Effects of *Lactiplantibacillus plantarum* Fermented Metabolites on the Regulation of Mitochondrial Function and Healthspan Extension in *Caenorhabditis elegans*

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Outline

1. Introduction
2. Urolithin A Produced by Novel Microbial Fermentation Possesses Anti-aging Effects by Improving Mitophagy and Reducing Reactive Oxygen Species in *Caenorhabditis elegans*
3. A Microbiota-Derived Metabolite, 3-Phenyllactic Acid, Prolongs Healthspan by Enhancing Mitochondrial Function and Stress Resilience via SKN-1/ATFS-1 in *C. elegans*
4. Conclusion

Abstract

In recent years, an aging society has become a global concern, with mitochondrial dysfunction being one of the key factors accelerating the aging process. Metabolites from microbial fermentation have attracted interest for their anticancer, antioxidant, and neuroprotective properties and potential to support healthy aging. Urolithin A (Uro-A) and 3-phenyllactic acid (PLA) are fermentation-derived metabolites whose anti-aging effects have been confirmed in *Caenorhabditis elegans*. Uro-A, formed from ellagitannins (ETs) via fermentation by *Lactiplantibacillus plantarum*, extended lifespan by up to 46.3% by improving mitochondrial membrane potential (MMP) and ATP, and promoting mitophagy and mitochondrial biogenesis. It also lowered reactive oxygen species (ROS) and age-related markers such as lipid accumulation, lipofuscin accumulation, and SA-β-GAL activity, thereby preserving mitochondrial function. PLA, identified as a metabolite produced in *C. elegans* after feeding with *L. plantarum* APSulloc 331261 (GTB1), extended lifespan in a dose-dependent manner by up to 23.3%. Additionally, PLA improved healthspan indicators, including motility, oxygen consumption rate (OCR), and resistance to thermal and oxidative stress. Mechanistically, PLA requires SKN-1 and ATFS-1 to maintain mitochondrial energy metabolism, stabilize ATP, and enhance activity of respiratory chain complexes II and V, thereby delaying mitochondrial aging. In human studies, plasma PLA levels were significantly lower in patients with sarcopenia and positively correlated with muscle function and physical performance. Overall, these findings suggest that both Uro-A and PLA have strong potential to slow aging and promote healthspan. By improving mitochondrial function and enhancing stress resistance, they represent promising natural intervention strategies for preventing age-related decline.

Kim, J., Jo, Y., Lim, G., Ji, Y., Roh, J.-H., Kim, W.-G., Yi, H.-S., Choi, D. W., Cho, D., & Ryu, D. (2024). A microbiota-derived metabolite, 3-phenyllactic acid, prolongs healthspan by enhancing mitochondrial function and stress resilience via SKN-1/ATFS-1 in C. elegans. *Nature Communications*, *15*(1), 10773.

Zhang, M., Cui, S., Mao, B., Zhang, Q., Zhao, J., Tang, X., & Chen, W. (2023). Urolithin A produced by novel microbial fermentation possesses anti-aging effects by improving mitophagy and reducing reactive oxygen species in Caenorhabditis elegans. *Journal of Agricultural and Food Chemistry*, *71*(16), 6348-6357.