L-proline supplementation for metabolic dysfunction-associated steatotic liver disease: A new use of a natural amino acid

Yidi Wu,[1] Chunhui Zhang,[2,*] and Dabin Liu[1,*]

[1]NHC Key Laboratory of Molecular Probes and Targeted Diagnosis and Therapy, The Fourth Hospital of Harbin Medical University, Harbin 150028, China
[2]Department of Student Affairs, The Fourth Hospital of Harbin Medical University, Harbin 150028, China
*Correspondence: 1280289406@qq.com (C.Z.); liudb526@hrbmu.edu.cn (D.L.)

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Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disease worldwide, affecting approximately 30% of the global adult population.[1] MASLD is closely associated with obesity, insulin resistance, type 2 diabetes, and dyslipidaemia, and it can progress to steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma.[2,3] Although the first pharmacotherapy has recently been approved, its high cost and limited accessibility mean that most patients, particularly those in resource-limited settings, still lack affordable options suitable for long-term use.[4] Therefore, safe, low-cost, and easily accessible nutritional interventions are urgently needed.

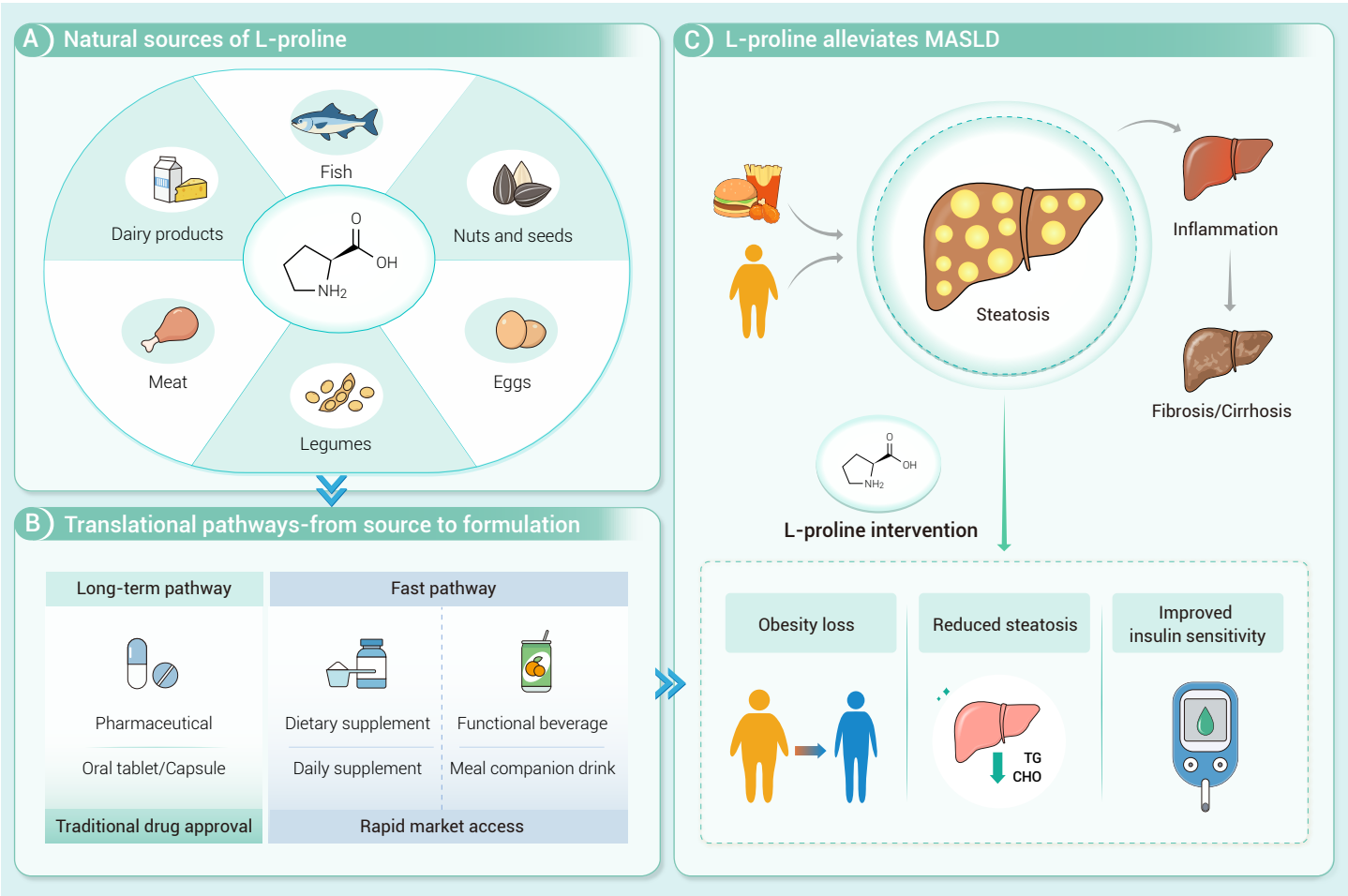

Figure 1. Translational potential of L-proline for MASLD prevention and treatment.

We recruited healthy subjects and MASLD patients matched for age, BMI and gender ratio to rule out confounding demographic factors. Targeted LC-MS/MS testing of peripheral blood L-proline showed that circulating L-proline levels were markedly lower in MASLD patients than in healthy controls. This obvious difference in systemic L-proline levels between the two groups prompted us to investigate whether L-proline supplementation could treat MASLD. We established a diet-induced MASLD mouse model to validate the intervention efficacy. Age-matched male C57BL/6 mice were randomly assigned to a control group and an oral L-proline treatment group, with continuous L-proline administration via drinking water throughout the entire modeling period of the methionine-choline-deficient (MCD) diet model. Comprehensive histological staining of liver tissues demonstrated that L-proline supplementation dramatically ameliorated hepatic steatosis and diminished intracellular lipid droplet accumulation in hepatocytes (Figures S1A-B). Measurements of physiological indicators and serum biochemistry further proved that L-proline slowed excessive weight gain, reduced liver weight, alleviated liver injury by lowering serum ALT and AST, and improved insulin resistance in model mice. Taken together, these findings suggest that oral L-proline supplementation raises systemic L-proline levels and effectively alleviates diet-triggered MASLD.

The translational potential of L-proline is illustrated in Figure 1. L-proline is a natural, proteinogenic amino acid that is generally recognized as safe (GRAS). It is abundant in protein-rich foods such as meat, fish, dairy products, and legumes, and can also be produced cost-effectively through fermenta-

tion or chemical synthesis. Unlike the recently approved MASLD pharmacotherapy, which is expensive and requires a lengthy and costly drug approval process, L-proline offers a unique advantage: it can be rapidly developed and marketed as a functional beverage or dietary supplement. This pathway bypasses the long drug approval timeline while still providing genuine therapeutic benefits. Of course, the possibility of pharmaceutical development remains open, but the supplement route offers a faster and more accessible path to reach patients in need. L-proline is highly suitable for long-term use in at-risk populations, including obese individuals, diabetics, and patients with early-stage MASLD. As a natural amino acid, it can be easily incorporated into daily diets or consumed as a standalone supplement, making it a practical and scalable solution for MASLD management. This invention has been granted Chinese patent (ZL 2024 1 0446501.6) and Hong Kong patent (40105997 B).

In conclusion, we have identified a new use of L-proline for MASLD therapy, based on the clinical observation of reduced L-proline levels in MASLD patients and preclinical validation of its efficacy in diet-induced mouse models.This work fits the scope of *The Innovation Oncology*, given the tight causal link between MASLD and hepatocellular carcinoma (HCC). MASLD-driven steatohepatitis and fibrosis are major precursors of liver malignancy, and targeting early metabolic liver damage represents a promising chemopreventive strategy aligned with the journal's focus on metabolic oncology. As a natural, safe, and affordable amino acid, L-proline has great potential for widespread translation as a nutritional intervention for MASLD, particularly as a functional beverage or dietary supplement for long-term use in resource-limited settings.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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