Research Article Open Access

Pasteurized *Akkermansia muciniphila* AKK ONE improves aging-related phenotypes and increases lifespan in zebrafish models

Yangwenshan Ou[1], Haotian Feng[2], and Nan Li[1]*

[1]Probiotics and Gut Health, Nutrition and Health, R&D, Sirio (Shanghai) Life Technologies Co., Ltd, Shanghai, 201703, China; [2]Nutrition and Health, R&D, Sirio Biotechnology (Shanghai) Co., Ltd, Shanghai, 200051, China

***Corresponding author:** Nan Li, PhD, Probiotics and Gut Health, Nutrition and Health, R&D, Sirio (Shanghai) Life Technologies Co., Ltd. 7F-8F, Building A2, No.99, Jiajie Road, Qingpu District, Shanghai, 201703, China

Submission Date: December 2nd, 2025; **Acceptance Date:** January 5th, 2026; **Publication Date:** December 12th, 2026

Please cite this article as: Ou Y., Feng H., Li N. Pasteurized Akkermansia muciniphila AKK ONE improves aging-related phenotypes and increases lifespan in zebrafish models. *Functional Foods in Health and Disease* 2026; 16(1): 29 – 41.
DOI: https://doi.org/10.31989/ffhd.v16i1.1848

ABSTRACT

Background: Aging is a biological process characterized by progressive compositional and functional alterations in the gut microbiota. *Akkermansia muciniphila*, a commensal bacterium of the human intestine, has been shown to confer significant metabolic and health benefits, particularly in the context of aging-associated physiological decline.

Objective: The primary objective of this study was to further evaluate the potential anti-aging effects of pasteurized *Akkermansia muciniphila* AKK ONE using aged zebrafish models.

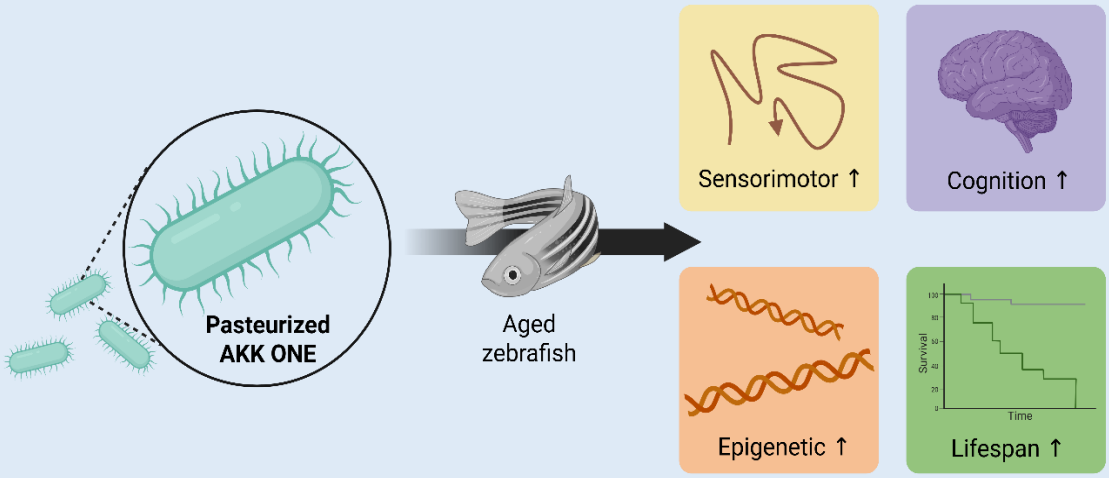
Methods: Three aging models were established in zebrafish through exposure to aluminum chloride hexahydrate, D-galactose, and hydrogen peroxide, respectively. Behavioral and physiological parameters were assessed, including light-dark transition time difference, total locomotor distance, movement distance within the blue region, telomere length, relative expression of the *spns1* gene, and survival rate.

Results: Administration of pasteurized AKK ONE significantly improved mobility as indicated by enhanced light-dark transition time difference and increased total moving distance. Additionally, after pasteurized AKK ONE treatment, the moving distance in the blue region of aged zebrafish rose compared to that of the normal control group, showing substantial improvements in learning and memory. At the epigenetic level, both telomere length and the relative

expression of the spns1 gene were significantly improved after administration of pasteurized AKK ONE. Noteworthy is the increased survival rate in the pasteurized AKK ONE group.

Conclusions: Pasteurized AKK ONE effectively ameliorated aging-related phenotypes in aspects of mobility, cognition, and epigenetics, and remarkably increased lifespan in aged zebrafish models.

Keywords: pasteurized *Akkermansia muciniphila* AKK ONE, zebrafish, lifespan, aging, mobility, cognition, telomere, *spns1* gene.



Graphical Abstract: Pasteurized Akkermansia muciniphila AKK ONE improves aging-related phenotypes and increases lifespan in zebrafish models

INTRODUCTION

The gastrointestinal (GI) tract of vertebrates is a highly dynamic and complex ecosystem harboring a vast and diverse microbial community. Among these microorganisms, bacteria reaching densities of up to 10^{14} CFU/g wet feces in humans have been the most widely explored. While the majority of gut bacteria reside freely in the intestinal lumen, only a limited subset colonizes the mucus layer of the GI tract and can utilize mucin as its sole carbon and nitrogen source [1]. The mucus layer, which lies in close proximity to the intestinal epithelial cells, serves as a critical protective barrier that shields the host from microbial invasion and from potentially harmful gut-derived metabolites [1]. Given its strategic location and protective function, the mucus layer plays a pivotal role in maintaining intestinal homeostasis.

Although important, Akkermansia muciniphila is one of the few bacteria that thrive in the mucus layer. This decides the critical role of *Akkermansia muciniphila* in the host-microbe interactions. *Akkermansia muciniphila* has been the most widely studied in metabolic diseases, e.g., obesity and diabetes, and has shown promising effects on weight gain, lipid levels, energy expenditure, GLP-1 regulation, glucose intolerance, and insulin sensitivity [2–9]. Interestingly, pasteurized *Akkermansia muciniphila* showed similar or even more notable improvements in overweight- and obesity-related outcomes compared with viable

Akkermansia muciniphila [2].

Metabolic dysbiosis is linked to the aging process, and therefore, Akkermansia muciniphila might be an interesting target for senile resistance. This hypothesis is further supported by a review that found elevated levels of *Akkermansia* in healthy centenarians [10]. Belzer et al. used accelerated aging Ercc1$^{-/\Delta 7}$ mice orally supplemented with *Akkermansia muciniphila* for ten weeks (2×10^8 CFU/time, three times per week) and found that such long-term *Akkermansia* intervention substantially rescued the colonic mucus layer by increasing its thickness about 3-fold [11]. Additionally, Chen et al. observed a relation between depleted *Akkermansia muciniphila* and impaired plasma L-arginine metabolic homeostasis in mice [12]. Supplementing the outer membrane protein Amuc_1100 for six months restored L-arginine dysbiosis and further rehabilitated the cognitive lesion in aging mice [12]. Notably, a modest lifespan extension was observed in progeroid mice after oral supplementation with Akkermansia muciniphila (2×108 CFU/time, three times per week) starting at 12 weeks of age and continuing until death [13], providing direct anti-aging evidence for Akkermansia muciniphila.

Akkermansia muciniphila AKK ONE, first isolated from a healthy Chinese athlete, has been investigated for its therapeutic potential in both dextran sulfate sodium DSS-induced ulcerative colitis and high-fat diet-induced hypercholesterolemia mouse models [14, 15]. In colitic mice, AKK ONE effectively restored intestinal barrier integrity by upregulating the relative expression of tight junction proteins and significantly reducing pro-inflammatory cytokine levels [14]. Furthermore, in hypercholesterolemic mice, oral administration of AKK ONE markedly decreased plasma total cholesterol, triglycerides, and low-density lipoprotein cholesterol, while simultaneously modulating the composition of the gut microbiota [15]. Given that chronic inflammation and gut microbiota dysbiosis are recognized as two of the fourteen major hallmarks of aging [16], these findings suggest that AKK ONE may confer potential anti-aging benefits to the host.

However, the anti-aging mechanisms of AKK ONE remain insufficiently characterized. Therefore, the present study aims to elucidate the effects of pasteurized AKK ONE on mobility, cognitive performance, epigenetic markers, and survival rates in aged zebrafish models.

MATERIALS AND METHODS

Zebrafish: Zebrafish (Danio rerio) were selected as the experimental model due to their high degree of genetic, anatomical, and physiological similarity to humans. Approximately 70% of human genes have at least one ortholog in the zebrafish genome, a level of conservation comparable to that observed between humans and mice (approximately 80%) [17]. In addition to genetic homology, zebrafish share key anatomical, histological, and physiological features with humans, particularly in the nervous, metabolic, and gastrointestinal systems. These characteristics, together with their rapid development, transparency during early life stages, cost-effectiveness, and suitability for large-scale experimentation, make zebrafish an established and powerful model organism. Consequently, zebrafish are widely used to investigate developmental, mental, neurological, and metabolic disorders, as well as to study systemic interactions between the brain and peripheral organs, including aging-related processes [17–20].

Zebrafish (wild type; AB strain) used in this study were housed in water at 28℃ with conductivities between 450 and 550 μS/cm, pH between 6.5 and 8.5, and water hardness ranging from 50 to 100 mg/L $CaCO_3$, which met the criteria of AAALAC (No. 001458). The study was performed under animal experiment license SYXK (ZHE) 2022-0004. The ethics approval No. of the

Institutional Animal Care and Use Committee is IACUC-2025-11816-01.

The preparation of AKK ONE: *Akkermansia muciniphila* AKK ONE was cultivated as previously described [14]. After harvest, AKK ONE was pasteurized at 80°C for 30 min before freeze-drying. Freeze-dried AKK ONE (2000 colony-forming units/g) was then stored at room temperature before use.

Determining maximum tolerated concentrations (MTCs) of AKK ONE: Mortality assays were conducted to determine the maximum tolerated concentration (MTC) of pasteurized AKK ONE. The MTC was defined as the highest administered dose resulting in a mortality rate of no more than 5%, as previously established [21]. Only concentrations equal to or below the MTC were used in subsequent experiments. In detail, five different doses (i.e., 125, 250, 500, 1000, and 2000 μg/mL) of AKK ONE were assessed in MTC tests. Thirty zebrafish were contained in each group and were treated with different concentrations of AKK ONE.

$AlCl_3$-treated zebrafish model with mobility impairments: $AlCl_3$ was used to induce motility impairments, as described previously [22]. Zebrafish aged 4-day post-fertilization (dpf) was divided into 6 groups (N=30/group), including normal control (without $AlCl_3$ treatment and without any interventions), model control (with $AlCl_3$ but without any interventions), positive control (with $AlCl_3$ and with donepezil hydrochloride intervention at 3.33 μg/mL; donepezil hydrochloride is an acetylcholinesterase inhibitor primarily used in treating Alzheimer disease), AKK ONE groups (with $AlCl_3$ and with AKK ONE intervention at suitable concentrations as suggested by MTC tests). Zebrafish were simultaneously treated with $AlCl_3$, donepezil hydrochloride, and AKK ONE for 1 day. Ten zebrafish in each group were randomly selected for the light-transition time difference test, and another 10 zebrafish in each group were randomly chosen for the total moving distance test in 30 min, which was measured by the zebrafish behavior system (Zebra Lab 3.22.3.31, Viewpoint, France).

D-galactose-treated zebrafish model with cognitive impairments: Zebrafish aged 3 dpf were divided into 6 groups as described (N=30/group). Instead of using $AlCl_3$, D-galactose (CAS 59-23-4, Aladdin) was used, along with stirring, to induce cognitive impairments [23]. Zebrafish were treated with D-galactose, 200 μg/mL of ginseng (used as a positive control), and AKK ONE for consecutive 2 days. Six zebrafish in each group were randomly selected for the blue region test (zebrafish prefer the blue region as previously reported [24]). In detail, the zebrafish was placed in the middle of 4 regions named yellow, red, green, and blue, respectively. The distance traveled in these 4 regions was recorded, and the percentage of the distance in the blue region was analyzed.

H_2O_2-treated zebrafish model with epigenetic impairments and shortened lifespan: Zebrafish at 6 hours post-fertilization (hpf) were randomly assigned to six experimental groups, as previously delineated. Hydrogen peroxide (H_2O_2) was used to induce oxidative stress, resulting in aging-related phenotypes, including epigenetic impairments (including telomere length and relative expression of *spns1* gene) and reduced lifespan [25]. Resveratrol (CAS 501-36-0, Macklin) at a concentration of 10 μg/mL served as the positive control.

Telomere length and relative expression of *the spns1 gene were measured daily for consecutive 6 days, in triplicate with N=30* zebrafish in each group. A

universal genomic DNA extraction kit (Lot No. 2ZAP14, KeFeiTe) and a universal RNA extraction kit (Lot No. TL643-03C, Onrew) were used to isolate total DNA and RNA of zebrafish, respectively. The concentration and purity of DNA and RNA were determined by a UV-visible spectrophotometer (Nanodrop2000, Thermo).

Telomere length was measured and presented as telomere-to-single *dio2* copy gene (T/S) ratio. Primer sequences (1) *dio2* gene, forward 5'-TGGCTTCTTCTCCAACTGCC-3', reverse 5'-GAGCAGCTTCGCCCAATTTC-3' (2) *telo* gene, forward 5'-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3, reverse 5'-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3.

A FastKing cDNA kit (Lot No. X1213, TIANGEN) was used to generate 20 µL cDNA from 2 µg RNA, before measuring the relative expression of the *spns1* gene to the reference *β-actin* gene. Primer sequences (1) *spns1* gene, forward 5'-TGCACGGTTCGATTCAAGTCT-3', reverse 5'-GACATCACTGCTGGAAAATGC-3' (2) *β-actin*, forward 5'-TCGAGCAGGAGATGGGAACC-3', reverse 5'-CTCGTGGATACCGCAAGATTC-3'.

As for lifespan, we measured the survival rates of zebrafish aged between 0 and 14 dpf.

Statistical analyses: Data analyses and visualization were performed in GraphPad Prism 8.0.2, using Wilcoxon tests to compare groups, with $p<0.05$ indicating statistical significance.

RESULTS

MTCs of AKK ONE in aged zebrafish model: MTCs of AKK ONE were 2000, 250, and 1000 µg/mL in $AlCl_3$, D-galactose, and H_2O_2-treated models, respectively (Table 1). The MTC was lowest under D-galactose treatment, likely due to stirring in this model. Based on MTCs, we selected 250, 500, and 1000 µg/mL of AKK ONE for the AlCl3 and H2O2 models, and 62.5, 125, and 250 µg/mL for the D-galactose model in the following experiments.

Table 1. MTCs in aged zebrafish models.

$AlCl_3$ model		**D-galactose model**		**H_2O_2 model**	
Group	**Mortality rates**	**Group**	**Mortality rates**	**Group**	**Mortality rates**
Normal control	**0% (0/30)**	**Normal control**	**0% (0/30)**	**Normal control**	**0% (0/30)**
$AlCl_3$	0% (0/30)	D-galactose	0% (0/30)	H_2O_2	0% (0/30)
125	0% (0/30)	125	0% (0/30)	125	0% (0/30)
250	0% (0/30)	250	0% (0/30)	250	0% (0/30)
500	0% (0/30)	500	100% (30/30)	500	0% (0/30)
1000	0% (0/30)	1000	100% (30/30)	1000	0% (0/30)
2000	0% (0/30)	2000	100% (30/30)	2000	100% (30/30)

AKK ONE improved mobility phenotypes of aged zebrafish: Pasteurized AKK ONE (i.e., 250, 500, and 1000 µg/mL) significantly increased the light-dark transition time difference and total moving dance in AlCl3-treated models (Figure 1), suggesting improvements in mobility phenotypes of aged zebrafish. Notably, AKK ONE at a concentration of 1000 µg/mL restored both the light-dark transition time difference and the total moving distance to normal levels, whereas this was not observed at the other two concentrations. Moreover, effectiveness was comparable between AKK ONE and the positive control using donepezil hydrochloride.

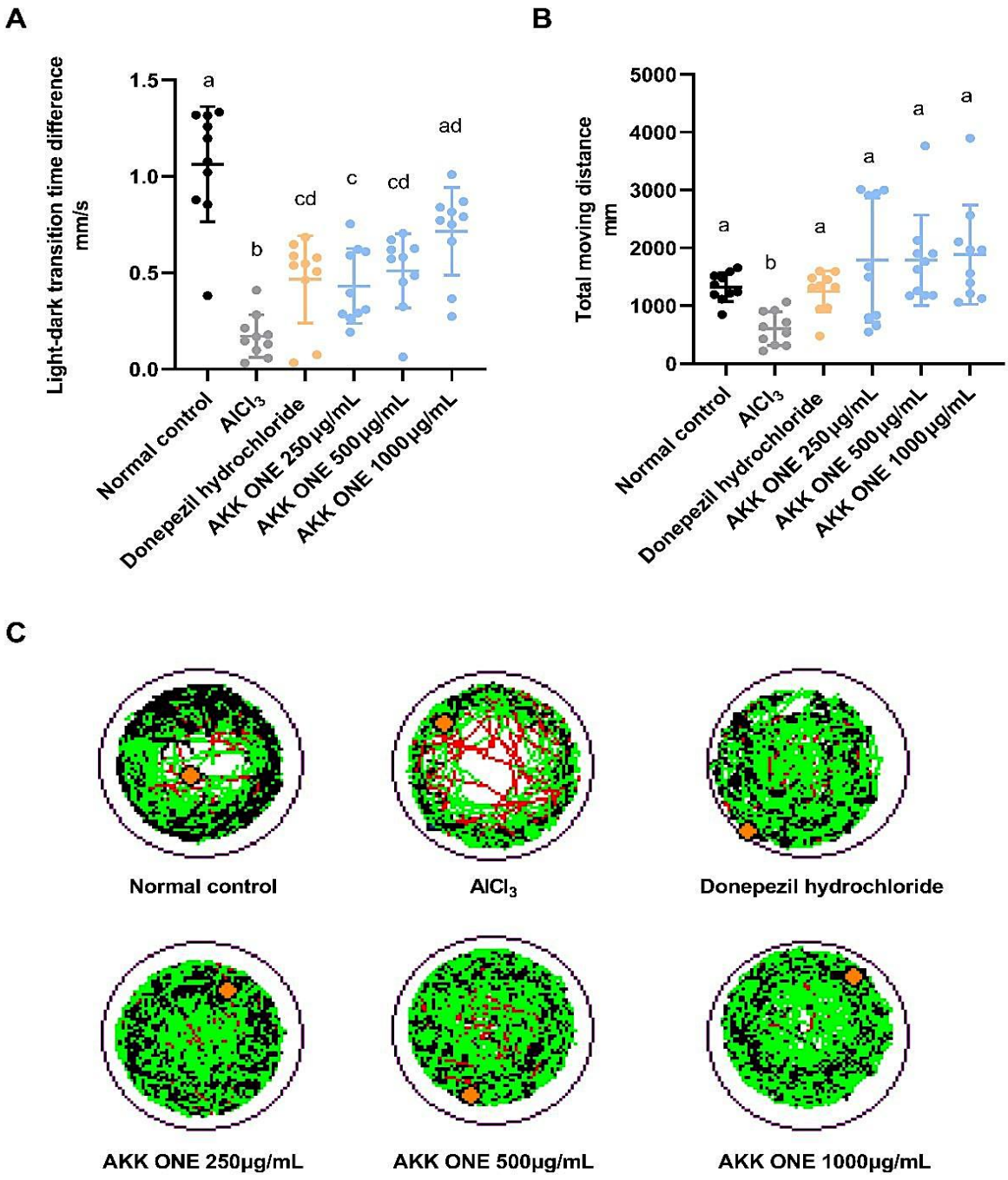


Figure 1. Mobility phenotypes of aged zebrafish. A, light-dark transition time difference. B, total moving distance in 30 min. C, the moving trajectory in 30 min. Ten zebrafish in each group were randomly selected for the light-transition time difference test, and another 10 zebrafish in each group were randomly chosen to test the total moving distance in 30 min. Different letters indicate statistical significance between groups.

AKK ONE improved cognitive phenotype of aged zebrafish: Only the highest dose of pasteurized AKK ONE (250 μg/mL), as well as the positive control of using ginseng, significantly restored the percent of moving distance in the blue region (Figure 2). No differences in the percent of moving distance in the blue region were observed among the AKK ONE (250 μg/mL), the ginseng group, and the normal control.

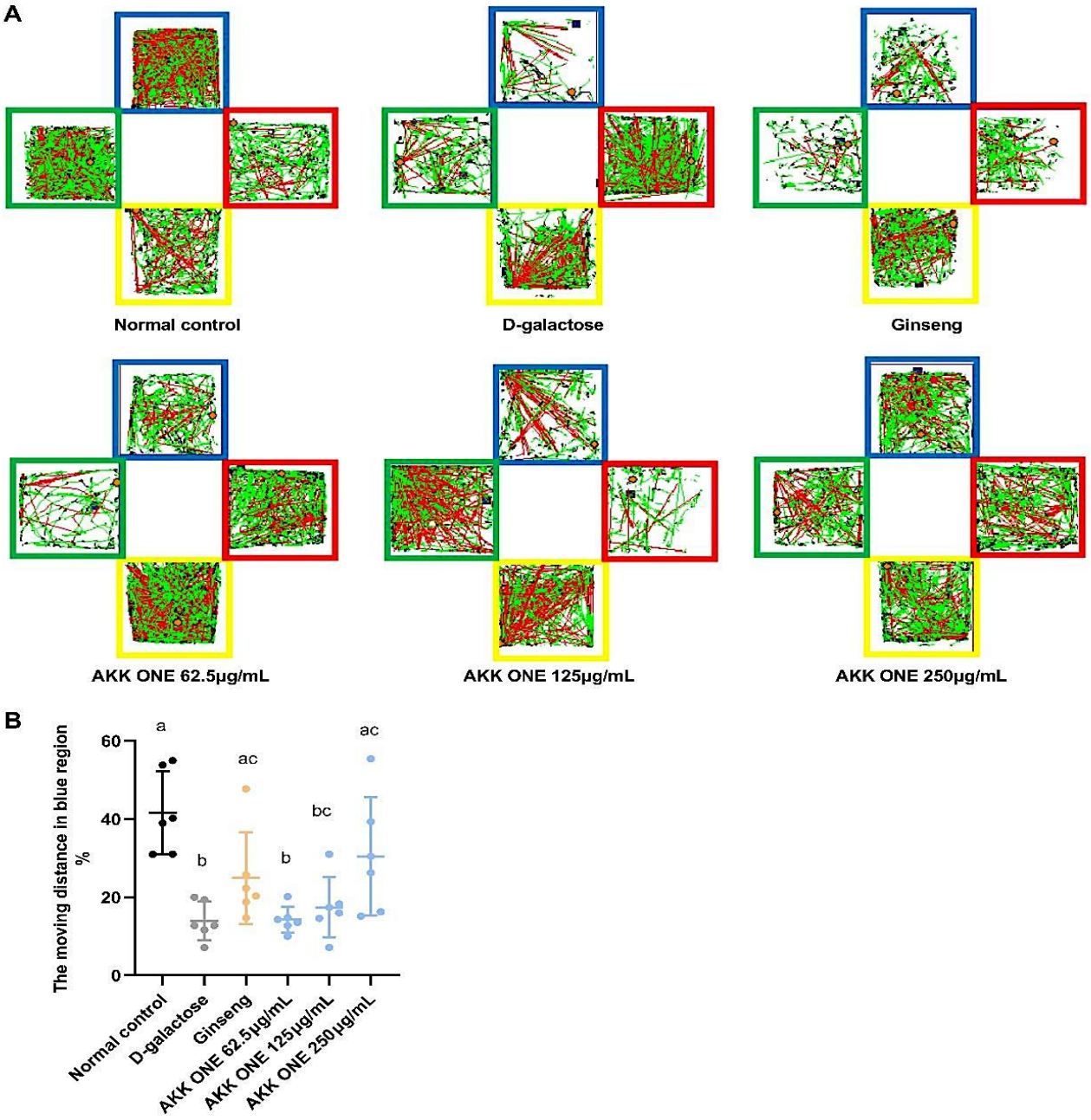


Figure 2. Cognitive phenotype of aged zebrafish. A, the moving trajectory in yellow, red, green, and blue regions. B, the percentage of moving distance in the blue region. Six of the 30 zebrafish in each group were randomly selected for the test. Different letters indicate statistical significance between groups.

AKK ONE improved epigenetic phenotypes of aged zebrafish: Pasteurized AKK ONE at both concentrations of 500 and 1000 μg/mL significantly recovered the telomere length to a normal level, while neither the lowest level of AKK ONE (250 μg/mL) nor resveratrol exhibited improvements on telomere length (Figure 3A). As for the relative expression of the *spns1* gene, an enhanced outcome was observed only at the highest AKK ONE level (1000 μg/mL; Figure 3B).

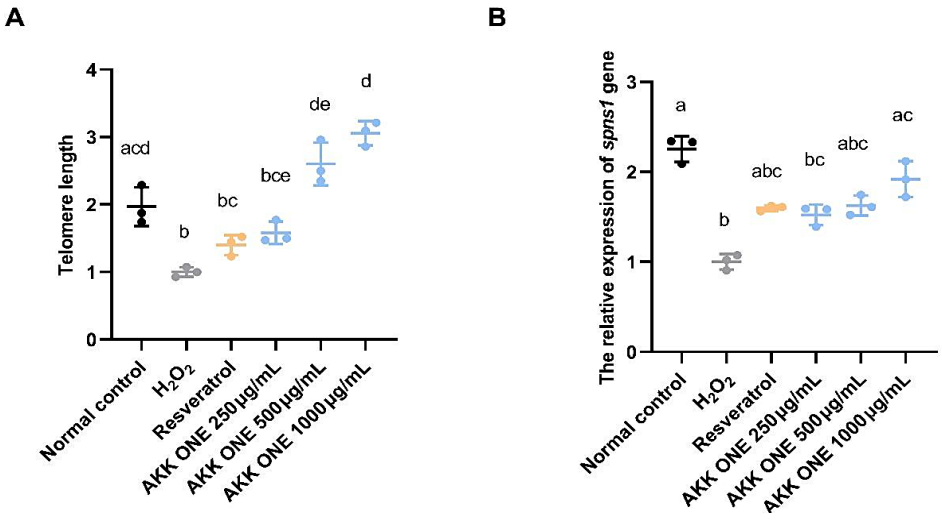


Figure 3. Epigenetic phenotype of aged zebrafish. A, telomere length. B, the relative expression of the spns1 gene. These two tests were performed in triplicate, with N=30 zebrafish per group each time. Each dot represents the result in one of the triplicates. Different letters indicate statistical significance between groups.

AKK ONE increased lifespan in aged zebrafish: All three studied levels of pasteurized AKK ONE (i.e., 250, 500, and 1000 μg/mL) significantly increased the survival rates of zebrafish at the age of 14 dpf after H_2O_2 treatment (Figure 4). Remarkably, AKK ONE at a concentration of 1000 μg/mL showed approximately a 50% increase in survival rate at 14 dpf compared with the H_2O_2 control.

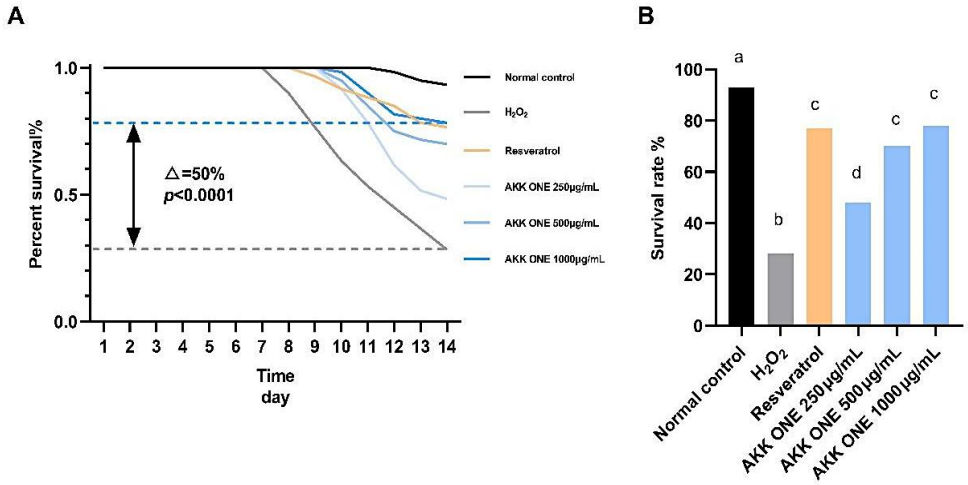


Figure 4. Survival curves of aged zebrafish. A percent survival rate from the age of 0 to 14 dpf. B, Survival rates of zebrafish at the age of 14 dpf. Each group consisted of 60 zebrafish. Different letters indicate statistical significance between groups.

DISCUSSION

The present study provides insight into the anti-aging effects of the next-generation probiotic *Akkermansia muciniphila* AKK ONE in zebrafish models. $AlCl_3$, D-galactose, and H_2O_2 caused aging phenotypes in mobility, cognition, and epigenetics, and shortened the lifespan of zebrafish, whereas pasteurized AKK ONE significantly restored these aging hallmarks. In detail, AKK ONE increased the light-dark transition time difference, total moving distance, the percentage of moving distance in the blue region, telomere length, the relative expression of the spns1 gene, and survival rates, suggesting a

promising strategy for using AKK ONE as an anti-aging biological therapy in dietary supplements. Importantly, this research aligns with steps 1 to 3 of a comprehensive 17-step process proposed by the Functional Food Center for the clear definition and categorization of functional foods. Specifically, step 1 defines the anti-aging goal of pasteurized AKK ONE, step 2 determines its anti-aging effects, and step 3 establishes the effective dose of pasteurized AKK ONE [26].

In parallel with previous research that used Akkermansia muciniphila or its metabolites as interventions [11–13, 27], this study demonstrated general benefits of an Akkermansia muciniphila strain, AKK ONE, in improving aging phenotypes in zebrafish. However, direct comparisons between studies were largely limited because most relevant studies were performed in mice [11–13]. Regardless of the use of different animal models, progeroid mice receiving oral gavage of *Akkermansia muciniphila* exhibited a modest 5% extension of lifespan [13], which is in line with our findings of an increased survival rate in H_2O_2-treated zebrafish with AKK ONE intervention. Such improvements in lifespan in aging-accelerated mice were accompanied by a significantly thicker gut mucus layer, suggesting an enhanced mucosal barrier function [11, 13].

In addition to extending lifespan, *Akkermansia muciniphila* and its outer membrane proteins may also benefit learning and memory ability. As a highly abundant outer membrane protein of *Akkermansia muciniphila*, Amuc_1100 exhibited resistance to pasteurization temperature [28]. Earlier findings show its role in improving metabolic diseases [28], while recent evidence supports its ability to regulate tryptophan metabolism and emotional and behavioral outcomes [29–32]. Supplementing naturally aged mice with Amuc_1100 significantly reduced latency to the target, indicating ameliorations on cognitive decline and impairment [12]. Similarly, in our study, we observed improved cognitive function, as indicated by a higher percentage of movement in the blue region. This was consistent with the results reported by Qu et al., who found that Akkermansia muciniphila increased total moving distance and decreased latency time, as measured by the T test, in aged zebrafish [27]. In terms of cognitive capacity, our study also found improved sensory and motor skills following AKK ONE administration.

Anti-aging effects of AKK ONE may be attributed to restored telomere length and elevated spns1 gene expression, both of which were observed in our study. It has been well accepted that lengthening telomeres and activating telomerase (i.e., a nuclear enzyme that maintains telomere length) improve metabolic health, preserve neuronal survival and cognitive function, and therefore extend lifespan and delay aging [33]. Spns1, encoded by the spns1 gene, is a lysosomal transporter that regulates the efflux of lysophospholipids (i.e., a bioactive lipid mediator responsible for cell signaling, growth, and migration) from the lysosome to the cytosol [34, 35]. Lysosomal dysfunction is strongly associated with cellular senescence and the loss of regenerative ability in stem cells, especially in neural stem cells [36, 37]. Activating lysosomal functions assisted neural stem cells in clearing unwilling aging-related protein aggregates and reaching a more youthful state [37].

Although the exploration of *Akkermansia muciniphila* in aging is still in its early stages, some pilot studies have pointed to potential mechanisms by which *Akkermansia muciniphila*-derived products interact with host immune signals [2]. For example, a novel tripeptide composed of arginine, lysine, and histidine, which is present in the cell membrane of *Akkermansia muciniphila*, has been shown to activate Toll-like receptor 4 (TLR4), thereby regulating inflammatory responses [38]. Additionally, ornithine lipids have been found to increase interleukin-10 (IL-10) production,

which may contribute to anti-inflammatory effects [39]. Furthermore, aminoacyl tRNA synthetases (AmTARS) have been shown to promote IL-10 upregulation by activating TLR2 [40]. These findings highlight the complex interplay between *Akkermansia muciniphila* and host immune signaling, though further research is needed to fully understand their implications in the context of aging.

Several limitations of the present study should be acknowledged:

(1) Rather than using $AlCl_3$, D-galactose, or H_2O_2 to trigger an aged model, a naturally aged model is preferred.

(2) Exploring the gut barrier and intestinal tight junctions may support a better understanding of AKK ONE on its potential anti-aging effects.

(3) Further analysis of spns1 and lysosomal functions might provide insight into novel mechanisms of AKK ONE in mitigating neuronal aging.

(4) Despite the widespread use of zebrafish models in exploring human diseases and disorders, it is important to recognize the limitations of zebrafish as a model organism. These limitations include genomic duplications, which may limit the accuracy of disease and disorder modeling; the absence of sex chromosomes, which can hinder studies of sex-specific traits; and difficulties in translating dosages between zebrafish and humans.

(5) When formulating a mature anti-aging dietary supplement, it is crucial to consider the potential synergistic effects of AKK ONE with other anti-aging herbal extracts, such as *Panax ginseng*, *Ganoderma lucidum*, and *Polygonati rhizome*, as well as minerals known for their anti-aging benefits, as previously reported [41–45].

Supplementation with pasteurized AKK ONE improved aging phenotypes in mobility, cognition, and epigenetics, and lengthened lifespan in AlCl3-, D-galactose-, or H2O2-induced aged zebrafish models. These findings suggest that pasteurized AKK ONE is a promising anti-aging biological therapy that can be further used in dietary supplements.

CONCLUSIONS

Supplementation with pasteurized *Akkermansia muciniphila* AKK ONE in aged zebrafish significantly improved multiple aging-related phenotypes, including enhanced functional mobility, improved cognitive performance, restored telomere length, normalized *spns1* expression, and notably increased survival rates, indicating an extension of lifespan. These results highlight the potential of pasteurized AKK ONE as a functional ingredient for the development of novel anti-aging dietary supplements. Nevertheless, carefully designed preclinical studies and clinical trials are required to further validate its efficacy, safety, and underlying mechanisms of action.

Abbreviations: GI, gastrointestinal; AKK ONE, *Akkermansia muciniphila* AKK ONE; MTC, maximum tolerated concentration; dpf, day post-fertilization; hpf, hour post-fertilization; IL-10, interleukin-10; AmTARS, aminoacyl tRNA synthetases.

Authors' Contributions: Y.O. and N.L. designed the study. Y.O. conducted the experiment, analyzed the data, and wrote the manuscript. All authors revised the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Acknowledgment and Funding: This work was financially supported by the National Key Research and Development Program of China (No. 2022YFF1100105).

REFERENCES

1. Luis AS, Hansson GC: Intestinal mucus and their glycans: A habitat for thriving microbiota. Cell Host & Microbe 2023. 31(7):1087–1100. DOI: https://doi.org/10.1016/j.chom.2023.05.026
2. Ioannou A, Berkhout MD, Geerlings SY, Belzer C: Akkermansia muciniphila: biology, microbial ecology, host interactions and therapeutic potential. Nature Reviews Microbiology 2025. 23(3):162–177. DOI: https://doi.org/10.1038/s41579-024-01106-1
3. Liu E, Ji X, Zhou K: Akkermansia muciniphila for the Prevention of Type 2 Diabetes and Obesity: A Meta-Analysis of Animal Studies. Nutrients 2024. 16(20):3440. DOI: https://doi.org/10.3390/nu16203440
4. Roshanravan N, Bastani S, Tutunchi H, Kafil B, Nikpayam O, Mesri Alamdari N, et al. A comprehensive systematic review of the effectiveness of Akkermansia muciniphila, a member of the gut microbiome, for the management of obesity and associated metabolic disorders. Archives of Physiology and Biochemistry 2023. 129(3):741–751.
5. Gofron K, Berezowski A, Gofron M, Borówka M, Dziedzic M, Kazimierczak W, et al. : Akkermansia muciniphila - impact on the cardiovascular risk, the intestine inflammation and obesity. Acta Biochimica Polonica 2024. 71:13550. DOI: https://doi.org/10.3389/abp.2024.13550
6. Zhang Y, Liu R, Chen Y, Cao Z, Liu C, Bao R, et al.: Akkermansia muciniphila supplementation in patients with overweight/obese type 2 diabetes: Efficacy depends on its baseline levels in the gut. Cell Metabolism 2025. 37(3):592-605.e6. DOI: https://doi.org/10.1016/j.cmet.2024.12.010
7. Liu Z, Chen M, Zheng W, Zhan X, Sui W, Huang H, et al. Effect of gut symbiotic bacteria Akkermansia muciniphila on aging-related obesity. Biochemical and Biophysical Research Communications 2025. 756:151606.
8. Vallianou NG, Kounatidis D, Tsilingiris D, Panagopoulos F, Christodoulatos GS, Evangelopoulos A, et al.: The role of next-generation probiotics in obesity and obesity-associated disorders: current knowledge and future perspectives. International journal of molecular sciences 2023. 24(7):6755.
9. Niu H, Zhou M, Zogona D, Xing Z, Wu T, Chen R, et al.: Akkermansia muciniphila: a potential candidate for ameliorating metabolic diseases. Frontiers in Immunology 2024. 15:1370658. DOI: https://doi.org/10.3389/fimmu.2024.1370658
10. Lozada-Martinez ID, Lozada-Martinez LM, Anaya J: Gut microbiota in centenarians: A potential metabolic and aging regulator in the study of extreme longevity. AGING MEDICINE 2024. 7(3):406–413. DOI: https://doi.org/10.1002/agm2.12336
11. Van Der Lugt B, Van Beek AA, Aalvink S, Meijer B, Sovran B, Vermeij WP, et al.: Akkermansia muciniphila ameliorates the age-related decline in colonic mucus thickness and attenuates immune activation in accelerated aging Ercc1−/Δ7 mice. Immunity & Ageing 2019. 16(1):6. DOI: https://doi.org/10.1186/s12979-019-0145-z
12. He J, Hou T, Wang Q, Wang Q, Jiang Y, Chen L, et al.: L-arginine metabolism ameliorates age-related cognitive impairment by Amuc_1100-mediated gut homeostasis maintaining. Aging Cell 2024. 23(4): e14081. DOI: https://doi.org/10.1111/acel.14081
13. Bárcena C, Valdés-Mas R, Mayoral P, Garabaya C, Durand S, Rodríguez F, et al.: Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. Nature Medicine 2019. 25(8):1234–1242. DOI: https://doi.org/10.1038/s41591-019-0504-5
14. Zhang H, Pan Y, Jiang Y, Chen M, Ma X, Yu X, et al.: Akkermansia muciniphila ONE effectively ameliorates dextran sulfate sodium (DSS)-induced ulcerative colitis in mice. npj Science of Food 2024. 8(1):97. DOI: https://doi.org/10.1038/s41538-024-00339-x
15. Li Y, Zhang H, Ma X, Yu X, Ren D: Alleviating effect of Akkermansia muciniphila ONE on hypercholesterolemia in mice. FOOD SCIENCE 2024. 45(19):65–76. DOI: https://doi.org/10.7506/spkx1002-6630-20240312-077
16. Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, et al.: From geroscience to precision geromedicine: Understanding and managing aging. Cell 2025. 188(8):2043–2062. DOI: https://doi.org/10.1016/j.cell.2025.03.011
17. Adhish M, Manjubala I: Effectiveness of zebrafish models in understanding human diseases—A review of models. Heliyon 2023. 9(3):e14557. DOI: https://doi.org/10.1016/j.heliyon.2023.e14557
18. Don DW, Choi T-I, Kim T-Y, Lee K-H, Lee Y, Kim C-H: Using zebrafish as an animal model for studying rare neurological disorders: A human genetics perspective. Journal of Genetic Medicine 2024. 21(1):6–13. DOI: https://doi.org/10.5734/JGM.2024.21.1.6
19. Aranda-Martínez P, Sayed RKA, Fernández-Martínez J, Ramírez-Casas Y, Yang Y, Escames G, et al.: Zebrafish as a

Human Muscle Model for Studying Age-Dependent Sarcopenia and Frailty. International Journal of Molecular Sciences 2024. 25(11):6166. DOI: https://doi.org/10.3390/ijms25116166

20. Angom RS, Nakka NMR: Zebrafish as a Model for Cardiovascular and Metabolic Disease: The Future of Precision Medicine. Biomedicines 2024. 12(3):693. DOI: https://doi.org/10.3390/biomedicines12030693
21. Ou Y, Zhang W, Lan J, Huang X, Li N: A combination of multi-strain probiotics, prebiotic, and plant extracts improves ethanol-induced hangover outcomes in a zebrafish model. Functional Foods in Health and Disease 2024. 14(10):728–738. DOI: https://doi.org/10.31989/ffhd.v14i10.1462
22. Chen H, Li H, Yin X, Liu Y, Zhang T, Wu H, et al.: The therapeutic effect of Zhenbao pills on behavioral changes in zebrafish caused by aluminum chloride. Biomedicine & Pharmacotherapy 2023. 160:114399. DOI: https://doi.org/10.1016/j.biopha.2023.114399
23. Luo L, Yan T, Yang L, Zhao M: Aluminum chloride and D-galactose induced a zebrafish model of Alzheimer's disease with cognitive deficits and aging. Computational and Structural Biotechnology Journal 2024. 23:2230–2239. DOI: https://doi.org/10.1016/j.csbj.2024.05.036
24. Hagen EV, Zhang Y, Hamilton TJ: Innate colour preference in zebrafish (Danio rerio). MethodsX 2023. 11:102342. DOI: https://doi.org/10.1016/j.mex.2023.102342
25. Xia H, Cheng X, Cao M, Sun X, He F, Yao X, et al.: Tetrahydroxystilbene Glucoside Attenuates Oxidative Stress-Induced Aging by Regulating Oxidation Resistance and Inflammation in Larval Zebrafish. Zebrafish 2023. 20(2):55–66. DOI: https://doi.org/10.1089/zeb.2022.0045
26. Stratton S, Martirosyan D: Comparing the FDA's process for health claim submission and the FFC's guidelines for regulating functional foods. Functional Foods in Health and Disease 2023. 13(9) DOI: https://doi.org/10.31989/ffhd.v13i9.1228
27. Qu L, Liu F, Fang Y, Wang L, Chen H, Yang Q, et al.: Improvement in Zebrafish with Diabetes and Alzheimer's Disease Treated with Pasteurized Akkermansia muciniphila. Microbiology Spectrum 2023. 11(3):e00849-23. DOI: https://doi.org/10.1128/spectrum.00849-23
28. Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L, et al.: A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nature Medicine 2017. 23(1):107–113. DOI: https://doi.org/10.1038/nm.4236
29. Gu Z, Pei W, Shen Y, Wang L, Zhu J, Zhang Y, et al.: Akkermansia muciniphila and its outer protein Amuc_1100 regulates tryptophan metabolism in colitis. Food & Function 2021. 12(20):10184–10195. DOI: https://doi.org/10.1039/D1FO02172A
30. Cheng R, Zhu H, Sun Y, Hang T, Zhang M: The modified outer membrane protein Amuc_1100 of Akkermansia muciniphila improves chronic stress-induced anxiety and depression-like behavior in mice. Food & Function 2022. 13(20):10748–10758. DOI: https://doi.org/10.1039/D2FO01198K
31. Cheng R, Xu W, Wang J, Tang Z, Zhang M: The outer membrane protein Amuc_1100 of Akkermansia muciniphila alleviates the depression-like behavior of depressed mice induced by chronic stress. Biochemical and Biophysical Research Communications 2021. 566:170–176. DOI: https://doi.org/10.1016/j.bbrc.2021.06.018
32. Wang J, Xu W, Wang R, Cheng R, Tang Z, Zhang M: The outer membrane protein Amuc_1100 of Akkermansia muciniphila promotes intestinal 5-HT biosynthesis and extracellular availability through TLR2 signalling. Food & Function 2021. 12(8):3597–3610. DOI: https://doi.org/10.1039/D1FO00115A
33. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G: Hallmarks of aging: An expanding universe. Cell 2023. 186(2):243–278. DOI: https://doi.org/10.1016/j.cell.2022.11.001
34. He M, Kuk AC, Ding M, Chin CF, Galam DL, Nah JM, et al.: Spns1 is a lysophospholipid transporter mediating lysosomal phospholipid salvage. Proceedings of the National Academy of Sciences 2022. 119(40):e2210353119. DOI: https://doi.org/10.1073/pnas.2210353119
35. Chen H, Ha HT, Elghobashi-Meinhardt N, Le NA, Schmiege P, Nguyen LN, et al.: Molecular basis of Spns1-mediated lysophospholipid transport from the lysosome. Proceedings of the National Academy of Sciences 2025. 122(1):e2409596121. DOI: https://doi.org/10.1073/pnas.2409596121
36. Tan JX, Finkel T: Lysosomes in senescence and aging. EMBO reports 2023. 24(11):e57265. DOI: https://doi.org/10.15252/embr.202357265
37. Leeman DS, Hebestreit K, Ruetz T, Webb AE, McKay A, Pollina EA, et al.: Lysosome activation clears aggregates and enhances quiescent neural stem cell activation during aging. Science 2018. 359(6381):1277–1283. DOI: https://doi.org/10.1126/science.aag3048
38. Xie S, Li J, Lyu F, Xiong Q, Gu P, Chen Y, et al.: Novel tripeptide

RKH derived from *Akkermansia muciniphila* protects against lethal sepsis. Gut 2024. 73(1):78–91.
DOI: https://doi.org/10.1136/gutjnl-2023-329996

39. Zhang Q, Linke V, Overmyer KA, Traeger LL, Kasahara K, Miller IJ, et al.: Genetic mapping of microbial and host traits reveals production of immunomodulatory lipids by Akkermansia muciniphila in the murine gut. Nature Microbiology 2023.
DOI: https://doi.org/10.1038/s41564-023-01326-w
40. Kim S-M, Park S, Hwang S-H, Lee E-Y, Kim J-H, Lee GS, et al.: Secreted Akkermansia muciniphila threonyl-tRNA synthetase functions to monitor and modulate immune homeostasis. Cell Host & Microbe 2023. 31(6):1021-1037.e10.
DOI: https://doi.org/10.1016/j.chom.2023.05.007
41. Lorenzetti A, Osato M, He F, Aperio C, Ayala A, Rasulova S, et al.: Interim report from a 2-year double-blind rct testing fermented papaya preparation on immune enhancement, endothelial health and qol in elderly adults. Functional Foods in Health and Disease 2023. 13(2):69.
DOI: https://doi.org/10.31989/ffhd.v13i2.1050
42. Gorchakov V, Nicolaychuk K, Gorchakova O, Demchenko G, Nurmakhanova B: Phytomineral complexes as elements of functional nutrition to enhance the protective function of the lymphatic system in aging. Bioactive Compounds in Health and Disease 2024. 7(1):1.
DOI: https://doi.org/10.31989/bchd.v7i1.1289
43. Lelong C, Mandoux A, Houyoux N, Defrere S, Mariage P-A: Red Panax ginseng root promotes neuronal plasticity in vitro and improves cognitive function in aged animals. Functional Foods in Health and Disease 2024. 14(8):574–588.
DOI: https://doi.org/10.31989/ffhd.v14i8.1388
44. Yuan L, Davis PF: Regetting-18 complex powder (R-18CP) - A formulation of components from food-medicine and its anti-aging effects. Functional Foods in Health and Disease 2025. 15(7):369. DOI: https://doi.org/10.31989/ffhd.v15i7.1647
45. Khonthun C, Khoothiam K, Chumphukam O, Thongboontho R, Oonlao P, Nuntaboon P, et al.: Screening and characterization of antioxidant, anti-aging, and anti-microbial activity of herbal extracts in Northern Thailand. Functional Foods in Health and Disease 2023. 13(2):52.
DOI: https://doi.org/10.31989/ffhd.v13i2.1070