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Research Progress on the Application of Pasteurized Akkermansia muciniphila in Weight Maintenance

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Abstract. Obesity treatment faces two major challenges: overcoming the weight-loss plateau and rapid weight rebound following medication discontinuation. While exogenous GLP-1 receptor agonists are effective, long-term use is associated with tolerance, and substantial weight rebound frequently occurs after discontinuation, which constrains their clinical utility. The study of the relationship between gut microbiota and host metabolism provides a new idea. *Akkermansia muciniphila*, a mucophilic bacterium, promotes endogenous GLP-1 secretion by secreting P9 protein and interacting with ICAM-2 receptors in intestinal L cells. This article examines the biological characteristics of pasteurized *Akkermansia* and its regulation of GLP-1 secretion, and reviews key clinical trials published in Nature Medicine in 2026. This experiment shows that daily supplementation of pasteurized *Akkermansia muciniphila* Muc^{T} after weight loss can help control weight rebound during the maintenance period. The study also pointed out the impact of initial microbiota status on intervention effectiveness and the practical difficulties in translational medicine. Currently, as a non living, non pharmacological approach, the pasteurization of *Akkermansia* supplementation may be an effective complementary therapy for weight maintenance after discontinuation of GLP-1 receptor agonists.

Keywords: *Akkermansia muciniphila*, Pasteurization inactivation, GLP-1, Weight rebound, Weight loss maintenance, gut microbiota

1. Introduction

The global prevalence of obesity has been recognized as a public health fact, and its association with type 2 diabetes, cardiovascular disease and multiple metabolic diseases has also been repeatedly confirmed. While medication can help patients achieve initial weight loss, sustaining this weight reduction over the long term remains challenging. Weight loss typically proceeds through a plateau phase, in which body weight stabilizes at a certain level and stops declining, before subsequent weight rebound occurs. That is to say, the body is not passively staying at a new weight, but actively returning to its original energy balance state.

Glucagon like peptide-1 (GLP-1) receptor agonists are one of the representatives of current weight loss drugs. Their mechanism is to promote glucose dependent insulin secretion, delay gastric emptying, and suppress appetite through exogenous GLP-1. However, long-term use may induce

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drug tolerance, undermining durable therapeutic effects. Once the medication is stopped, patients frequently regain lost weight and it's difficult for them to get rid of drug dependence. A deeper issue is that GLP-1 receptor agonists have not reversed the existing metabolic "memory" of adipose tissue, and the set point for energy homeostasis has not been readjusted. Therefore, how to maintain weight loss without relying on continuous injection of exogenous drugs has become an urgent problem to be solved in the treatment of obesity.

Akkermansia muciniphila has entered the research field due to its role in intestinal barrier integrity, energy metabolism regulation, and anti-inflammatory effects. Populations living with obesity, type 2 diabetes and metabolic syndrome often exhibit markedly reduced *Akkermansia* abundance. Animal experiments have also shown that supplementing *Akkermansia* can improve metabolic abnormalities in diet induced obese mice. It is interesting that the metabolic benefits of strains treated with pasteurization are even better than those of live bacteria, which has a significant impact on the development direction of non live bacterial preparations [1].

This article focuses on three aspects: first, the discovery process and functional verification of the P9-ICAM-2 signaling pathway, which serves as the molecular basis for endogenous GLP-1 regulation, and what evidence has been accumulated, second, the composition of active ingredients in pasteurized strains and their multi pathway mechanisms of action, third, the collective findings from multiple clinical trials examining weight-loss maintenance and metabolic improvement, as well as how baseline microbiota dependent effects have become a consistent finding across studies.

2. Molecular basis of endogenous GLP-1 regulation

2.1. Discovery and functional identification of P9 protein

In 2021, Yoon used proteomics to identify a secreted protein of approximately 84 kDa in the supernatant of *Akkermansia muciniphila* culture, which was named P9. This was the first time that P9 protein could specifically bind to intercellular adhesion molecule 2 (ICAM-2) on the surface of intestinal L cells, promoting GLP-1 secretion through activated calcium signaling. When obese mice induced by high-fat diet were treated with P9, brown adipose uncoupling protein 1 (UCP1) increased, systemic GLP-1 levels increased, and glucose tolerance improved [2].

On this basis, subsequent research has expanded the application potential of P9 from two directions. Di have achieved heterologous secretion and expression of P9 using lactobacilli, and the resulting recombinant strain supernatant can significantly promote the release of GLP-1 from intestinal L cells. For obese animals, oral administration of P9 class lactobacilli can inhibit weight gain, control food intake, and increase the expression of thermogenic genes [3]. Long provided a comprehensive discussion on the ICAM-2/IL-6 signaling involved in P9 and its engineering potential, recommending P9 as a potential multi-purpose candidate molecule in oral metabolic therapy [4].

Overall, the discovery of the P9-ICAM-2 signal axis has a dual significance. At the mechanistic level, it provides a molecular level causal explanation for Akkermansia's regulation of host metabolism, surpassing previous inferences based on microbiota associations. At the conversion level, the GLP-1 receptor targeted by this pathway is different from the targets of traditional drugs, so it may be used in conjunction with existing drugs or as an alternative after discontinuation. Notably, GLP-1 receptor agonists themselves promote the expansion of intestinal *Akkermansia*. This positive feedback loop implies a bidirectional causal relationship between the P9 pathway and GLP-1-based drugs, laying a theoretical foundation for combination therapy [2].

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2.2. Active ingredients of pasteurized strains

Pasteurization is typically performed at 70 ℃ for 30 minutes. At this time, the P9 protein may be partially inactivated due to heat sensitivity, but it can still bring clear benefits to host metabolism after pasteurization. This raises a question: are there any other thermally stable effector molecules at work besides?

A clear understanding has been formed through research on this issue. Plovier have demonstrated that pasteurization exposes the outer membrane protein Amuc_1100, which can bind to Toll like receptor 2 (TLR2) to affect intestinal immunity and correct metabolic abnormalities. Amuc_1100 is a thermally stable substance, and its activity is not affected by pasteurization [1]. This discovery explains at the molecular level why pasteurized strains still exhibit metabolic activity.

Subsequent research provided a more comprehensive explanation of the situation involved. Except for P9 and Amuc_1100, this bacterium can utilize several host related effector molecules, namely glycosidases, sulfatase, or proteases involved in mucus breakdown. Yang analyzed the inactivation of *Akkermansia* AKK PROBIO by pasteurization as an example of gut microbiota SFA-GLP-1, and discussed its anti obesity effect using the AMPK/PPAR-α pathway as an example. They pointed out that short chain fatty acids (SCFAs) promote the release of GLP-1 and PYY from L cells in the manner of GPR41 and GPR43, and the mechanism involved is independent of the metabolic regulation of P9 protein [5]. The above components all belong to the "molecular arsenal" of *A. muciniphila* in regulating metabolism.

Based on the evidence from multiple studies, it can be inferred that pasteurization does not mean a simple treatment of "retaining all" or "losing all" activity, but rather a processing form that retains certain specific functional components as needed. The substances contained in P9 lose their activity due to thermal instability, while Amuc_1100 class heat stable proteins remain effective, and the metabolites of SCFA can continue to function. The phenomenon of multiple components coexisting above indicates that the mechanism involved in pasteurization cannot be explained solely by a single pathway. In fact, metabolic regulation is mostly achieved through the combination of pathways such as P9-ICAM-2, Amuc_1100-TRL2, and SCFA-GPR41/43 [1，5].

3. Clinical evidence of pasteurization of Akkermansia

3.1. Efficacy

In the discourse on therapeutic efficacy, there have been multiple independent human studies demonstrating the metabolic benefits of pasteurization of *Akkermansia*. Depommer published the first *Akkermansia* human concept validation experiment in *Nature Medicine*. In this study, 40 overweight or obese individuals with insulin resistance were randomly divided into a live bacteria group, an inactivated bacteria group, and a placebo group, with outcomes monitored over 3 months. The conclusion drawn is that pasteurization of *Akkermansia* can promote insulin sensitivity, reduce plasma total cholesterol and insulin levels, and its inactivated form is more effective in improving insulin resistance than live bacteria [6].

Mount reported evidence of the efficacy of weight loss maintenance using a randomized controlled trial method in *Nature Medicine*. The study referred to in the article is an analysis of 90 overweight or obese adults. After participants achieved ≥8% weight loss via an 8-week low-energy diet, 84 individuals entered a 24-week maintenance phase and were randomized to receive daily pasteurized *A. muciniphila* Muc^T or placebo. The conclusion drawn from this design is that the

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weight gain during the maintenance period corresponding to Muc^T is much less than that of the placebo group (only returning to 13.6% and 32.9% of weight loss, respectively), About 40% of Muc^T treatment patients still show a decreasing trend in weight during the maintenance period [7].

The experiment published by Suenaert in *Gut Microbes* provides evidence for populations with metabolic syndrome. The data of 142 adults with metabolic syndrome were analyzed in the article, and pasteurized *Akkermansia* Muc^T was used as an intervention for 4 months. The main results determined according to the principle of intention to treat have not been confirmed, but the exploratory investigation of some subgroups found that GLP-1 increased in prediabetes patients or those aged ≥ 63 years after three months of intervention [8].

Zhang used the randomized control method to investigate the metabolic effect caused by the living bacterium *A. muciniphila* WST01, that is, its effect on overweight, obesity and type 2 diabetes patients simultaneously has a significant effect in low baseline flora [9].

If we compare the various studies listed, even if the strains, methods, subjects, and basic endpoints used in each experiment are different, the overall conclusion is still close: supplementing with pasteurized *Akkermansia* is beneficial for insulin sensitivity, has an inhibitory effect on weight rebound after weight loss, and shows additional metabolic benefits in some people.

3.2. Security

Safety constitutes a foundational consideration for the clinical translation of pasteurized *Akkermansia*. Among the human trials reviewed, neither the Depommer nor the Mount study indicated severe treatment-related adverse events. By 2025, the European Food Safety Authority (EFSA) had provided a safety assessment for the extended use of pasteurized *Akkermansia muciniphila* as a new type of food and delivered a favorable opinion on the associated regulatory questions. Based on toxicological analysis and triple evidence from clinical and regulatory studies, there is already a relatively complete explanation of the safety of this strain, so the possibility of its long-term use in non pharmaceutical form can be reasonably considered [10].

3.3. Population stratification

Several independent studies have indicated that the abundance of baseline *Akkermansia* has a significant regulatory effect on the intervention administered. This observation was first reported by Depommer through experimental methods and subsequently validated and explained in larger studies [6].

In the subgroup analysis of Mount's experiment, it has been pointed out that individuals with low initial abundance of *Akkermansia* spp. often benefit greatly in weight control and insulin sensitivity if treated accordingly, while those with high abundance may not necessarily do so [7]. Zhang have done similar research on type 2 diabetes patients, and found that those with low *Akkermansia* abundance have obvious improvement in blood glucose and insulin, and those with high *Akkermansia* abundance have less benefits, The intestinal growth of *Akkermansia* after supplementation was only effective for the low baseline group [9]. The trend observed by Suenaert is roughly the same: the low baseline *Akkermansia* subgroup showed significant weight loss and improvement in insulin response [8].

From a mechanistic perspective, the phenomenon involved can be explained by niche competition.When the target bactera already occupies a large fraction of the intestinal niche, exogenous supplementation may fail to induce overall systemic shifts. But if its original abundance

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is low, supplementation may "fill the gap" and promote a more natural bacterial host relationship [11]. This conclusion is supported by multiple studies, multiple strain forms (Muc^T pasteurizer and living WST01), and different populations (people with stable weight or abnormal metabolism, patients with type 2 diabetes). From a practical application perspective, analyzing the baseline microbiota is likely a necessary preliminary task for *Akkermansia* intervention.

4. Mechanism exploration and combination therapy strategy

4.1. Mechanism exploration

At the mechanism level, several studies have validated the multiple pathways involved in the inactivation of *Akkermansia* by pasteurization from various perspectives. After analyzing the transcripts of adipose tissue in Mount's experiment, it was found that during the maintenance phase of the Muc^T group, immune inflammatory genes were expressed at a low level, while corresponding mitochondrial or energetic genes were expressed at a high level. Therefore, adipose tissue is likely to transition from a pro-inflammatory state to a metabolically active state [7].

Depommer et al. proposed another clue based on lipidomics: both live and pasteurized bacteria studied can alleviate the reduction of 1- or 2-palmitoylglycerol observed in the placebo group to a certain extent, and it has been proven that lipids are endogenous activators of peroxisome proliferator activated receptor alpha (PPAR alpha). Based on this, a hypothesis analysis can be made: Palmitoyl glycerol may promote the benefits of *Akkermansia* for metabolic syndrome by activating PPAR α [12].

If the results observed from transcriptomics and lipidomics are combined with the previously mentioned pathways such as P9-ICAM-2, Amuc1100-TLR2, and SCFA-GPR41/43, the effect of pasteurization of *Akkermansia* should be multi-layered: for the intestine itself, P9 proteins and SCFA are used to control the hormones produced by L cells, In terms of adipose tissue, transcriptional reprogramming is used to redirect fat from a pro-inflammatory state to a metabolically active state, Overall, nuclear receptors such as PPAR α are used to regulate lipid metabolism processes. This multi-target phenomenon is a great supplement to the single-target mechanism of GLP-1 receptor agonists, perhaps the cause of slowing down rebound after discontinuation.

4.2. Combination therapy strategy

In the information on the combination of *Akkermansia* and existing drugs, Gao studied and analyzed the effect of GLP-1 receptor agonist used together with *Akkermansia muciniphila Akk*11 on obesity and MASLD in type 2 diabetes mice in *Cell&Bioscience*, and explained the pre clinical feasibility of combining the two methods [13]. From the perspective of complementary mechanisms, GLP-1 receptor agonists use exogenous activation methods, while pasteurization of *Akkermansia* promotes GLP-1 secretion in an endogenous manner. The two target different parts of the same signaling chain and can theoretically be used in combination. Cani mentioned in their review that *Akkermansia* belongs to the new generation of probiotics and should be comprehensively combined with metabolic drugs [11].

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5. Challenges and prospects

5.1. Limitations of clinical research

As far as the current evidence system is concerned, there are still universal limitations to clinical studies on the inactivation of *Akkermansia* by pasteurization. In terms of sample size, the number of subjects in existing experiments is generally only 32-84, and the ability to conduct statistical analysis on subgroups is still lacking. A 24-week follow-up period is insufficient to explain safety and efficacy over one year or longer. From a dietary perspective, experiments related to weight loss maintenance have not established a uniform maintenance period, which is close to reality but introduces more variables. In addition, authors of existing studies are sometimes associated with the industry, and truly independent revalidation is not yet common.

5.2. Unsolved issues at the mechanism level

The mechanism involved in the inactivation of *Akkermansia* by pasteurization is currently not fully understood. Although P9 protein is a thermosensitive substance, the inactivated strains used can still have metabolic benefits, so Amuc_1100 or other heat stabilizers may promote related effects alone or in combination [2]. The respective proportions of several pathways (P9-ICAM-2, Amuc_1100-TRL2, SCFA-GPR41/43) are still uncertain, and different situations (physiological or pathological) may be regulated by a certain type of pathway. Moreover, the effects of *Akkermansia* are not universally beneficial. Previous studies have shown that it may be a pathogenic factor in certain conditions, and this dependence should be included in the background analysis of its effects [11].

5.3. Key obstacles to clinical translation

If clinical translation is used as a standard for examination, there are three major difficulties in the application of pasteurized *Akkermansia*. Firstly, the analysis of baseline microbiota does not yet constitute a routine clinical procedure, and the cost and time involved hinder extensive research stratified by population. Secondly, there is currently a lack of a unified and recognized standard cut-off (i.e. abundance limit) to help determine "who is suitable to supplement", and the usage and threshold of different literature vary, making it difficult to establish comparisons or transformations. Thirdly, treating pasteurized bacteria as food supplements rather than drugs cannot guarantee absolute efficacy, and the pharmaceutical industry has little motivation to conduct large-scale confirmation trials.

5.4. Future research directions

The above analysis outlines priorities for future investigation. First, a confirmatory test will be conducted on patients who have discontinued GLP-1 receptor agonists, using pasteurized *Akkermansia* to assess the possibility of maintaining therapeutic efficacy after discontinuation. Second, using non-invasive indicators such as ICAM-2 mRNA contained in fecal exosomes as a reference for individual medication, without relying on invasive intestinal biopsy methods. Third, think about the problem according to the principle of dosage and find the optimal dosage. Fourth, investigate the combined effect of probiotics and prebiotics. Fifth, conduct long-term (≥ 1 year) safety tracking of treatment.

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From a broader perspective, the research involved in the pasteurization of *Akkermansia* is an example of the shift from "association description" to "mechanism driven" precise intervention of gut microbiota. The pathway represented by P9-ICAM-2 is currently a more specific target for molecular analysis of the relationship between hosts and microbiota, and multiple clinical trials have shown that population stratification has universal significance in microbiota therapy. The "screening-stratification-matched intervention" framework built on baseline microbiota testing may emerge as a new paradigm for managing metabolic diseases.

6. Conclusion

The inactivation of *Akkermansia muciniphila* by pasteurization promotes endogenous GLP-1 secretion through the P9-ICAM-2 axis and may exert metabolic regulatory effects through multiple pathways such as Amuc1100-TLR2 and SCFA-GPR41/43. Multiple independent clinical trials have consistently shown that this intervention can improve insulin sensitivity, slow down weight rebound after weight loss, and has good safety, with individuals with low baseline *Akkermansia* abundance benefiting more prominently. However, the relative contributions between multiple pathways and their dominant mechanisms in different populations are not yet clear, and the residual activity of P9 after pasteurization also needs to be quantitatively evaluated. In the future, larger-sample and longer-duration confirmatory trials should be conducted among populations discontinuing GLP-1 receptor agonists. Meanwhile, a "screening-stratification-matched intervention" workflow based on baseline microbiota profiling should be established to facilitate the clinical translation of this non-pharmacological strategy.

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