and improved insulin sensitivity and total cholesterol versus placebo; live cells showed directionally favorable but non-significant trends. A separate multicenter randomized trial of a five-strain consortium that included *A. muciniphila* improved post-prandial glucose and HbA1c in type 2 diabetes, supporting translational potential while underscoring the need for strain-resolved studies. Evidence for liver and cardiovascular benefits is strong in animals (e.g., MASLD and atherosclerosis models) but remains preliminary in humans. Inter-individual response heterogeneity—potentially influenced by baseline *Akkermansia* levels and gut-barrier status—highlights the value of personalized, microbiome-guided approaches. Larger, longer clinical studies are now warranted to define optimal dosing and formulation (live vs. pasteurized), durability, safety across populations, and impacts on hard outcomes (clinically meaningful weight change, glycemic endpoints, and cardiometabolic events). Overall, *A. muciniphila* represents a promising microbial adjunct for metabolic health with a plausible path from postbiotic concepts to clinical application, pending confirmatory trials.

Keywords: *Akkermansia muciniphila*; gut microbiota; obesity; metabolic syndrome, inflammation

1. Introduction

Akkermansia muciniphila is a Gram-negative, non-spore-forming, non-motile, strictly anaerobic bacterium that resides in the mucus layer of the gut [1-3]. First isolated in 2004 by Derrien and colleagues (strain Muc^T), this oval-shaped bacterium belongs to the phylum Verrucomicrobiota (formerly Verrucomicrobia) and has since been recognized as a key member of the healthy human gut microbiota [3]. *A. muciniphila* specializes in degrading mucin, the glycoprotein component of mucus, and in turn produces short-chain fatty acids (SCFAs) like acetate and propionate that nourish other beneficial gut bacteria [3]. Its presence is associated with a thicker intestinal mucus layer and enhanced gut barrier function in animal studies [4]. Over the past decade, accumulating evidence has linked *A. muciniphila* to various aspects of human health, sparking interest in its potential as a "next-generation probiotic" [5].

Notably, numerous human studies have observed an inverse correlation between *A. muciniphila* abundance and metabolic disorders. Individuals with obesity, type 2 diabetes, or metabolic syndrome often have reduced levels of *A. muciniphila* in their gut, whereas lean and healthy individuals show

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higher levels [6-12]. Similar patterns are seen in animal models: mice with diet-induced obesity or diabetic traits tend to have diminished *A. muciniphila* populations [13]. These findings suggest that *A. muciniphila* may play a protective role against metabolic dysfunctions. Indeed, *A. muciniphila* has been proposed as a promising therapeutic microbe for alleviating obesity, diabetes, and related comorbidities [14]. Beyond metabolic health, correlations extend to gut inflammatory conditions; lower levels of *A. muciniphila* have been reported in patients with inflammatory bowel disease (IBD) and other chronic inflammatory states [15]. Such observations imply that boosting *A. muciniphila* might benefit not only metabolism but also gut health and immune balance.

Prompted by these correlations, researchers have investigated whether supplementing the diet with *A. muciniphila* can improve health outcomes. Early experimental studies in rodents provided proof-of-concept: administration of *A. muciniphila* to mice on a high-fat diet curbed weight gain, improved metabolic parameters, and reduced inflammation [13]. These findings were pivotal in demonstrating a causal link between *A. muciniphila* and host health, fueling the idea that this bacterium could be harnessed as a probiotic. Importantly, *A. muciniphila*'s mode of action appears to involve strengthening the gut's defensive barrier and modulating host metabolic and immune pathways [16]. Until recently, *A. muciniphila* had never been given as a supplement to humans, but pioneering clinical trials have now begun to test its safety and efficacy [17]. Early human data show promise in metabolic health improvement, aligning with the animal studies.

In light of these developments, *A. muciniphila* has moved from being merely a gut microbe of interest to an active ingredient in new probiotic (or "postbiotic") formulations. This review provides a clinical overview of the role of *A. muciniphila* supplementation on health. We examine its impacts on obesity, diabetes, gut health, and inflammation, among other conditions. We discuss the mechanisms by which *A. muciniphila* exerts its effects, the results of preclinical and clinical studies, and the emergence of commercially available *A. muciniphila* supplements. By surveying the current literature, we aim to clarify how supplementing with *Akkermansia muciniphila* might be leveraged to improve human health and what considerations accompany its use.

2. Methods

A literature search was conducted using PubMed to identify relevant publications on *Akkermansia muciniphila* supplementation through September 2025. Search terms included "Akkermansia muciniphila", "supplementation", "probiotic", "obesity", "diabetes", "inflammation", "gut barrier", and related keywords. Priority was given to peer-reviewed studies and meta-analyses focusing on human clinical trials. Animal and in vitro studies were included when they elucidated mechanisms or provided important proof-of-concept data. Key reference lists were also scanned to capture additional relevant studies. We included pivotal early studies (e.g., in animal models) that established mechanisms of action, as well as all available human trials of *A. muciniphila* or *A. muciniphila*-containing formulations. Only studies indexed in PubMed and published in English were considered. In total, dozens of articles were reviewed, and those most pertinent to *A. muciniphila*'s effects on obesity, type 2 diabetes, gut health (including gut inflammation), and related conditions were synthesized for this manuscript.

3. Results

3.1. Impact on Obesity and Metabolic Syndrome

One of the most extensively studied areas for *A. muciniphila* supplementation is obesity and the cluster of conditions known as metabolic syndrome. In animal models, the introduction of *A. muciniphila* has consistently yielded anti-obesity effects. Research by Everard and colleagues reported that adding *A. muciniphila* to the diet of mice fed a high-fat, obesogenic diet led to a significant reduction in body fat accumulation and metabolic disturbances [13]. In these mice, *A. muciniphila* treatment attenuated weight gain without altering food intake, suggesting improved metabolic efficiency rather than caloric intake reduction. Notably, markers of metabolic health improved:

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treated mice showed reduced adipose tissue inflammation and enhanced insulin sensitivity compared to untreated obese mice. The presence of *A. muciniphila* was also associated with higher levels of endocannabinoids, molecules that help regulate glucose and energy homeostasis, and a strengthening of the intestinal barrier. These changes collectively contributed to better metabolic outcomes. Early studies indicated that live, active bacteria were required for these benefits, as heat-killed bacteria initially showed no effect in the 2013 mouse experiments. This finding pointed to the importance of *A. muciniphila*'s metabolic activity or structural integrity in conferring benefits (a point later revisited in human studies with pasteurized bacteria).

Further rodent studies reinforced the anti-obesity impact of *A. muciniphila* [18]. In diet-induced obese mice, daily oral gavage of *A. muciniphila* for several weeks significantly alleviated weight gain and reduced fat mass accumulation. Treated mice had improvements in metabolic syndrome indicators, including lower fasting blood glucose and insulin levels, improved insulin sensitivity, and better lipid profiles. For example, one study found *A. muciniphila* administration led to a reduction in plasma cholesterol and triglycerides, accompanied by decreased adipose tissue inflammation [19]. Mechanistically, the anti-obesity effect in mice has been linked to *A. muciniphila*'s ability to enhance the gut barrier and reduce systemic inflammation. Treated obese mice exhibit increased expression of intestinal tight junction proteins and a thicker mucus layer, which together reduce gut permeability and endotoxin leakage [20,21]. By preventing the passage of pro-inflammatory bacterial components like lipopolysaccharide (LPS) into circulation, *A. muciniphila* lowers the chronic low-grade inflammation that characterizes obesity. Indeed, mice receiving *A. muciniphila* show reduced levels of inflammatory cytokines in fat tissue and increased markers of anti-inflammatory regulatory T cells, reflecting an attenuation of obesity-related inflammation [22].

Crucially, benefits of *A. muciniphila* supplementation on obesity are not limited to rodents. Plovier and colleagues published the first-in-human, proof-of-concept study (NCT02637115) of *A. muciniphila* MucT in 2017 [23]. In a preliminary analysis, they randomized 20 adults (5 per group) to placebo, live *A. muciniphila* (10^9 or 10^{10} cells/day), or pasteurized *A. muciniphila* (10^{10} cells/day) for two weeks and observed no safety signal: standard safety parameters (inflammation, hematology, kidney, liver, muscle) were unchanged and adverse-event frequency was similar across groups (a few cases of borborygmi with live bacteria, not significantly different from other arms). The full results of this pilot were published by Depommier and colleagues in 2019 and included overweight and obese, insulin-resistant adults [17]. In this randomized, double-blind, single-center, placebo-controlled trial (40 randomized; 32 completed), participants received either live *A. muciniphila* (10^{10} bacteria per day), pasteurized *A. muciniphila* (10^{10} bacteria per day), or a placebo daily for three months. The primary outcomes were safety, tolerability, and metabolic parameters. Supplementation (live or pasteurized) was safe and well tolerated, with adverse-event rates comparable to placebo.

In terms of efficacy, while live *A. muciniphila* trended toward improvements (insulin sensitivity +42.4% vs placebo; insulinemia −12.0%; plasma total cholesterol −6.7%; body weight −0.81 kg; fat mass −0.79 kg; hip circumference −1.05 cm; changes generally not statistically significant), it was the pasteurized *A. muciniphila* that achieved significant benefits. The pasteurized bacteria supplementation resulted in increased insulin sensitivity (+28.6%; P=0.002), decreased insulinemia (−34.1%; P=0.006), and lower plasma total cholesterol (−8.7%; P=0.02) versus placebo. Reductions in body weight (−2.27 kg over 3 months; P=0.09), fat mass (−1.37 kg; P=0.09), and hip circumference (−2.63 cm; P=0.09) showed clear trends without reaching statistical significance. While these anthropometric changes were moderate, they occurred without any other lifestyle intervention, underscoring the potential of *A. muciniphila* to aid weight management. Overall, both animal and human findings support that *A. muciniphila* supplementation can beneficially influence weight and adiposity, particularly in the context of a high-fat diet or metabolic syndrome. The consistent observation is that *A. muciniphila* helps create a metabolic environment less prone to fat storage and inflammation, thereby counteracting obesity's drivers.

In addition, more recent human trials extend these findings. First, a multicenter RCT in adults with overweight/obese type 2 diabetes reported that supplementation with *A. muciniphila* (strain

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AKK-WST01) improved clinical endpoints—but predominantly in those with low baseline intestinal *A. muciniphila*, who showed higher colonization alongside significant reductions in body weight, fat mass, and HbA1c; participants with high baseline *Akkermansia* exhibited poor colonization and no significant benefit (NCT04797442) [24]. These data suggest efficacy may depend on baseline gut levels, pointing to a microbiota-guided personalization strategy. Second, an 8-week randomized, double-blind trial testing postbiotic (heat-inactivated) *A. muciniphila* delivered in yogurt in adults with overweight/obesity (n=66) found significant between-group reductions in waist circumference, waist-to-height ratio, body fat percentage, and AST in the *Akkermansia*-yogurt arm versus control, while a comparator yogurt fortified with *Lactobacillus rhamnosus* postbiotic showed no between-group benefits [25].

In addition to weight changes, other components of metabolic syndrome are positively affected by *A. muciniphila*. Supplemented mice have exhibited reduced hepatic steatosis (fatty liver) and improved liver metabolic function [26]. In a mouse model of obesity-related metabolic dysfunction-associated steatotic liver disease (MASLD), treatment with *A. muciniphila* significantly lowered liver fat accumulation and prevented progression of liver injury [27]. Mice given *A. muciniphila* had reduced liver inflammation markers compared to controls, indicating protection against MASLD severity. Supporting these findings, *A. muciniphila*-treated mice in the MASLD study showed activation of beneficial metabolic regulators in the liver (such as the farnesoid X receptor, FXR) and upregulation of intestinal tight junction proteins. These molecular changes corresponded with better insulin sensitivity and less weight gain in the treated group. Such results highlight that *A. muciniphila*'s anti-obesity effects extend to improvements in liver health, which is a critical aspect of metabolic syndrome. By reducing hepatic fat deposition and metabolic inflammation, *A. muciniphila* may help break the link between obesity and downstream complications like MASLD.

Overall, the results across multiple studies indicate that supplementing with *Akkermansia muciniphila* produces beneficial outcomes in obesity and metabolic syndrome. In obese hosts, it promotes a leaner phenotype, improves metabolic markers (glucose, lipids), and mitigates tissue inflammation. These effects have been demonstrated robustly in animal models and are now being observed to some extent in humans [17]. The ability of *A. muciniphila* to fortify the gut barrier and reduce systemic inflammatory tone appears central to its impact on obesity. Notably, its efficacy in reducing weight gain and metabolic dysfunction positions *A. muciniphila* as a unique probiotic candidate targeting obesity–a condition traditionally managed with diet, exercise, and medication. The promising human data (albeit from a small trial), together with baseline-dependent efficacy in type 2 diabetes and positive signals from a postbiotic yogurt delivery, further suggest that *A. muciniphila* supplementation could become a novel tool in weight management and metabolic health, pending confirmation from larger studies. A side-by-side summary of human clinical studies of *A. muciniphila* (and consortia including *A. muciniphila*) is provided in **Table 1**.

Table 1. Human clinical studies of *Akkermansia muciniphila* (or consortia including *A. muciniphila*).

Study (year)	Design & population	Intervention (dose; formulation)	Control	Duration	Primary/Key outcomes	Safety/tolerability
Depommier et al., 2019	RCT, double-blind, single-center; overweight/obese insulin-resistant adults; 40 randomized (32 completed)	Live *A. muciniphila* 10^{10}/day **or** pasteurized *A. muciniphila* 10^{10}/day (oral)	Placebo	3 mo	Pasteurized arm: ↑ insulin sensitivity (+28.6%), ↓ insulinemia (−34.1%), ↓ total cholesterol (−8.7%);	Well tolerated; AE rates similar to placebo

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					weight/fat mass trends only	
Zhang et al., 2025 (AKK-WST01)	Phase 2 RCT, double-blind, placebo-controlled; drug-naïve adults with overweight/obese T2DM; n=58	Live *A. muciniphila* (AKK-WST01), daily (oral)	Placebo	12 wk	Overall: weight & HbA1c fell similarly in both arms; **pre-specified subgroup** with low baseline *Akkermansia*: successful colonization + significant ↓ body weight, ↓ fat mass (incl. visceral), ↓ HbA1c	Well tolerated
Perraudeau et al., 2020 (WBF-011)	Multicenter RCT, double-blind, placebo-controlled; adults with T2D on standard care; ITT n=76	Five-strain consortium including *A. muciniphila* + *Anaerobutyricum hallii* (capsules, bid)	Placebo (and WBF-010 3-strain backbone arm)	12 wk	vs placebo: ↓ post-prandial glucose AUC; ΔHbA1c −0.6% (p=0.054); within-group −32.5% total post-prandial glucose	Well tolerated; no major safety signals
Aalipanah et al., 2025	RCT, double-blind; adults with overweight/obesity; n=66	Yogurt with heat-inactivated *A. muciniphila* ("postbiotic")	Control yogurt; comparator yogurt with *L. rhamnosus* postbiotic	8 wk	↓ waist circumference, ↓ waist-to-height ratio, ↓ body fat %, ↓ AST vs control; comparator *L. rhamnosus*	Well tolerated

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					yogurt: no between-group benefits	

3.2. Impact on Type 2 Diabetes and Glycemic Control

Type 2 diabetes mellitus (T2DM) is another major condition where *A. muciniphila* shows significant promise. Given the close relationship between obesity and T2DM, many of the metabolic improvements described with *A. muciniphila* supplementation translate into better glycemic control and insulin function. In high-fat diet mouse models that develop insulin resistance, *A. muciniphila* administration improved glucose homeostasis. Treated mice consistently show lower fasting blood glucose levels and enhanced glucose tolerance tests compared to untreated diabetic mice [13,28]. Insulin resistance, a hallmark of T2DM, is alleviated: *A. muciniphila*-fed mice have higher insulin sensitivity and require less insulin to manage blood sugar [23]. One mechanism for this is a reduction in metabolic endotoxemia–the leakage of LPS from the gut–which otherwise drives inflammation and insulin resistance. By sealing a leaky gut, *A. muciniphila* prevents LPS-induced inflammation that interferes with insulin signaling [29]. Animal studies also report that *A. muciniphila* increases the expression of genes involved in energy expenditure and fat oxidation (such as Ucp1 in brown adipose tissue and lipid metabolism genes in the liver), changes that can improve overall insulin sensitivity [30-32]. Additionally, *A. muciniphila*'s production of SCFAs like propionate may stimulate gut hormones that benefit glucose regulation. Propionate released by *A. muciniphila* has been shown to trigger the secretion of glucagon-like peptide 1 (GLP-1), an incretin hormone that boosts insulin secretion and lowers blood glucose [5]. Experiments indicate that *A. muciniphila* can augment GLP-1 levels via multiple pathways–not only through SCFAs, but also through a specific protein it produces (called *P9*) that interacts with host receptors to induce GLP-1 from intestinal L-cells [32]. This dual action on GLP-1 and possibly other gut peptides contributes to better glycemic control in *A. muciniphila*-treated animals.

The positive impact on diabetic parameters has been borne out in emerging human studies as well. The proof-of-concept trial in 40 overweight/obese individuals mentioned earlier also measured diabetes-related outcomes, since many participants were insulin-resistant [17]. After 3 months of *A. muciniphila* supplementation, those receiving pasteurized *A. muciniphila* showed a marked improvement in insulin sensitivity (+28.62% ± 7.02; P=0.002) and a significant reduction in fasting plasma insulin (−34.08% ± 7.12; P=0.006) relative to placebo; total cholesterol also fell (−8.68% ± 2.38; P=0.02). Live *A. muciniphila* showed directionally favorable but non-significant changes: insulin sensitivity +42.42% ± 20.44 (ns), insulinemia −12.02% ± 4.12 (ns), and total cholesterol −6.70% ± 2.47 (P=0.088). Fasting glucose did not change dramatically (likely because participants were not frank diabetics), but the lowered insulinemia with pasteurized product points to reduced insulin resistance. These changes imply that the body was able to use insulin more effectively after supplementation (rather than "colonization," since the pasteurized product is non-viable). The study also reported modest, trend-level effects on anthropometrics: with pasteurized bacteria, body weight −2.27 ± 0.92 kg (P=0.091), fat mass −1.37 ± 0.82 kg (P=0.092), hip circumference −2.63 ± 1.14 cm (P=0.091); with live bacteria, body weight −0.81 ± 0.64 kg, fat mass −0.79 ± 0.47 kg, hip circumference −1.05 ± 0.88 cm (all ns). Participants were instructed to maintain their usual diet and activity, so these metabolic improvements occurred without prescribed lifestyle changes. Overall, the data support a direct metabolic benefit of pasteurized *A. muciniphila* in this population, with smaller, non-significant shifts in the live arm.

A more recent randomized, double-blind, placebo-controlled phase 2 trial (NCT04797442) in drug-naïve adults with overweight/obese T2DM (n=58) tested live *A. muciniphila* (AKK-WST01) once daily for 12 weeks [24]. Overall, weight and HbA1c fell similarly in both arms; however, pre-specified subgroup analyses revealed a clear baseline-dependence: participants with low baseline fecal *A. muciniphila* exhibited successful strain colonization and significant within-group reductions in body

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weight, fat mass (including visceral fat), and HbA1c, whereas those with high baseline levels showed little colonization and no clinical benefit. The product was well tolerated. Parallel fecal-transplant experiments in germ-free mice recapitulated the "low-baseline-benefits" pattern, strengthening the biological plausibility of a precision, microbiome-guided use case.

Beyond pure *A. muciniphila* supplementation, a multicenter, double-blind, placebo-controlled trial (NCT03893422) tested a five-strain consortium (WBF-011) in individuals with T2DM on standard treatment (diet, exercise, and metformin) [33]. The trial had three arms—placebo, WBF-010 (a 3-strain butyrate-focused backbone: *Bifidobacterium infantis* [*Bifidobacterium longum* biotype *infantis*], *Clostridium butyricum*, *Clostridium beijerinckii* plus inulin), and WBF-011 (the WBF-010 backbone plus *Akkermansia muciniphila* and *Anaerobutyricum hallii* [formerly *Eubacterium hallii*])—and randomized adults with T2D to capsules twice daily for 12 weeks (n=76 ITT: placebo 26; WBF-010 27; WBF-011 23; per-protocol n=58: 16/21/21). WBF-011 significantly improved postprandial glucose control versus placebo and produced an HbA1c difference of −0.6% vs placebo (p=0.054); within-group, median total postprandial glucose fell 32.5% with WBF-011 (placebo +3.2%). The product was well-tolerated with no major safety signals. Because only the arm that added *A. muciniphila* and *A. hallii* to the base consortium improved glycemic endpoints, the authors infer one or both may be necessary, though the design cannot isolate each strain's contribution. The fact that metformin (a first-line diabetes drug) is known to increase *A. muciniphila* levels in the gut lends further plausibility to the idea that *A. muciniphila* contributes to improved glycemic control. In essence, the probiotic cocktail's success highlights *A. muciniphila*'s role: by reintroducing this bacterium (and its SCFA-producing partners) into the gut ecosystem, patients achieved better glucose control than with standard care alone.

Preclinical research has also uncovered other diabetes-related benefits of *A. muciniphila*. For instance, *A. muciniphila* treatment in mice has been linked to preservation of pancreatic islet cell function [10]. Some studies indicate that maintaining *A. muciniphila* levels prevents the deterioration of insulin secretion capacity that occurs in diabetes [34]. Moreover, *A. muciniphila* can influence the metabolism of bile acids and other molecules that affect insulin sensitivity [10]. In murine models, *A. muciniphila* administration activated the insulin signaling pathway in the liver (PI3K-Akt pathway), which is often impaired in insulin-resistant states [35]. By restoring this pathway's activity, *A. muciniphila* helps the liver respond to insulin and regulate glucose production better. *A. muciniphila* has also been observed to increase levels of endocannabinoids in the gut, compounds that can improve gut barrier function and glucose homeostasis [13]. All these multifaceted actions contribute to an overall antidiabetic effect.

In summary, both animal and human studies strongly support the idea that *A. muciniphila* supplementation can benefit glycemic control and type 2 diabetes management. It appears to work by improving insulin sensitivity, enhancing gut-derived hormones (e.g., GLP-1), reducing inflammation, and potentially preserving insulin-secreting cell function. Human evidence now includes: (i) a placebo-controlled trial in insulin-resistant volunteers showing metabolic improvements—most notably with pasteurized *A. muciniphila*—and good tolerability; and (ii) a phase 2 RCT in drug-naïve T2DM demonstrating that efficacy of live *A. muciniphila* depends on low baseline *Akkermansia* abundance (with successful colonization and improvements in weight/adiposity and HbA1c confined to that subgroup). Finally, a multicenter trial of a five-strain consortia that added *A. muciniphila* to a butyrate-focused backbone improved post-meal glucose and trended to lower HbA1c versus placebo. Collectively, these data suggest *A. muciniphila* is an emerging adjunct for metabolic disease—especially when guided by baseline microbiome profiling—while larger, longer trials will be needed to define indications, formulation (live vs. pasteurized), and patient selection.

3.3. Impact on Gut Health and Intestinal Function

Given that *A. muciniphila* naturally dwells in the gut's mucus layer, its supplementation may have pronounced effects on gut health and integrity. One of the hallmark benefits observed is an improvement in intestinal barrier function. The intestinal barrier is formed by epithelial cells lining the gut, sealed by tight junction proteins, and covered by mucus; it regulates the passage of

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substances from the gut into circulation. In conditions like obesity, diabetes, or under stress, this barrier often becomes "leaky" (known as increased intestinal permeability), allowing endotoxins and antigens to cross and trigger inflammation [36]. *A. muciniphila* has demonstrated a remarkable ability to fortify this barrier. In vitro studies showed that *A. muciniphila* can adhere to intestinal epithelial cells and enhance the integrity of the cell monolayer [16]. This suggests that *A. muciniphila* may directly interact with the gut lining to stimulate mucus production and tighten junctions between cells. Indeed, rodent studies confirm that *A. muciniphila* supplementation increases the number of goblet cells (the mucus-producing cells in the gut lining) and the thickness of the mucus layer [4,37]. In obese mice, treatment with *A. muciniphila* elevated the expression of tight junction proteins like occludin and Zonula occludens-1 in the colon [20,21]. These changes translate to a less permeable intestinal wall–often evidenced by lower levels of circulating LPS in *A. muciniphila*-treated animals, indicating reduced leakage of endotoxins from the gut. By essentially "patching up" a leaky gut, *A. muciniphila* creates a healthier intestinal environment and prevents harmful inflammatory triggers from reaching the bloodstream.

A. muciniphila's impact on gut health also extends to conditions of gut inflammation and disease. Chronic disorders such as inflammatory bowel disease are characterized by disrupted gut barriers and dysregulated immune responses in the intestine. Experimental models of colitis have provided insight into *A. muciniphila*'s potential benefits and caveats in such contexts. In one study using dextran sulfate sodium (DSS) to induce colitis in mice (a model for ulcerative colitis), administration of *A. muciniphila* or its purified components significantly attenuated the severity of colitis [38]. Mice receiving *A. muciniphila* had reduced weight loss, less intestinal bleeding, and improved histological appearance of the colon compared to controls. The beneficial effect was associated with a decrease in pro-inflammatory immune cells infiltrating the colon: treated mice showed fewer macrophages and cytotoxic T cells in colitic lesions, as well as lower levels of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1β [39,40]. Additionally, an *A. muciniphila*-derived outer membrane protein (Amuc_1100) was able to mimic these benefits, suggesting that specific molecules from *A. muciniphila* can directly interact with the host to quell inflammation [39]. Another protein secreted by *A. muciniphila*, identified as Amuc_2109 (an enzyme with N-acetylhexosaminidase activity), also protected mice from DSS-induced colitis by upregulating tight junction proteins and downregulating the gut's inflammatory sensor NLRP3 inflammasome [41]. These findings indicate that *A. muciniphila* strengthens gut defenses and moderates immune responses during acute intestinal inflammation, at least in some experimental settings.

However, the role of *A. muciniphila* in gut inflammatory conditions is complex. While the DSS model suggests benefits, another preclinical model of colitis has raised caution. In IL-10 knockout mice, which spontaneously develop IBD-like colitis due to immune dysregulation, supplementation with *A. muciniphila* was found to exacerbate colonic inflammation in some cases [42]. The absence of the anti-inflammatory cytokine IL-10 creates a highly susceptible environment where the mucus layer is compromised. In such a context, the mucin-degrading activity of *A. muciniphila* might further erode the already-thin mucus, potentially worsening barrier damage. The study noted that *A. muciniphila* administration led to earlier onset of colitis in IL-10 deficient mice, suggesting that when the gut barrier is severely impaired, adding *A. muciniphila* could be detrimental. This highlights an important nuance: *A. muciniphila* thrives in the mucus layer and usually induces the host to produce more mucus, but if the mucus layer is pathologically thin, its presence might not be beneficial until stability is restored. Conditions like active IBD, severe gut infections, or immediate post-antibiotic gut may not benefit from *A. muciniphila* in the short term. For example, increasing *A. muciniphila* during an acute *Salmonella* infection in mice did not aid recovery and in fact correlated with worse inflammation [43]. These results underline that context matters; *A. muciniphila* is highly beneficial for gut health when it can reinforce a moderately disturbed barrier, but in cases of extreme barrier failure, it might need to be used cautiously. Context-dependent effects of *A. muciniphila* across preclinical gut models (beneficial and potentially adverse) are synthesized in **Table 2**.

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Table 2. Disease models and context-dependent effects (preclinical).

Domain / model	Preparation	Direction of effect	Endpoints	Notes / caveats
Diet-induced obesity (mice)	Live/pasteurized cells; EVs	Beneficial	↓ weight gain/fat mass; ↑ insulin sensitivity; ↓ adipose inflammation	Early work suggested live>HK; later pasteurized also effective via surface proteins
MASLD / steatosis (mice)	Live cells (± antibiotics pretreat)	Beneficial	↓ liver fat; ↓ TNF-α/IL-6; tissue-specific FXR changes	Anti-fibrotic signals model-dependent; not uniform across MASH models
Atherosclerosis (Apoe−/− mice)	Live cells	Beneficial	↓ lesion area/size; ↓ aortic MCP-1/ICAM-1/TNF-α; ↓ LPS	Protection mediated via reduced endotoxemia; HK ineffective in this model
DSS colitis (mice)	Cells / Amuc_1100 / Amuc_2109	Beneficial	↓ clinical/histologic colitis; ↓ TNF-α/IL-1β; ↑ junction proteins	Multiple components reproduce benefit
IL-10−/− colitis (mice)	Cells	Potentially harmful	↑ colitis severity/onset	Severe barrier compromise context; timing matters
Acute *Salmonella* infection (gnotobiotic mice)	Cells	Potentially harmful	↑ inflammation	Infection model caveat

In terms of general gut homeostasis, *A. muciniphila* tends to have a normalizing effect on the microbiome and gut environment. Its ability to degrade mucin and produce SCFAs can help support a diverse microbial community. Studies have shown that *A. muciniphila* can stimulate the growth of other beneficial bacteria by releasing nutrients from mucin metabolism [44]. For instance, the acetate and propionate produced by *A. muciniphila* serve as fuel for butyrate-producing bacteria, which are crucial for colon health [45]. In supplementation experiments, *A. muciniphila* has been observed to increase levels of commensal microbes and overall microbial diversity, especially when the gut ecosystem is out of balance [38,40,46,47]. In the human trial, daily *A. muciniphila* (pasteurized or live) did not drastically alter the overall gut microbiome composition, which is a positive sign that it does not disrupt the native community [17]. Instead, it can coexist and perhaps nudge the ecosystem toward a healthier state by occupying its niche in the mucus layer and contributing beneficial metabolites. Participants in the trial did not experience dysbiosis or opportunistic infections; rather, gut health markers like decreased plasma LPS indicated an improvement.

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Beyond pathology, even for general gut wellness, *A. muciniphila* might confer advantages. Some preliminary evidence in humans links higher *A. muciniphila* levels to better gut function and bowel regularity. Although formal supplementation studies for conditions like irritable bowel syndrome (IBS) are lacking, one can speculate that *A. muciniphila*'s barrier-enhancing, anti-inflammatory actions could alleviate certain GI symptoms related to mild gut permeability or immune activation. In summary, *A. muciniphila* supplementation usually promotes a healthier gut environment: it thickens the protective mucus, tightens cell junctions, reduces pro-inflammatory signaling, and harmonizes interactions between the microbiota and the immune system. These effects protect the gut from insults and may speed recovery from metabolic or dietary stresses. Nonetheless, in extreme cases of gut barrier damage or active colitis, its mucin-degrading nature necessitates careful consideration (a point further discussed later). Overall, the net impact on gut health is positive, positioning *A. muciniphila* as a guardian of the gut lining and a modulator of gut microbiome homeostasis.

3.4. Impact on Inflammation and Immune Modulation

Chronic inflammation is a common thread linking obesity, diabetes, and gut disorders, and *A. muciniphila* supplementation has been shown to exert notable anti-inflammatory effects in these contexts. In obese individuals and animals, excess adipose tissue and a leaky gut lead to systemic low-grade inflammation (elevated cytokines like TNF-α, IL-6, etc.), which exacerbates insulin resistance and cardiovascular risk [48]. By sealing the gut barrier, *A. muciniphila* reduces the influx of inflammatory LPS from the gut, thereby lowering the trigger for systemic inflammation [13,20]. For example, *A. muciniphila*-treated mice on a high-fat diet had significantly lower plasma LPS levels and reduced expression of inflammatory genes in adipose tissue than untreated mice [13]. These mice also showed a reduction in macrophage infiltration into fat depots, indicating that *A. muciniphila* curtailed the inflammatory response to obesity. Adipose tissue of treated mice had higher levels of Foxp3+ regulatory T cells (Tregs), which are immune cells that temper inflammation [28]. The increase in Tregs suggests that *A. muciniphila* actively promotes an anti-inflammatory immune environment. One study found that *A. muciniphila* induced Tregs in obese mice, correlating with improved glucose tolerance and less adipose inflammation . This immunomodulatory effect extends beyond the gut, as Tregs can circulate and act on multiple tissues to reduce inflammatory signaling.

In systemic metabolic inflammation, *A. muciniphila*'s impact is also evidenced by changes in liver and blood inflammatory markers. In the mouse model of atherosclerosis (Apoe^-/- mice on a Western diet), *A. muciniphila* supplementation prevented the diet-induced rise in pro-inflammatory cytokines both in circulation and within atherosclerotic plaques [20]. Treated mice had less macrophage accumulation in their arterial lesions and lower expression of chemokines that recruit immune cells. These anti-inflammatory outcomes were linked with the observed reduction in metabolic endotoxemia and better gut barrier integrity. As the authors concluded, *A. muciniphila* attenuated atherosclerotic lesions by ameliorating inflammation triggered by metabolic endotoxemia, essentially through gut barrier restoration. This is a powerful demonstration that a probiotic can modulate systemic inflammation enough to impact disease processes in distant organs like blood vessels. Similarly, in the MASLD study in mice, those given *A. muciniphila* had reduced levels of inflammatory cytokines in the liver and decreased proportion of pro-inflammatory Th17 cells, alongside an increase in anti-inflammatory Tregs [27]. By shifting the balance from pro-inflammatory Th17 cells to Tregs, *A. muciniphila* created an environment favoring resolution of inflammation in the liver. These immunological shifts are crucial, as chronic liver inflammation drives the progression from fatty liver to steatohepatitis and fibrosis. Thus, *A. muciniphila*'s anti-inflammatory effect can halt or slow disease progression.

At the mechanistic level, *A. muciniphila* appears to interact with the host immune system both locally in the gut and systemically. It has molecular components that engage with pattern recognition receptors on immune cells. One well-studied example is the outer membrane protein Amuc_1100, which is recognized by Toll-like receptor 2 (TLR2) on immune cells [23]. Instead of provoking a strong inflammatory response (as many bacterial proteins might), Amuc_1100 signaling through TLR2 has

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been shown to have immunomodulatory effects that strengthen the mucus barrier and induce anti-inflammatory cytokines like IL-10 [49]. This helps explain why even pasteurized (non-living) *A. muciniphila* can reduce inflammation: components (postbiotics) like Amuc_1100 on the bacterial surface remain intact after pasteurization and can still interact with host receptors to drive beneficial immune outcomes. Additionally, *A. muciniphila* secretes small proteins such as *P9* that can cross-talk with immune cells. As noted earlier, *P9* was found to bind to ICAM-2 on intestinal L-cells, stimulating GLP-1 release [32]. Intriguingly, ICAM-2 is also expressed on some immune cells, and its engagement can influence immune cell trafficking and activation [50]. While research is ongoing, it's possible that *A. muciniphila* releases factors that encourage an immune tolerance profile–for example, pushing dendritic cells to favor Treg induction over inflammatory T-cell responses. The observation that *A. muciniphila* increases IL-10 (an anti-inflammatory cytokine) and Tregs in multiple studies is a consistent theme [28]. See **Table 2** for a model-by-model overview of inflammatory contexts in which *A. muciniphila* has been tested.

Beyond chronic metabolic inflammation, *A. muciniphila*'s role in immune modulation has implications for other inflammatory or autoimmune conditions. There is emerging interest in how the presence or absence of *A. muciniphila* might affect disorders like allergies, autoimmune diseases, or even neurological conditions that have an immune component. For instance, some studies have noted that patients with multiple sclerosis or Parkinson's disease have an unusually high abundance of *A. muciniphila* in their gut [51]. The significance of this is not fully understood—it could be a compensatory response or a contributor to disease. In animal models of multiple sclerosis (experimental autoimmune encephalomyelitis), manipulating the gut microbiota can alter disease severity, and researchers are investigating if *A. muciniphila* plays a part in either exacerbating or alleviating such neuroinflammation [52-55]. It should be cautioned that in conditions like Parkinson's, where *A. muciniphila* is already elevated, adding more might not be advisable until we know more [14]. Conversely, in conditions like atopic dermatitis or asthma (which are linked to gut microbiota composition and immune regulation), boosting *A. muciniphila* might prove beneficial by promoting regulatory immune responses, though direct evidence is still forthcoming.

In summary, the results show that *A. muciniphila* supplementation generally leads to a reduction in inflammatory markers and a rebalancing of immune responses towards an anti-inflammatory state in metabolic and gut-related diseases. By reducing gut-derived inflammatory triggers and actively engaging immune regulatory pathways, *A. muciniphila* helps to quell the smoldering inflammation that underpins many chronic conditions. This anti-inflammatory prowess not only improves metabolic indices but could have broader therapeutic implications. However, it's also clear that *A. muciniphila* is not a one-size-fits-all immunotherapy; its effects can vary depending on the existing immune environment. Most studies paint *A. muciniphila* as inflammation-attenuating, but a few indicate it could exacerbate inflammation if the gut barrier is severely damaged or in certain dysregulated immune states. These nuances highlight the need for careful application in clinical settings, which we will explore further in the discussion. Nonetheless, the balance of evidence positions *A. muciniphila* as a valuable ally in reducing chronic inflammation and promoting immune homeostasis.

3.5. Impact on Liver and Cardiovascular Health

Although improvements in liver and cardiovascular health have been touched upon in the sections above, they warrant a focused look because of their importance and the distinct evidence available. Metabolic disorders often harm the liver (leading to MASLD) and the cardiovascular system (promoting atherosclerosis and heart disease).[56] Encouragingly, *A. muciniphila* supplementation has shown protective effects in these domains, largely by virtue of its metabolic and anti-inflammatory actions.

In the liver, *A. muciniphila*'s benefits are evident in MASLD. MASLD is strongly associated with obesity and insulin resistance; by improving those conditions, *A. muciniphila* indirectly aids the liver. But studies also indicate direct effects on liver pathways. In a high-fat diet (HFD) mouse model with

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antibiotic pretreatment, *A. muciniphila* reduced liver weight/liver index and attenuated hepatic steatosis versus HFD controls, despite identical diets [27]. Liver sections showed fewer/smaller lipid droplets and lower hepatic TG/TC. Systemically, treatment lowered TNF-α, IL-6, IL-17A and raised IL-10, with a shift toward Tregs over Th17. Mechanistically, *A. muciniphila* increased hepatic FXR while suppressing intestinal FXR and upregulated colonic tight-junction proteins (ZO-1, occludin), consistent with gut-liver axis modulation and barrier reinforcement. Notably, intestinal FGF15 decreased (non-significantly), and the study did not assess MASH/fibrosis endpoints, so anti-fibrotic claims from this experiment are premature. Overall, these data support steatosis improvement and systemic anti-inflammatory effects, with FXR changes differing by tissue.

In several mouse models, *A. muciniphila* supplementation has been associated with lower hepatic fibrosis markers. For example, in an HFD + CCl_4 injury model, live or pasteurized *A. muciniphila* (and its extracellular vesicles) reduced collagen deposition and profibrotic genes (e.g., Col1a1, α-SMA, TGF-β) and improved liver histology [57]; in a murine cirrhosis model, administering a commensal *A. muciniphila* strain improved liver fibrosis (quantified on collagen stains) and hyperammonemia [58]. However, effects are model- and preparation-dependent: in a chronic, diet-induced MASH model (Ldlr−/−.Leiden; 28 weeks), heat-inactivated *A. muciniphila* did not reduce hepatic collagen/fibrosis despite gut benefits [59]. This suggests anti-fibrotic signals seen in some studies may not generalize across all disease contexts or formulations. While human data on liver outcomes are not yet available, the pilot trial did note reduced blood markers of liver dysfunction in the *A. muciniphila*-treated participants [17]. This suggests that even over just three months, *A. muciniphila* might alleviate liver stress or inflammation in overweight individuals. Taken together, these findings point to *A. muciniphila* as a potential strategy to combat MASLD. By improving metabolic parameters and exerting local effects in the liver (through bile acid metabolism and inflammation reduction), *A. muciniphila* could halt the early stages of fatty liver disease or even facilitate regression of hepatic fat.

Regarding cardiovascular health, one of the key risk factors is atherosclerosis—the buildup of plaques in arteries, which can lead to heart attacks or strokes. Chronic inflammation and dyslipidemia drive atherosclerosis, and as we have detailed, *A. muciniphila* favorably influences both factors. In a dedicated Apoe-/- atherosclerosis mouse model, daily oral *A. muciniphila* for 8 weeks significantly reduced aortic atherosclerotic lesions (area ↓31%, size ↓48%) despite unchanged hypercholesterolemia, compared to control mice on the same high-fat Western diet [20]. Protection tracked with less macrophage infiltration and lower aortic expression of MCP-1, ICAM-1, and TNF-α, alongside improved gut barrier function (↑ ZO-1/occludin, ↓ FITC-dextran permeability) and reduced circulating LPS. Importantly, long-term LPS infusion reversed these benefits, indicating that *Akkermansia* acts by limiting metabolic endotoxemia and vascular inflammation. Heat-killed bacteria were ineffective in this model. In essence, *A. muciniphila* maintained the gut barrier, which kept the inflammatory cascade in check, thereby guarding the arteries from the usual damage of a fatty diet. This is a remarkable insight, as it links gut health directly to heart health. It suggests that therapies aimed at the gut microbiome (like *A. muciniphila* supplements) could complement traditional cardiovascular risk reduction strategies (like statins or diet changes) by targeting the inflammatory aspect of heart disease. Additionally, *A. muciniphila*'s slight cholesterol-lowering effect observed in humans and its known impact on lipid metabolism genes in mice could have direct cardiovascular benefits [5,17]. Lower total cholesterol and improved lipoprotein profiles reduce the substrate for plaque formation. A concise overview of cardiovascular and hepatic preclinical models is presented in **Table 2**.

Outside of atherosclerosis, cardiovascular health encompasses blood pressure and heart function, though these have not been deeply studied yet with respect to *A. muciniphila*. It is known that metabolic syndrome and gut dysbiosis can contribute to hypertension. By improving insulin sensitivity and reducing inflammation, *A. muciniphila* might indirectly help normalize blood pressure (for example, improved endothelial function due to less inflammation). Human blood pressure data are mixed and largely observational, with small or inconsistent associations so far [60].

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Taken together, *A. muciniphila* supplementation shows significant potential for liver and cardiovascular health. In mice, it mitigates fatty liver/steatosis and attenuates atherosclerosis—the latter via gut-barrier reinforcement and reduced endotoxemia-driven inflammation—even without lowering cholesterol (Apoe−/− model). In humans, a proof-of-concept trial showed improved insulin sensitivity, lower insulinemia, and a modest reduction in total cholesterol with pasteurized *A. muciniphila* over 3 months, supporting cardiometabolic risk modification but not yet clinical CVD outcomes. For liver disease, multiple mouse models report benefits from steatosis reduction and—in some contexts—lower fibrosis markers, although effects are model- and preparation-dependent (e.g., fibrosis improvement in a cirrhosis model vs. no fibrosis prevention in long-term diet-induced MASH with heat-inactivated cells). If these findings translate in larger trials, *A. muciniphila* could complement standard strategies by targeting gut-derived inflammation and metabolic dysregulation at their source.

4. Discussion

4.1. Mechanisms of Action

The diverse health benefits of *A. muciniphila* supplementation observed across obesity, diabetes, gut health, and inflammation can be traced back to several key mechanisms of action. Foremost among these is the strengthening of the gut barrier. *A. muciniphila* actively reinforces the intestinal lining by increasing mucus production and tight junction integrity. Its presence stimulates goblet cells to secrete more mucin, thickening the protective mucus layer that separates microbes from the intestinal epithelium. This is somewhat paradoxical at first glance—one might expect a mucin-degrading bacterium to thin the mucus layer, but *A. muciniphila* seems to trigger a compensatory response from the host to produce even more mucus, resulting in an overall enhancement of the barrier. Additionally, *A. muciniphila* or its components can upregulate tight junction proteins between epithelial cells, as shown in mice and cell culture models. The net effect is reduced intestinal permeability. A less "leaky" gut means fewer endotoxins like LPS escaping into circulation. Since metabolic endotoxemia is a driver of systemic inflammation and insulin resistance, *A. muciniphila*'s ability to reduce LPS translocation is fundamental to its benefits. By resealing the gut barrier, *A. muciniphila* cuts off the trigger for the cascade of inflammation that links an unhealthy gut to obesity-related disorders. This gut barrier fortification is arguably the cornerstone of *A. muciniphila*'s action—it creates a healthier separation between the gut microbiota and the host, thereby maintaining immune equilibrium and metabolic homeostasis.

Another mechanism is the production of bioactive metabolites. *A. muciniphila* feeds on mucin and in the process releases SCFAs (like acetate and propionate) and possibly other metabolites such as amino acids and indole derivatives. SCFAs have multiple beneficial effects on the host: they serve as energy sources for colon cells, lower gut pH to inhibit pathogens, and act as signaling molecules [61]. Propionate and acetate produced by *A. muciniphila* can bind to free fatty acid receptors (such as FFAR2/3) on enteroendocrine cells, stimulating the secretion of satiety and metabolic hormones [32,62,63]. In particular, propionate is known to induce GLP-1 and peptide YY (PYY) release, hormones that improve insulin secretion, reduce appetite, and slow gut motility (contributing to weight management). The elevation of GLP-1 observed with *A. muciniphila* supplementation in mice aligns with this mechanism, as do the improved glucose tolerance and reduced food intake in some studies. Moreover, *A. muciniphila*'s metabolic byproducts may influence gene expression in tissues. For example, SCFAs can act as histone deacetylase inhibitors, modulating gene transcription in the liver and adipose tissue to favor fat burning over storage [64]. The metabolite-driven activation of the AMPK pathway in the liver (noted in one mouse study) suggests improved energy sensing and reduction of fat synthesis [31]. Evidence that *A. muciniphila* raises circulating phospholipids or lowers plasma branched-chain amino acids (BCAAs) in humans is indirect; its bacterial phospholipid can signal to the host, and BCAAs are linked to insulin resistance, but direct *Akkermansia*-driven changes in these plasma metabolites remain to be demonstrated [65]. Thus, via its metabolic outputs, *A.*

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muciniphila communicates with the host's physiology, essentially extending the functionality of our own metabolism.

Direct host-microbe signaling molecules from *A. muciniphila* represent another mechanism. We have mentioned proteins like Amuc_1100 (an outer membrane protein) and P9 (a small secreted protein) which have specific interactions with host receptors. Amuc_1100, identified by Plovier et al., can bind to TLR2 on intestinal epithelial and immune cells, triggering pathways that enhance mucus production and anti-inflammatory IL-10 release, without causing the pro-inflammatory effects that typical TLR2 agonists (like certain peptidoglycans) might [23]. This selective activation helps fine-tune the immune system toward tolerance. P9, as discovered by Yoon et al., binds to ICAM-2 on L cells, driving GLP-1 secretion and thus improving glucose handling [32]. These are examples of *A. muciniphila* essentially delivering therapeutic molecules to the host. Importantly, pasteurization (mild heat-killing) of *A. muciniphila* preserves these proteins, which explains why pasteurized *A. muciniphila* was effective in the human trial [17]. The bacterial cells need not be alive to confer benefits; they can act as a rich package of beneficial molecules—a concept known as postbiotics. In fact, the successful use of pasteurized *A. muciniphila* in humans led to its designation as a novel food ingredient (since it's not a traditional probiotic, being non-living) [14]. This could mark a paradigm shift: leveraging bacterial components (like surface proteins, membrane fragments, metabolites) to achieve health outcomes, which can simplify regulatory approval and safety profiles (no risk of live infection).

4.2. Clinical Studies and Translational Insights

Translation of *A. muciniphila* from bench to bedside is in early stages, but initial trials are informative. The 2019 Belgian randomized trial established that daily 10^{10} cells (live or pasteurized) is feasible and well tolerated, with no bacterium-attributed adverse events, and that pasteurized cells outperformed placebo on several metabolic endpoints (e.g., insulin sensitivity, insulinemia, total cholesterol) in overweight/obese insulin-resistant adults [17]. Because *A. muciniphila* is a commensal of the human gut, this amounts to boosting a native species rather than introducing an exogenous microbe. Regulatory momentum followed: in 2021 the European Food Safety Authority (EFSA) concluded pasteurized *A. muciniphila* is safe for adult consumption up to ~3.4×10^{10} cells/day, provided viable cells remain < 10 CFU/g, leading to EU market authorization—facilitating development of heat-inactivated, lyophilized formulations that are easier to handle than live anaerobes [14]. In 2025, EFSA extended safety to adolescents with age-specific dose caps; safety in pregnancy/lactation remains unestablished. Separately, a US multicenter RCT in type 2 diabetes tested a five-strain consortium including *A. muciniphila* (WBF-011), dosed twice daily for 12 weeks, which improved postprandial glucose AUC and reduced A1c versus placebo with no safety signals, supporting the concept that *A. muciniphila* can synergize with other anaerobes in disease-focused probiotics [33]. Finally, diet remains a key lever: while human trials to date typically do not restrict fiber, animal work shows prebiotic fibers (e.g., fructooligosaccharides/inulin) can markedly increase *A. muciniphila* and improve metabolic outcomes, motivating future synbiotic strategies that pair *A. muciniphila* with targeted prebiotics [13]. A consolidated snapshot of human trials—including design, dose/formulation, and key readouts—appears in **Table 1**.

4.3. Commercialization and Available Supplements

A. muciniphila has entered the market in both live-strain and pasteurized ("postbiotic") formats. In the United States, Pendulum offers Glucose Control, a physician-supervised medical food/medical probiotic for type 2 diabetes whose five-strain formulation (including *A. muciniphila*) improved postprandial glucose AUC and lowered A1c in a randomized controlled trial, and Pendulum Akkermansia, a standalone live *A. muciniphila* capsule for gut-lining support. Pendulum specifies zero-oxygen formulation and encapsulation to deliver viable anaerobes, and sells via subscription as well as one-time purchase. Current storage guidance is room temperature, with refrigeration optional (best for potency), and no cold shipping required. In Europe, The Akkermansia Company (A-Mansia) commercializes pasteurized *A. muciniphila* following EFSA's 2021 novel-food safety opinion (viable

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cells <10 CFU/g in the final product). Their Healthy Weight postbiotic combines pasteurized *A. muciniphila* with EGCG (green tea) and chromium, reflecting a multi-component metabolic-health positioning that can be deployed in food-supplement formats. Pasteurization and lyophilization simplify logistics versus live anaerobes.

4.4. Limitations and Considerations

Despite the excitement, there are several considerations and open questions regarding *A. muciniphila* supplementation. First, individual variability: not everyone may respond the same way to *A. muciniphila*. Baseline microbiome composition could influence its colonization. If someone already has abundant *A. muciniphila*, supplementing more might have diminishing returns. Conversely, someone with none (perhaps due to long-term low fiber diet or antibiotic use) might benefit greatly, but the bacteria will need a hospitable environment (sufficient mucin or prebiotics) to establish. There is also the question of long-term safety and effects. The trials so far have been short-term (3 months). Long-term supplementation is presumed safe given *A. muciniphila*'s commensal nature, but we should monitor whether the gut adapts (e.g., does endogenous mucin production continually increase, and is that always good?). Extremely high levels of *A. muciniphila* might conceivably alter the gut ecosystem in unknown ways. As noted in the "critical perspective" review, excessive enrichment of *A. muciniphila* might not be beneficial in every circumstance. For example, if someone is on a mucin-free diet or has a genetic mucus disorder, flooding the gut with a mucin-degrader could hypothetically cause problems.

Population exceptions warrant personalized guidance. In IBD, *A. muciniphila* is often reduced, and some models show barrier support, but disease activity and mucosal integrity likely modulate effects; prudence suggests focusing on remission-maintenance rather than active flares until more human data accrue. In neurologic conditions (e.g., Parkinson's disease), higher *Akkermansia* abundance is consistently observed, yet causality is unresolved; supplementation in such groups should be studied in trials before routine use. Finally, with respect to blood pressure, human evidence remains preliminary and heterogeneous—current data are drawn largely from observational cohorts and small interventional paradigms (e.g., dietary programs that alter multiple variables alongside the microbiome), and there are no randomized trials of *A. muciniphila* monotherapy showing antihypertensive efficacy, so any impact on blood pressure should be considered speculative pending dedicated studies. Overall, current evidence is strongest in metabolically unhealthy but otherwise generally well adults, while special populations should be approached cautiously pending long-term and condition-specific data. Practical implications for study design and patient selection are compiled in **Table 3**.

Table 3. Practical use considerations.

Consideration	Rationale	Suggested approach in practice
Baseline *Akkermansia* abundance	Efficacy of live strain may depend on low baseline levels (colonization succeeds)	Consider baseline microbiome profiling for precision use
Formulation (live vs pasteurized)	Pasteurized showed clear metabolic signals in RCT; safer/logistically easier	Favor pasteurized in general wellness; reserve live for trials/defined use cases
Special populations (IBD flares, severe barrier defects, certain neurologic conditions)	Context-dependent effects; some models show harm	Avoid during active severe mucosal injury; consider remission-maintenance trials

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Combination strategies	Metformin enriches *Akkermansia*; GLP-1R agonists shift microbiome	Study microbe–drug and synbiotic combinations prospectively
Outcomes & duration	Current human trials are short; hard outcomes pending	Design/seek longer RCTs with weight/A1c and cardiometabolic endpoints

4.5. Future Directions

Larger, confirmatory trials of *Akkermansia muciniphila* in metabolic disease are now underway, including randomized studies in hyperglycemia/overweight and in weight maintenance after diet-induced loss; these trials will enable dose-finding and may compare live vs. pasteurized directly, extending the initial 3-month Belgian proof-of-concept that showed safety and metabolic signals—particularly with pasteurized cells (e.g., NCT05114018). Key endpoints will expand from surrogate measures to clinical outcomes (e.g., A1c, body weight trajectories). Given that metformin consistently enriches *Akkermansia* in humans and that GLP-1R agonists are associated with microbiome shifts (often including *Akkermansia*), it is reasonable to test combination strategies (microbe + drug) and diet–microbe programs prospectively, while recognizing that synergy remains unproven. Beyond obesity/T2D, MASLD represents a high-priority target (animal data promising; human RCTs needed), and oncology trials may examine whether adding *A. muciniphila* improves immune checkpoint inhibitors responses, given repeated human associations between baseline *Akkermansia* and PD-1/PD-L1 efficacy. For polycystic ovary syndrome (PCOS), human microbiome studies report dysbiosis involving *Akkermansia*, but interventional data and IBD-risk linkage remain uncertain, warranting cautious exploration.

Mechanistically, discovery will likely accelerate. Amuc_1100 (outer-membrane, heat-stable; TLR2 signaling) and P9 (a GLP-1–inducing secreted protein binding ICAM-2) exemplify how *A. muciniphila* communicates with the host. Extracellular vesicles (EVs) and pasteurized whole-cell postbiotics already show robust preclinical or early clinical activity. A key open question is how far cell-free fractions (culture supernatants) can reproduce benefits in mammals/humans—early model systems are encouraging, but translational studies are needed. These lines of work point toward drug-like, defined postbiotics that could be trialed where whole-cell administration is impractical. Planned/ongoing clinical questions and how they map onto existing evidence are cross-referenced in **Table 1** (human trials) and **Table 3** (practical considerations).

5. Conclusions

Akkermansia muciniphila has progressed from commensal curiosity to a credible therapeutic candidate. In preclinical models, live and pasteurised preparations—and defined components such as Amuc_1100—consistently improve adiposity and insulin resistance, strengthen the mucus/epithelial barrier, and dampen inflammatory signaling. Early human data echo parts of this signal: in a randomized proof-of-concept trial in overweight/obese insulin-resistant adults, pasteurised *A. muciniphila* was safe and well tolerated and improved insulin sensitivity and lowered total cholesterol versus placebo, while anthropometric changes trended but were not statistically significant. A separate multicenter RCT testing a five-strain consortium that included *A. muciniphila* improved post-prandial glucose control and A1c in type 2 diabetes. Together, these findings support a mechanistic framework—barrier reinforcement and host-pathway modulation—with promising early clinical signals that now require confirmation at scale. Commercial translation has begun. In the EU, pasteurised *A. muciniphila* is authorized as a novel food for adults (finished products <10 CFU/g viable), with a 2025 EFSA extension specifying adolescent use at capped doses; this has enabled room-temperature postbiotic formulations. In the US, a multistrain product containing *A. muciniphila* is marketed and backed by an RCT, illustrating cautious, stepwise clinical adoption.

Going forward, responsible integration will depend on larger, longer trials that define optimal dosing, durability, and patient selection, and that test hard outcomes (clinically meaningful weight

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loss, A1c trajectories, progression to diabetes). Given metformin-associated enrichment of *Akkermansia* and microbiome shifts with GLP-1R agonists, combination strategies and diet–microbe programs are plausible but remain unproven. Precision use may matter: one phase-2 study in drug-naïve T2D found benefits concentrated among those with low baseline *Akkermansia* who achieved colonization. Finally, while improving gut health could secondarily influence systemic immunity and the gut–brain axis, *A. muciniphila*–specific benefits in these domains are not yet established in interventional human studies and should be treated as hypotheses. A measured conclusion is therefore warranted: *A. muciniphila* is a promising adjunct for metabolic health, with postbiotic (pasteurised) formats de-risking safety and logistics; yet context matters, and excessive enrichment may not be universally beneficial, underscoring the need for condition-specific trials and careful patient selection.

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Abbreviations

The following abbreviations are used in this manuscript:

A. muciniphila	*Akkermansia muciniphila*
A1c	Glycated hemoglobin (HbA1c). (Used interchangeably with HbA1c in the text.)
AMPK	AMP-activated protein kinase
Apoe−/−	Apolipoprotein E knockout (mouse model)
AST	Aspartate aminotransferase
BCAA(s)	Branched-chain amino acid(s)
CCl_4	Carbon tetrachloride
CFU	Colony-forming units
CONSORT	Consolidated Standards of Reporting Trials
CVD	Cardiovascular disease
DSS	Dextran sulfate sodium
EFSA	European Food Safety Authority
EU	European Union
EV(s)	Extracellular vesicle(s)
FFAR2/3	Free fatty acid receptor 2 / 3
FGF15	Fibroblast growth factor 15
FXR	Farnesoid X receptor
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1R	GLP-1 receptor (appears in “GLP-1R agonists”)
HbA1c	Hemoglobin A1c (glycated hemoglobin) (Also appears as A1c.)
HFD	High-fat diet
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICAM-2	Intercellular adhesion molecule-2
IL-10 / IL-6 / IL-17A	Interleukin-10 / -6 / -17A
ITT	Intent-to-treat (analysis set)
LPS	Lipopolysaccharide

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MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
NLRP3	NOD-like receptor family pyrin domain containing 3 (inflammasome sensor)
PCOS	Polycystic ovary syndrome
PI3K-Akt	Phosphoinositide-3-kinase/AKT signaling pathway
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PYY	Peptide YY
RCT	Randomized controlled trial
SCFA(s)	Short-chain fatty acid(s)
T2D / T2DM	Type 2 diabetes / Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
Th17	T helper 17 cell
TLR2	Toll-like receptor 2
Treg(s)	Regulatory T cell(s)
US	United States
ZO-1	Zonula occludens-1

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