Research progress on the next-generation probiotic *Akkermansia muciniphila* in the intestine

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Abstract
Probiotics are widely used for various fields, such as agriculture, food, and treatment and so on. *Akkermansia muciniphila*, the candidate for next-generation probiotics, is an intestinal bacterium that was isolated from a human fecal sample. It has been proved that *A. muciniphila* is closely related to multiple disease and metabolic disorders. What’s more, its functions are not limited to intestinal diseases only, and even affect aging and cognition. Therefore, we would like to summarize the related research progress on *A. muciniphila* though this review, which help us to learn its role in the microbial networks, as well as to understand its positive impacts on the health of animals and human.

KEYWORDS
*Akkermansia muciniphila*, intestinal bacterium, probiotics, *Verrucomicrobia*

1 | INTRODUCTION

A dense and diverse microbial community colonizes the human intestine, namely the microflora (10^{13}-10^{14}, about 1.3 times than the total number of human cells). Over 1000 microbes have been obtained by pure cultures, including *Bacteria*, *Archaea*, and *Eukarya*. They are the important players in human health and physiology with a great number of functions, such as the inhibition of pathogen, stimulation of immunity, digestion of unprocessed nutrients, and production of vitamins (e.g., Vitamin K). However, we have to face one problem that the intestinal microbiome and its metabolic functions are often impaired in many circumstances. In addition, many diseases are also associated with microbiota imbalance, such as type 2 or type 1 diabetes, obesity, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS) and so on (Derrien et al., 2017; Ouwerkerk et al., 2013; Ropot et al., 2020; Sender et al., 2016).

A growing amount of evidence have shown that probiotics are the strategy to maintain and improve intestinal homeostasis. But classical probiotics have shown the limited effects on the microbiota modulation in humans (El Hage et al., 2017). So, we need to develop new probiotic members that can cope with dysbiosis.

Maybe these aforementioned kinds of probiotics live in the intestine. A mucus layer (mainly composed of mucin) usually covers the intestinal epithelial cells (IECs), which can protect IECs from microbial invasion, and also provide growth energy for microbes as nutrients (Gao et al. 2013; Zhao & Li, 2017). The mucus-degrading *Akkermansia muciniphila* (AKK) are found to be enriched in the mucus layer, which implicates the colonization of the only known *Verrucomicrobia* in the gut. AKK is abundantly present in the colon, varying from 1% to 4% of the bacterial population (Ouwerkerk et al., 2013). In an investigation in southern China, AKK, colonized in intestinal samples of the different aged people, has a high colonization rate and over 12 different subtype strains (Guo et al., 2015). In recent decades, due to the significant role for hosts’ nutritional metabolism, diseases, and immunity, AKK related researches have become a hot spot in the domestic and foreign studies (Feng et al., 2016).

This review is devoted to the description of the current research on AKK, which is summarized into four aspects: AKK’s properties...
that include the physiological characteristics and genetic information, AKK’s functions and effects that may affect hosts’ health, factors that have a positive or negative effect on the abundance of AKK, and possibility that AKK becomes the commercial probiotic.

## 2 | AKK’S PROPERTIES

AKK, the only cultivated representative of the *Verrucomicrobia*, is an intestinal bacterium that was isolated from a human fecal sample through strict anaerobic condition in 2004, which was first identified and named by Wageningen University. Usually, AKK can utilize the viscous substrate as the sole source of nutrients for growth. AKK is Gram-negative, nonmotile, nonspore-forming, and elliptical, which can grow alone, in pairs, or in clumps (in the medium containing mucin). In strictly anaerobic circumstances, its main metabolite of that is propionic acid (Derrien et al., 2004; Zhao & Li, 2017). AKK’s growth relies on high-energy nitrogen-carbon compounds in mucin, such as fucose, galactose, N-acetylgalactosamine, and so on, but it still retains the ability to utilize glucose (Fenn, 2014; Ropot et al., 2020). Lipopolysaccharide (LPS) also exists in the outer membrane of AKK, which is considered to be a potential stimulation of inflammation, but AKK has not been found that there is a negative correlated to any sign of pathogenicity so far (Karls-son et al., 2012).

In 2011, genome sequence and functional gene information of AKK had been reported. In its genome of 2.66 M bp, the related genes encoding the mucin-degrading enzymes were more than 61, for 11% of the total genes. Some AKK strains’ whole genome, which were derived from human and mouse feces, included genome size ranging from 2.65 to 3.20 0 M bp and more than 2192 genes of ATCC BAA-835 (the AKK type strain) genome (Caputo et al., 2015; Guo et al., 2017). By proteomic analysis, a lot of mucin-degrading enzymes, such as glycosidase, sulfatase, and sialidase, were also found in human feces (Zhao & Li, 2017). Among them, four sialidase isoenzyme genes were cloned, expressed, and purified from human intestinal AKK (Huang, 2015; Huang et al., 2015). GH35 (one of glycoside hydrolase families) β-galactosidase gene from AKK was successfully cloned and its purified enzyme’s properties were clarified (Guo et al., 2018).

## 3 | FUNCTIONS AND EFFECTS OF AKK ON HOSTS

To better understand AKK’s properties, it is important to clarify the functions and effects of AKK. Numerous evidence have showed that AKK is closely related to the hosts’ immunity and diseases (Feng et al., 2016). Moreover, AKK is not only related to lipid metabolism and intestinal diseases, but also affects nervous system diseases, respiratory diseases, and so on (Table 1).

### 3.1 | Intestinal diseases

Ye’s (2009) study was the first to report an association of AKK with IBD. According to the author, the ratio of AKK/total bacteria was about 0.5% in healthy groups, and decreased in the IBD groups. And the population of AKK also decreased in colitis model. Earley et al. (2019) found that AKK abundance was reduced in ulcerative colitis, with lower percentage of sulphated mucin than healthy controls; AKK’s abundance was positively associated with the percentage of sulphated

| Target | Microbiota analysis approach | Samples | AKK population | References |
|--------|-----------------------------|---------|----------------|------------|
| IBD    | 16S rRNA gene sequence; qPCR | IL-10−/− mice | Negatively associated with IBD | Ye, 2009 |
| Colitis| qPCR                        | Healthy humans and patients | Reduced in ulcerative colitis | Earley et al., 2019 |
| Obese and overweight | qPCR | C57BL/6J mice; Healthy and obese children | Negatively associated with obese and overweight | Karlsson et al., 2012; Wang et al., 2020 |
| Autism | qPCR                        | Autistic and normal children | Negatively associated with autistic children | Wang et al., 2011 |
| Alzheimer | qPCR                  | patients | Accepted as a key bio-marker for Alzheimer’s disease | Ou et al., 2020 |
| Asthma | 16S rRNA gene sequence   | Obese asthmatics | Negative-correlated with asthma | Michalovich et al., 2019 |
| Alcoholic liver | –                    | Lieber-DeCarli mouse and patients | Negatively associated with Alcoholic liver | Neyrinck et al., 2017 |
| Type 2 diabetes | qPCR | C57BL/6 mice | Negatively associated with type 2 diabetes | Amandine, et al., 2017; Everard et al., 2013 |
| Type 1 diabetes | DGGE; 16S rRNA gene sequence | NOD/BomTac mice | Negatively associated with type 1 diabetes | Hansen et al., 2012 |
| Stress-related disorders | 16S rRNA gene sequence | C57BL/6J and CD-1 mice | Negatively associated with stress | McGaughey et al., 2019 |
mucin (\( \rho = 0.546, p = 0.000 \)) and inflammatory scores (\( \rho = 0.294, p = 0.001 \)).

3.2 | Lipid metabolism

Wang et al. (2020) evaluated whether alginate oligosaccharides can protect from diet-induced metabolic disorders and modulate gut microbial communities. According to the authors, alginate oligosaccharide intervention significantly prompted the growth of AKK under this premise that AKK was thought to be related to lipid metabolism. Being obese and overweight can also bring about dramatic changes in microbiota. In obese/overweight children, the abundance of the Gram-negative family (Enterobacteriaceae, Desulfovibrio, and AKK) showed significant differences. However, in children with normal weight, the abundance of AKK-like bacteria and Desulfovibrio did not show significant differences (Karlsson et al., 2012).

3.3 | Other intestinal microflora

AKK could accelerate the cogrowth of some mucus-dependent microorganisms, for example, Bacteroides vulgatus and Ruminococcus gnavus (Fenn, 2014). However, the mechanism through which AKK promotes the growth of other bacteria in hosts is still unknown.

3.4 | Autism

In the intestine of autistic children, the average abundance of AKK was \( 1.18 \times 10^5 \) CFU/g, respectively; which was significantly lower than those of normal children \( (1.51 \times 10^{14} \) CFU/g) (Wang et al., 2011).

3.5 | Alzheimer’s disease

Treated with AKK by gavage for 6 months, the test mice’s blood glucose, blood lipid, serum diamine oxidase levels were significantly reduced. Moreover, AKK treatment promoted the reduction of amyloid \( \beta \)-protein 40-42 levels, which was widely accepted as a key biomarker for Alzheimer’s disease (Qu et al., 2020).

3.6 | Asthma

According to Michalovich et al. (2019), asthma severity was significantly negatively correlated with AKK abundance. Meanwhile, AKK administration could significantly reduce airway hyperreactivity and airway inflammation in mice.

3.7 | Other diseases

AKK was associated with some chronic diseases, such as colitis (Seregín et al., 2017), alcoholic liver (Neyrinck et al., 2017), type 2 diabetes (Amandine et al., 2017; Everard et al., 2013b), type 1 diabetes (Hansen et al., 2012), stress-related disorders (McGaughey et al., 2019), and so on. Furthermore, it was found that AKK could modulate gut intestinal tumor development and microbiota composition in mice (Dingemanse et al., 2015). AKK could also activate the proliferation of intestinal cells and protect poultry from intestinal mucosal damage (Zhu et al., 2020).

4 | INFLUENCING FACTORS OF AKK ABUNDANCE

4.1 | Diet

Diet is one of the most direct and significant factors influencing intestinal microbiota in human and animals. High-fat intake damaged gut barrier integrity and increased translocation of proinflammatory gut bacteria; however, AKK administration restored gut barrier function and reduces endotoxemia (Underwood, 2014).

It was found that the high-fat diet-induced metabolic disorders (including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance) could be reversed by AKK treatment, while AKK abundance decreased in obese and type 2 diabetic mice model (Everard et al., 2013). Kefir could up-regulate AKK ratio and down-regulate Alistipes indistinctus of the hamster model (Gao et al., 2017). After drinking Pu-er tea for 4 weeks, the healthy young volunteers had four dominant microflora, namely, Firmicutes, Bacteroidetes, Proteobacteria, and Verrucomicrobia. Among them, the relative abundance of Verrucomicrobia changed significantly, with a trend of increasing first, then decreasing slightly, and increasing as a whole. The quantity of AKK increased significantly during the intervention of Pu-er tea (Gao, 2017). In the gut of Yukihikari (a Japanese rice) fed mice, AKK was associated with the intestinal barrier function and intestinal permeation of food antigens (Sonoyama et al., 2009).

4.2 | Antibiotic

Antibiotic treatment affects the composition of intestinal microflora. AKK abundance was fourfold lower in the subtherapeutic-antibiotic-treat than the control (Christine, 2014). AKK was sensible to doxycycline and imipenem, while resistant to vancomycin and metronidazole (Dubourg et al., 2013). AKK level in the vancomycin-treated mice was negatively related to NKG2D level, whereas AKK level was not increased in the ampicillin-treated mice (Hansen et al., 2013).

4.3 | Medicines

AKK abundance was higher in mice treated with metformin than the control, which suggested that the administration in favor of AKK may be a potential treatment for type 2 diabetes (Lee & Koa, 2014; Shin et al., 2014). In C57BL/6J mice with experimental autoimmune encephalomyelitis, the relative abundance of AKK decreased after
Omeprazole treatment (Sand et al., 2014). In Zucker (fa/fa) rats given pterostilbene for 6 weeks, the levels of Firmicutes phyla decreased and that of Verrucomicrobia phyla and AKK increased (Etzeberria et al., 2017).

### 4.4 Probiotics and prebiotics

*Lactobacillus casei* SY13 and lactulose had the remarkable effect on increasing the abundance of AKK in the intestine of mice; and the mice age and gavage-time could affect remarkably the abundance of AKK. At the same time, a long gavage-time could extend the retention time of AKK (Ti et al., 2018). After 135 obese participants consumed one capsule (10^{10} CFU) of *Bifidobacterium animalis* subsp. *lactis* for 3 months, AKK abundance was significantly increased ($p = 0.003$)(Pedret et al., 2018). In the rats inoculated long-chain arabinoxylans and inulin for 6 weeks, AKK abundance increased continuously in cecum, colon, and feces (Van den Abbeele et al., 2011). The microbiota including AKK were also altered by oligofructose intake during pregnancy and lactation (Paul et al., 2016).

### 4.5 Other natural products

Flaxseed diet altered the fecal microbial community structure, including a 30-fold reduction in AKK in face (Power et al., 2016). After 8-week-old C57BL/6 male mice were fed with fucoidans for 16 weeks, AKK was highly enriched (Shang et al., 2017). Similarly, the rhubarb extract altered the intestinal microbiota in favor of AKK (Neyrinck et al., 2017). Supplementation of culture broth with ellagic acid did not change AKK growth, while the addition of pomegranate extract altered the intestinal microbiota in favor of AKK (Neyrinck et al., 2017). After 135 obese participants consumed one capsule (10^{10} CFU) of *Bifidobacterium animalis* subsp. *lactis* for 3 months, AKK abundance was significantly increased ($p = 0.003$)(Pedret et al., 2018). In the rats inoculated long-chain arabinoxylans and inulin for 6 weeks, AKK abundance increased continuously in cecum, colon, and feces (Van den Abbeele et al., 2011). The microbiota including AKK were also altered by oligofructose intake during pregnancy and lactation (Paul et al., 2016).

### 4.6 Temperature

Cold exposure led to significant changes in the gut microbiota composition and reduced the quantity of AKK (Chevalier et al., 2015).

### 5 POSSIBILITY OF BECOMING COMMERCIAL PROBIOTICS AND CONCLUSION

The mucus layer, which covers the intestinal epithelial, can serve as an ecological niche for human intestinal bacteria, such as mucosa-associated bacteria—AKK. AKK, one novel candidate for promising next-generation probiotics, have been searched among the gut bacteria that are associated with health. AKK can be colonized in a wide range, with unrelated to the intestinal location, dietary, and mucin type (Ouwerkerk et al., 2013). However, if people want to use AKK for foods, dietary supplements, medical foods, and medical drugs, this will depend on demonstration of safety and efficacy for these uses within regulatory frameworks (Cani & Hul, 2015; Hill et al., 2014). For example, there exist four obvious problems: (1) To date, AKK available strains is too few, which include several cultures (such as DSM 22959, ATCCBAA-835T) in a majority of papers. (2) AKK’s mechanism is not completely clear. We have realized the relationship between AKK’s amounts and certain targets, but it is not sure what has happened between them. (3) At present, there are no appropriate application methods for AKK, such as fecal microbiota transplantation is not the reliable administration routes yet. (4) The effective dose of AKK required for treatment and probiotic-function to humans remains unknown.

In summary, as one of the potential functional probiotics, AKK has a profound impact on host immunity, metabolism, and disease, and shows good symbiotic characteristics. Therefore, there is no denying that AKK has a wide application prospect and market potential. Moreover, AKK’s inactivated cells or metabolites may exist the unpredictable value. The future work should focus on clarifying the safety and function of AKK to the human intestinal tract, and developing various means for regulating the quantity of AKK.

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### CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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