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***Akkermansia muciniphila*: a promising target for the therapy of metabolic syndrome and related diseases**

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Available online 20 Nov., 2019

[ABSTRACT] The probiotic *Akkermansia muciniphila* (*A. muciniphila*) is an intestinal bacterium that was first identified in human feces in 2004. Its specialization in mucin degradation makes it a key microorganism that maintains intestinal mucosal barrier function. As an unique representative strain of the phylum *Verrucomicrobia* that can be cultured *in vitro*, *A. muciniphila* is much easier to detect by metagenomic analysis of intestinal flora. In the past few years, *A. muciniphila* has been getting increasing attention for the positive correlation between its intestinal colonization and host homeostatic metabolism. In this review, we summarize the relationship between *A. muciniphila* and host health and diseases, especially focusing on metabolic diseases and related mechanisms, as well as the natural food and drug-derived substrates affecting its colonization in the host, expecting to provide evidence and clues for the development of drugs targeting *A. muciniphila*.

[KEY WORDS] Gut microbiota; Metabolic syndrome; Diabetes; Atural medicine

[CLC Number] R965 **[Document code]** A **[Article ID]** 2095-6975(2019)11-0835-07

Introduction

The vertebrate gut microbiota is one of the most complex ecosystems on earth. Emerging evidence implicates that the gut microbiota is an important player in maintaining energy metabolism and host susceptibility or mediating the development of carbohydrate, lipid and protein metabolic disorders [1]. As early as in 1983, Wostmann and colleagues observed that the calorie intake in sterile rodents is 30% higher than those in conventional environments [2]. Thereafter, Bäckhed and Hooper *et al.* found that the intestinal flora contributes to the absorption of carbohydrates and lipids and confirmed the crucial roles of gut microbiota in energy metabolism [3-4]. *Akkermansia muciniphila* (*A. muciniphila*), a species of intestinal bacteria initially isolated from human feces, was identified

as a new mucolytic bacterium *via* diluting the feces in an anaerobic medium containing gastric mucin as the carbon and nitrogen sources [5]. *A. muciniphila* produces more than 60 enzymes, including glycosidase, sulfatase and sialidase, which degrade oligosaccharide chains to adapt to the mucus-rich and endogenous glycoprotein-rich living environment. The main growth and metabolism matrix of *A. muciniphila* is mucin, which is secreted by the goblet cells in the gastrointestinal tissue of the host, so *A. muciniphila* colonization is not strictly dependent on diet and has a unique survival advantage. *A. muciniphila* releases monosaccharides and amino acids while degrading host mucin, providing nutrients to other resident bacteria. As a representative bacterium of *Verrucomicrobia* in the gut microbiota, *A. muciniphila* is relatively easier to distinguish from other gut microorganisms, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* [6-7]. Since its discovery in 2004, accumulated evidence has linked the abundance of *A. muciniphila* to its beneficial effects in various metabolic disorders, such as obesity, diabetes and metabolic syndrome.

As *A. muciniphila* is mainly located in the mucus layer, it plays an important role in maintaining homeostasis of intestinal barrier, which might be closely related to nutrient exchange, information exchange, immune system development

[Received on] 29-Sep.-2019

[Research funding] This work was supported by the National Key R&D Program of China (No. 2017YFA0205400), the National Natural Science Foundation of China (No. 81773800), National Drug Innovation Major Project of China (No. 2018ZX09711001-003-009), Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (No. 2016-I2M-1-010).

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These authors have no conflict of interest to declare.

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and resistance to invasion of pathogenic microorganisms. Particularly, *A. muciniphila* exhibited potent immunostimulatory ability in an *in vitro* model, including the induction of cytokine production and activation of Toll-like receptors 2 and 4 (TLR2 and TLR4). The molecular mechanisms by which *A. muciniphila* mediates the immune response have been the subject of recent studies. For example, the IL-10 level induced by live *A. muciniphila* is similar to those induced by *Faecalibacterium prausnitzii* A2-165 and *Lactobacillus plantarum* WCFS1 [8]. In IFN- γ -deficient mice, increased *A. muciniphila* abundance is responsible for better glucose tolerance, which could be reversed by restoring IFN- γ levels. Although the mechanism of the effect of this bacterium on host immunity has not been fully elucidated, it has been found that *A. muciniphila* expresses plenty of highly abundant proteins on its outer membrane. Among these proteins, Amuc_1100 is the most specific protein, which is involved in the formation of fimbriae in *A. muciniphila*, and could partially

reproduce the beneficial effects of live *A. muciniphila* through activating TLR2-mediated immune homeostasis in the intestinal mucosa and improving intestinal barrier function [9]. Interestingly, either TNF- α , IFN- γ or IL-10 could be provoked in *A. muciniphila* treated peripheral blood mononuclear cells [8, 10], indicating that its immunomodulatory properties cannot be simply restricted as anti-inflammatory or pro-inflammatory, but may play a more complex role in maintaining the balance of the immune microenvironment as well as gut ecosystem.

Relationship Between *A. muciniphila* and Host Metabolic Diseases

In the past few years, the enthusiasm in investigating the benefits of *A. muciniphila* on human diseases has yielded a couple of positive results. Here, we summarize the current understanding and comprehensive progress of the dynamic regulating effects of this bacterium on host metabolic diseases (Fig. 1).

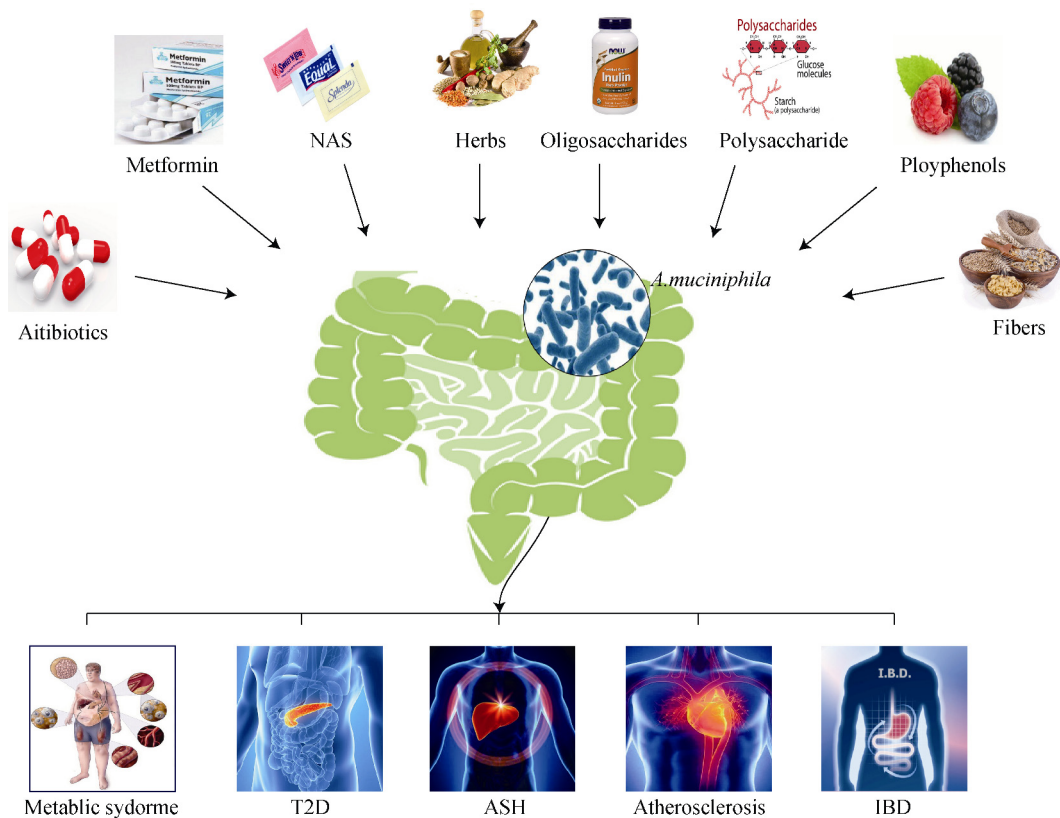


Fig. 1 Intervention factors and potential health effects of *A. muciniphila* in the gut

A. muciniphila and obesity

Obesity and related metabolic disorders, such as metabolic syndrome, have been associated with the composition and function of the intestinal microbiota. In 2011, Everard *et al.* found that inulin-type fructans, a kind of prebiotic, affected the colonization of more than 100 different microbial taxa in the gut. The relative abundance of *A. muciniphila* increased more than 100-fold after prebiotic ingestion, suggest-

ing that *A. muciniphila* may act as a probiotic improving metabolic disorders [11]. They further observed that the high-fat diet (HFD)-fed mice showed a 50% reduction in body weight gain, visceral and subcutaneous fat amount as well as alleviated metabolic symptoms after treatment with *A. muciniphila* live bacteria by gavage for 4 weeks [12]. Unexpectedly, pasteurization, a milder heat inactivation method than autoclaving, did not eliminate the beneficial effects of *A.*

muciniphila in the reduction of fat mass development but even improved the effect of the bacteria on dyslipidemia and insulin resistance in HFD-fed mice, which were regardless of food intake. Moreover, pasteurized *A. muciniphila* increased the energy in the mouse feces, indicating a decrease in energy absorption in the body, which may explain the decrease in weight gain [9]. Using a novel *ex vivo* model of mouse ileal organoids to characterize the effects of microbiota on host epithelium, Lukovac *et al.* observed that *A. muciniphila* and its metabolite propionate could participate in cell lipid metabolism by affecting the expression of various metabolic regulators such as Fiaf, Gpr43, HDACs, and Ppar γ , which supports the previous *in vivo* findings and provides a novel model for evaluating host-microbial interactions [13].

In clinical practice, the abundance of *Akkermansia* in the intestinal tract of patients with metabolic disorders (obese children and adults) has generally declined [14-15], and other studies have shown a negative correlation between *Akkermansia* and metabolic disorder markers [16]. In a large-scale observational epidemiological study involving obese and lean individuals, researchers found that subjects with a higher richness of gut bacteria were healthier than individuals with a lower richness, and the abundance of *A. muciniphila* was also significantly associated with a ‘high gene count’ population [17]. Recently, a 6-week calorie restriction test on obese and overweight people was conducted to analyze the relationship between the intestinal microbiota, metabolic syndrome and dietary intake before and after intervention. The data showed that *A. muciniphila* abundance was negatively correlated with fasting blood glucose, subcutaneous fat cell diameter and waist-to-hip ratio. Interestingly, individuals with a higher abundance of *A. muciniphila* exhibit better metabolic characteristics, including improved insulin sensitivity [18]. A research team at Stanford University found that the abundance of *A. muciniphila* was significantly increased after insulin-sensitive subjects fed with a high-fat diet but exhibited no remarkable change in its low basic content in the gut of insulin-resistant subjects, suggesting that *A. muciniphila* plays a protective role in helping the body cope with insulin resistance [19].

A. muciniphila and diabetes

Accumulated evidence has revealed the involvement of *A. muciniphila* in the regulation of metabolism and how the intestinal colonization of *A. muciniphila* can contribute to the resistance of metabolic abnormalities during the process and development of diabetes. Hänninen *et al.* examined the incidence of diabetes in NOD mice from Jackson Laboratories and found that the high incidence of diabetes was also related to *A. muciniphila* deficiency. Oral transfer of *A. muciniphila* to NOD mice reduced the incidence of diabetes, the specific mechanism of which is related to the promoted mucus secretion, increased expression of the antibacterial peptide Reg3 γ in the colon, lowered plasma endotoxin level and islet TLR expression, as well as the increased recruitment of Foxp3⁺ Treg cells in islets [20]. However, a metagenome-wide associa-

tion study of gut microbial DNA from 345 Chinese patients with type 2 diabetes and healthy people showed that *A. muciniphila* was more abundant in T2D patients than in healthy controls [21], which was most likely due to gene and diet differences. There is evidence that the anti-diabetic effects of *A. muciniphila* were mainly dependent on its beneficial effects in alleviating intestinal barrier damage and insulin resistance. Chelakkot *et al.* evaluated the regulating effect of *A. muciniphila*-derived extracellular vesicles (AmEVs) on intestinal permeability and found that there were more AmEVs in the fecal samples of healthy controls compared to T2D patients. In addition, administration of AmEVs enhanced intestinal tight junction function, reduced weight gain, and improved glucose tolerance in high-fat diet-induced diabetic mice. Furthermore, these AmEVs could remarkably reduce the permeability of lipopolysaccharide-treated colon adenocarcinoma cells (Caco-2), whereas extracellular vesicles derived from *Escherichia coli* had no significant effect [22].

A. muciniphila and other diseases

Recent evidence indicates that *A. muciniphila* abundance was reduced in feces of alcoholic steatohepatitis (ASH) patients and experimental alcoholic liver disease (ALD) mouse models. Administration of *A. muciniphila* by gavage could increase mucus layer thickness and tight junction protein expression, as well as promote intestinal barrier repairment in ALD mice [23]. In the high fat diet-induced apolipoprotein E-deficient (Apoe^{-/-}) atherosclerosis model mouse, replenishment with live *A. muciniphila* could remarkably inhibit atherosclerotic lesion formation, accompanied by the reduction in circulating endotoxin levels, through ameliorating metabolic endotoxemia-induced inflammation in both the circulation and local atherosclerotic lesion [24].

Several studies have shown that *A. muciniphila* is associated with inflammatory bowel disease (IBD). Png *et al.* found that the total abundance of mucus-degrading bacteria was increased in the intestinal tract of IBD patients, while the amount of *A. muciniphila* was reduced, suggesting that *A. muciniphila* may have potential anti-inflammatory effects [25]. In addition, both *A. muciniphila* and *Bacteroides acidifaciens* were reduced in the feces of dextran sulfate sodium (DSS)-induced colitis mice. Oral administration of *A. muciniphila* EVs also ameliorated DSS-induced enteritis phenotypes such as weight loss, colon shortening, and inflammatory cell infiltration in the colon wall [26]. Clinical reports have also shown that the amount of *A. muciniphila* in feces from patients with acute appendicitis is negatively correlated with the severity of the disease [27].

Natural Products Affecting Intestinal Abundance of *A. muciniphila*

In recent years, a large number of studies have confirmed that antibiotics, food-derived prebiotics, and drugs have shown astonishing effects on the colonization of *A. mucini-*

phila, suggesting that the elevated abundance of *A. muciniphila* in the intestinal flora via dietary structure adjustment or drug intervention would be a promising strategy for treating metabolic diseases. As alternatives to synthetic chemical compounds or biochemical reagents, natural products or

compounds derived from medicinal plants or microbes are the most important source for increasing the intestinal colonization of *A. muciniphila*. Here, we will summarize these natural products and discuss their potential as therapeutic reagents for metabolic diseases (Table 1).

Table 1 Interventions that affect and regulate the abundance of *Akkermansia* in vivo

Intervention	Subject	<i>Akkermansia</i> population	Microbiota analysis approach	Reference
Combined antibiotics (including doxycycline, hydroxy chloroquine, piperacillin/tazobactam and teicoplanin)	Patients infected by <i>Coxiella burnetii</i>	<i>A. muciniphila</i> significantly increased, accounts for more than 44.9% in total bacteria	16S sequencing	28
Imipenem	ICU patients	<i>A. muciniphila</i> significantly increased, accounts for more than 84.6% in total bacteria	16S sequencing / FISH	28
Vancomycin	NOD adult or infant mice	<i>A. muciniphila</i> significantly increased, accounts for more than 80% in total bacteria	16S sequencing	29
Tylosin	C57BL/6J mice	Large blooms of <i>Akkermansia</i>	16S sequencing	30
β -Lactam	Patients	<i>Akkermansia</i> significantly increased	16S sequencing	31
Oligofructose	<i>ob/ob</i> mice or high-fat diet induced C57BL/6 mice	<i>A. muciniphila</i> significantly increased	qPCR	11, 12, 34
Polyphenol-rich cranberry extract	High-fat diet induced C57BL/6J mice	A striking 30% increase of <i>Akkermansia</i>	16S sequencing	36
Green tea polyphenols	High-fat diet induced C57BL/6J mice	<i>A. muciniphila</i> correlated negatively with aberrant metabolic parameters	qPCR	38
Grape polyphenols	High-fat diet induced C57BL/6J mice	<i>A. muciniphila</i> was uniquely elevated	16S sequencing	39
Conjugated linoleic acid	High-fat diet induced C57BL/6J mice	<i>A. muciniphila</i> significantly increased	qPCR	41
Oats	Female C57BL/6J mice	<i>A. muciniphila</i> significantly increased	qPCR	42
FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols)	Patients with IBS and healthy individuals	Low FODMAP diet reduced <i>A. muciniphila</i> abundance	qPCR	43
Whole-grain barley	Male Waister rats	<i>A. muciniphila</i> significantly increased	16S sequencing / qPCR	44
Polyamines	BALB/c mice	<i>A. muciniphila</i> significantly increased	FISH (Fluorescent <i>in situ</i> hybridisation)	45
Red pitaya betacyanins	High-fat diet induced male C57BL/6J mice	Increase the relative abundance of <i>Akkermansia</i>	16S sequencing	46
Non-caloric artificial sweeteners	Male C57BL/6J mice	Reduce <i>A. muciniphila</i> abundance	16S sequencing / Metagenome sequencing	48
Metformin	High-fat diet induced male C57BL/6J mice	<i>Akkermansia</i> significantly increased	16S sequencing	50, 51
<i>Flos Lonicera</i>	High-fat diet induced male SD rats	<i>Akkermansia</i> significantly increased	qPCR	52
Fermented <i>Rhizoma Atractylodis Macrocephalae</i>	High-fat diet induced male SD rats	<i>Akkermansia</i> significantly increased	16S sequencing	53, 54
<i>Moutan Cortex</i>	High-fat diet induced male C57BL/6J mice	<i>Akkermansia</i> increased	16S sequencing	55
<i>Ganoderma lucidum</i>	High-fat diet induced C57BL/6NCR1Blw mice	Increased <i>A. muciniphila</i> abundance	16S sequencing	56

Antibiotics

Antibiotics are powerful agents used to fight certain infections via inhibiting the colonization and amplification of intestinal bacteria. However, in a number of animal and human experiments, the administration of specific antibiotics has led to large outbreaks in the *Akkermansia* genus [28-31]. Most of these results are based on 16S RNA sequencing, which only indicates the relative abundance of the bacteria in the entire intestinal flora but not the absolute content of the bacteria. Therefore, whether the absolute content of *A. muciniphila* is increased after treatment with antibiotics is still unclear. An antibiotic susceptibility assay showed that *A. muciniphila* was susceptible to doxycycline, imipenem and piperacillin/tazobactam, but not penicillin G, vancomycin and metronidazole [28], which explains why *A. muciniphila* in the gastrointestinal mucus layer of NOD mice became dominant after treatment with vancomycin for 8 weeks, although vancomycin is the ultimate antibiotic of most microorganisms, including resistant bacteria [29]. In the clinical study conducted by Dubourg et al., stool samples from two subjects who received broad-spectrum antibiotic therapy were analyzed and showed that the *Akkermansia* genus proliferated in a large amount. More interesting, neither of the subjects presented obvious gastrointestinal disorders, which confirms that *A. muciniphila* has no obvious harmful effects on the human body [28]. In addition, recent studies have also shown that the dominance of the *Akkermansia* genus was dramatically increased in the gastrointestinal tract of mice following tylosin or β -lactam treatment [30, 31].

Prebiotics

Inulin-type oligofructose, as a prebiotic, affects more than 100 different intestinal flora taxa via mimicking a competitive inhibitor of bacterial membrane receptor to inhibit the invasion of pathogenic microorganisms [32]. On the other hand, soluble oligofructose could be a mucin analogue to bind to pathogenic microorganisms and facilitate their excretion through the intestinal tract [33]. Everard et al. found that *A. muciniphila* was less abundant in the gut microbiota of genetically or diet-induced obese and diabetic mice, while the relative abundance of *A. muciniphila* could be increased by more than 100 times after ingesting inulin-type oligofructose [11-12, 34].

Polyphenols are also an important class of prebiotics affecting the abundance of *A. muciniphila*, even though its antioxidant activity is much more widely investigated [35]. Anhe et al. reported that polyphenol-rich cranberry extract could improve high fat/high sucrose diet-induced metabolic syndrome by directly increasing the abundance of the *Akkermansia* genus [36]. Consistent with this result, a previous *in vitro* study showed that the polyphenol mixture extracted from black tea or red wine/grape juice also increased the abundance of *A. muciniphila* in an *in vitro* gut microbial ecosystem [37]. Interestingly, the benefits of green tea polyphenols in high-fat-fed mice are also associated with an increased abun-

dance of *A. muciniphila* in the intestinal microbiota [38]. Another study by Roopchand et al. indicated that grape polyphenols significantly promoted the colonization of *A. muciniphila* and decreased the proportion of *Firmicutes* to *Bacteroidetes*, which was consistent with previous reports that altered microbial community structure can protect against obesity and metabolic diseases [39].

Other specific dietary ingredients also increase the colonization and amplification of *A. muciniphila*. Reid et al. found that supplementation of prebiotic fiber to the diet increased the abundance of *A. muciniphila* in the gut of overnourished rats, which might be helpful to improve their metabolic characterization [40]. Additionally, conjugated linoleic acids [41], oat bran [42], and short-chain carbohydrates that are difficult for the human body to absorb, including fermentable oligosaccharides, disaccharides, monosaccharides and polyols [43], whole-grain barley [44] and polyamines [45], red pitaya betacyanins [46], and maize-derived non digestible feruloylated oligo- and polysaccharides [47], can also increase the abundance of *A. muciniphila* in the gut.

Food additives and drugs

Noncaloric artificial sweeteners (NAS) are one of the most widely used food additives in the world. Because of their low calorie content, they are generally considered to be safe for humans, but Suez et al. found that NAS could induce dysbiosis and glucose intolerance by altering intestinal microbial structure, specifically reducing the abundance of *A. muciniphila* in the healthy human intestinal tract [48].

Metformin has been widely used to treat type 2 diabetes through activation of AMP-activated protein kinase (AMPK) to suppress the transcription of genes involved in gluconeogenesis [49]. Accumulated evidence has revealed that intestinal microbiota could be an indispensable participator to mediate its glucose-lowering effect. Shin et al. found that oral administration of metformin significantly increased the abundance of *A. muciniphila* in the bacterial population, which was correlated with its ability to improve glucose tolerance in high-fat fed mice [50]. In addition, Lee et al. also demonstrated that metformin enriched the proportion of *A. muciniphila* in fecal microbiota incubated in brain heart infusion (BHI) medium [51]. Moreover, there are reports indicating that *Flos Lonicera* [52], fermented *Rhizoma Atractylodis Macrocephalae* [53, 54], *Moutan Cortex* [55] and *Ganoderma lucidum* [56] also have beneficial effects on host metabolism as well as the potential to increase the proportion of *A. muciniphila* in intestinal bacteria.

Prospects and Future Challenges

Although several negative effects of *A. muciniphila* have been reported, it is consistently found that *A. muciniphila* has a positive role in improving host metabolism and that its abundance is generally negatively correlated with metabolic disorders in most preclinical and clinical studies. *A. muciniphila*, the specific representative strain in the phylum *Verrucomicrobia*, is the unique strain that can be cultured *in vitro*.

Although this anaerobic bacterium can tolerate the micro-oxygen environment [57], its *ex vivo* amplification is still relatively sensitive to oxygen and requires specific culture conditions. For instance, it is necessary to add animal-derived mucin as its energy source, which hinders the clinical application of *A. muciniphila*. Recently, Plovier *et al.* successfully developed a synthetic medium to allow high-yield culture of *A. muciniphila*, and this medium does not contain any compounds incompatible with human administration, solving a major obstacle in the clinical application of *A. muciniphila* [9]. Furthermore, this team also identified that the surface membrane protein Amuc_1100 plays a key role in the interaction between *A. muciniphila* and host immunity and provides a potential target for treating metabolic diseases. Microencapsulated *A. muciniphila* based on microencapsulation and freeze-drying technology make the storage and clinical administration of *A. muciniphila* much more viable [58]. More importantly, a growing number of studies have indicated that the utilization of *A. muciniphila*-enhancing foods or drugs has a bright future in the treatment for metabolism-associated diseases. It would be quite necessary to evaluate the therapeutic benefits of these interventions against its potential risks, and the combination of *A. muciniphila*-modulating agents with other anti-metabolic drugs may be helpful to avoid the undesirable side effects caused by *A. muciniphila*.

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Cite this article as: ZHOU Ji-Chao, ZHANG Xiao-Wei. *Akkermansia muciniphila*: a promising target for the therapy of metabolic syndrome and related diseases [J]. *Chin J Nat Med*, 2019, 17(11): 835-841.