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Oral vaccination of *Lactococcus lactis* expressing Ling Zhi 8 protein prevents nonalcoholic fatty liver and early atherosclerosis in cholesterol-fed rabbits

W.W. Lin¹, M.F. Lee², S.J. Lin³, T.J. Wu¹

¹Taichung Veterans General Hospital, cardiovascular center, Taichung, Taiwan; ²Taichung Veterans General Hospital, medical research center, Taichung, Taiwan; ³Chung Shan Medical University Hospital, School of Medical Laboratory and Biotechnology, Taichung, Taiwan

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Background: Atherosclerosis is an inflammatory disease characterized by lipid deposits in the subendothelial space leading to severe inflammation. Nonalcoholic fatty liver disease (NAFLD) shares several risk factors with atherosclerosis. Epidemiology studies have indicated that NAFLD may be an independent risk factor for atherosclerosis. Anti-inflammation therapy by inhibiting IL-1 β led to a significantly lower cardiovascular event rate in recent clinical trial (CANTOS trial). Ling Zhi 8 (LZ8) is an immunomodulatory protein that possesses a broad range of pharmacological properties, including anti-inflammatory activities.

Methods and findings: In this study, we developed an oral vaccination of *Lactococcus lactis* expressing LZ8 protein in a nisin-controlled gene expression system and investigated its anti-inflammation properties. Exper-

imental rabbits received commercial rabbit chow supplemented with 2% cholesterol for 5 weeks and recombinant LZ8 *L. lactis* vaccine once a day on weekdays. The expression of IL-1 β in the aorta (Figure A) was significantly suppressed after LZ8 vaccination. Moreover, in hematoxylin and eosin staining of the aorta, the intima-medial thickness was decreased, and foam cells were significantly reduced in the sub-endothelial space (Figure C). LZ8 also inhibited the expression of IL-1 β in the liver (Figure B), decreased fat droplet deposits and infiltration of inflammatory cells (Figure D), and improved liver function by decreasing liver enzymes.

Conclusions: Our results suggest that LZ8 could be used as a therapeutic tool to improve both atherosclerosis and NAFLD due to its anti-inflammatory effect.

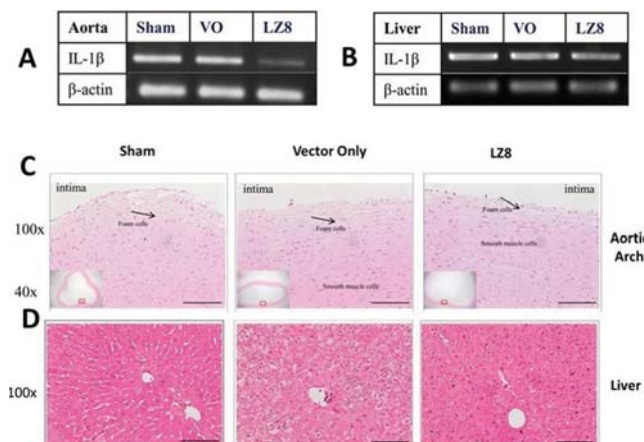


Figure 1