Ginseng-Derived Nanovesicles Suppress Liver Fibrosis via TIMP2 Pathway Modulation and Gut Microbiota balance.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are chronic liver diseases that can progress to fibrosis, cirrhosis, and liver cancer. Both diseases are closely linked to gut–liver axis dysfunction, including intestinal barrier damage, inflammation, and liver fibrosis. Ginseng-derived exosome-like nanovesicles (GNVs) contain bioactive ginsenosides and have therapeutic potential, but their effects on MASLD and ALD remain unclear. In this study, we evaluated whether orally administered GNVs protect against gut barrier disruption and liver fibrosis in diet-induced MASLD and ethanol-induced ALD mouse models.

Study Results

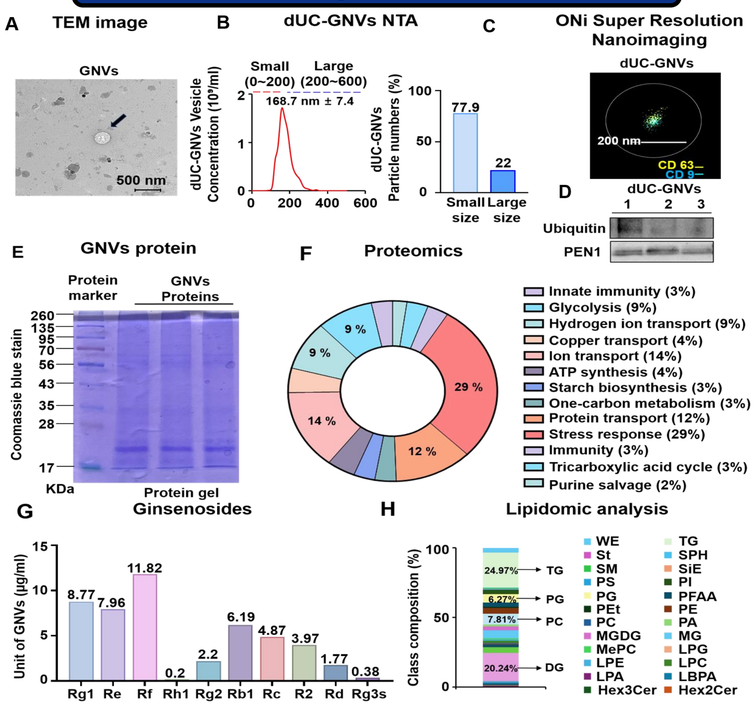


Fig. 1. characterization of GNVs. (A) TEM image of GNVs. (B) NTA of GNVs. (C)super-resolution nanoimaging of GNVs. (D) Detection of plant EV marker proteins GNVs. (E) Coomassie blue staining. (F–H) Proteomic, ginsenoside, and lipidomic profiles.

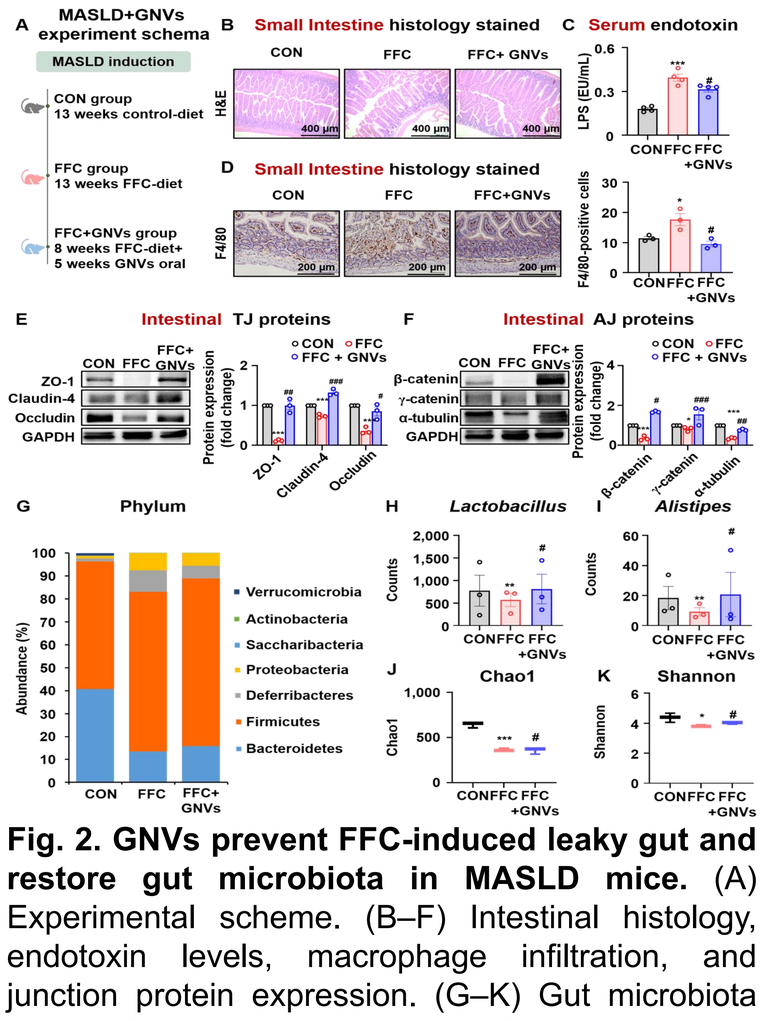


Fig. 2. GNVs prevent FFC-induced leaky gut and restore gut microbiota in MASLD mice. (A) Experimental scheme. (B–F) Intestinal histology, endotoxin levels, macrophage infiltration, and junction protein expression. (G–K) Gut microbiota composition and alpha diversity. Data are mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001 vs. CON; #p < 0.05, ##p < 0.01, ###p < 0.001 vs. FFC.

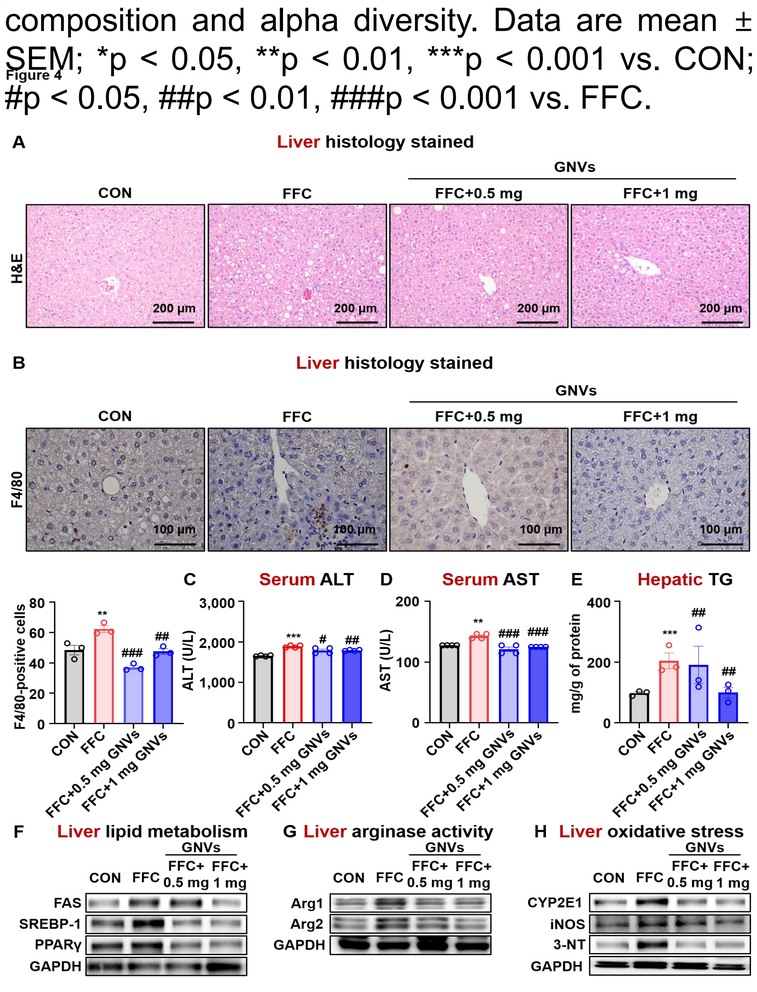


Fig. 3. GNVs attenuate FFC-induced liver injury in MASLD mice. (A, B) H&E and F4/80 staining of liver sections. (C–E) Serum ALT/AST and hepatic TG levels. (F–H) Western blot analysis of indicated hepatic protein. Data are mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001 vs. CON; #p < 0.05, ##p < 0.01, ###p < 0.001 vs. FFC.

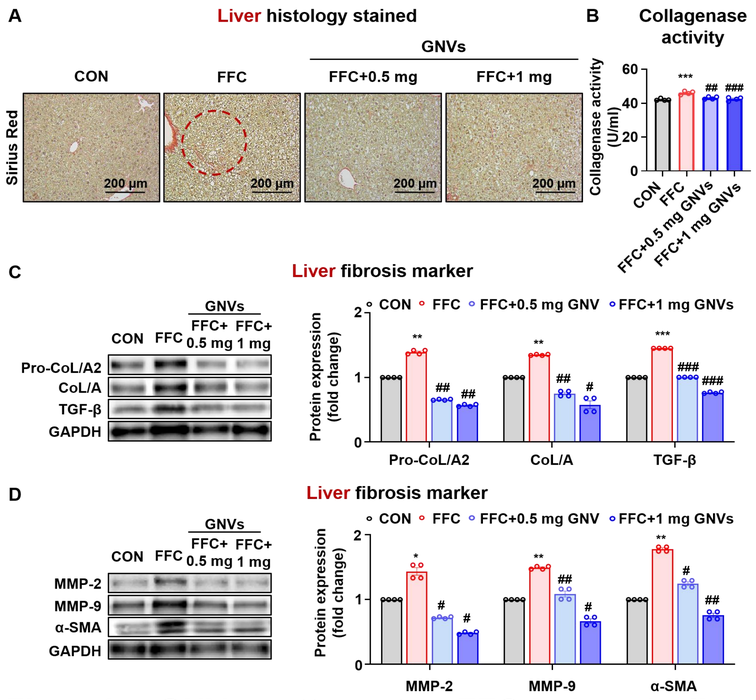


Fig. 4. GNVs attenuate FFC-induced liver fibrosis in MASLD mice. (A) Sirius Red staining. (B) Collagenase activity. (C, D) Western blot analysis of fibrosis-related proteins. Data are mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001 vs. CON; #p < 0.05, ##p < 0.01, ###p < 0.001 vs. FFC.

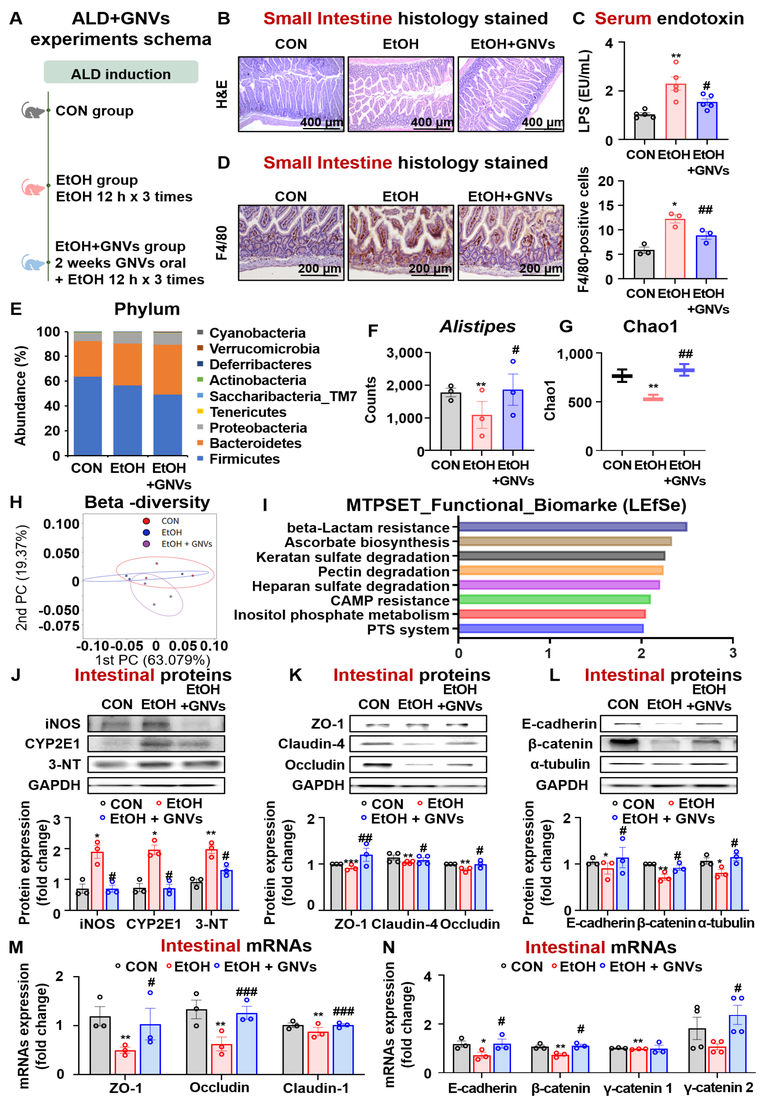
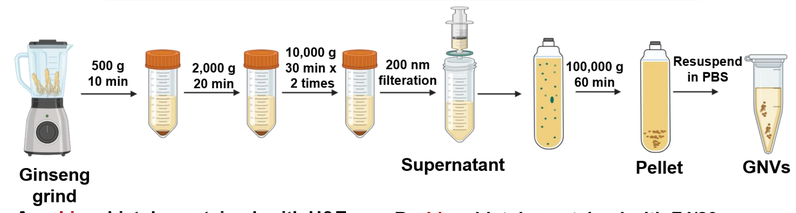


Fig. 5. GNVs prevent alcohol-induced leaky gut in ALD mice. (A) Experimental scheme. (B, D) H&E and F4/80 staining of small intestine. (C) Serum endotoxin levels. (E–I) Gut microbiota composition, diversity, and functional biomarker analysis. (J–L) Western blot analysis of oxidative stress and junctional complex proteins. (M, N) qRT-PCR analysis of gut junction-related genes. Data are mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001 vs. CON; #p < 0.05, ##p < 0.01, ###p < 0.001 vs. EtOH.

Materials



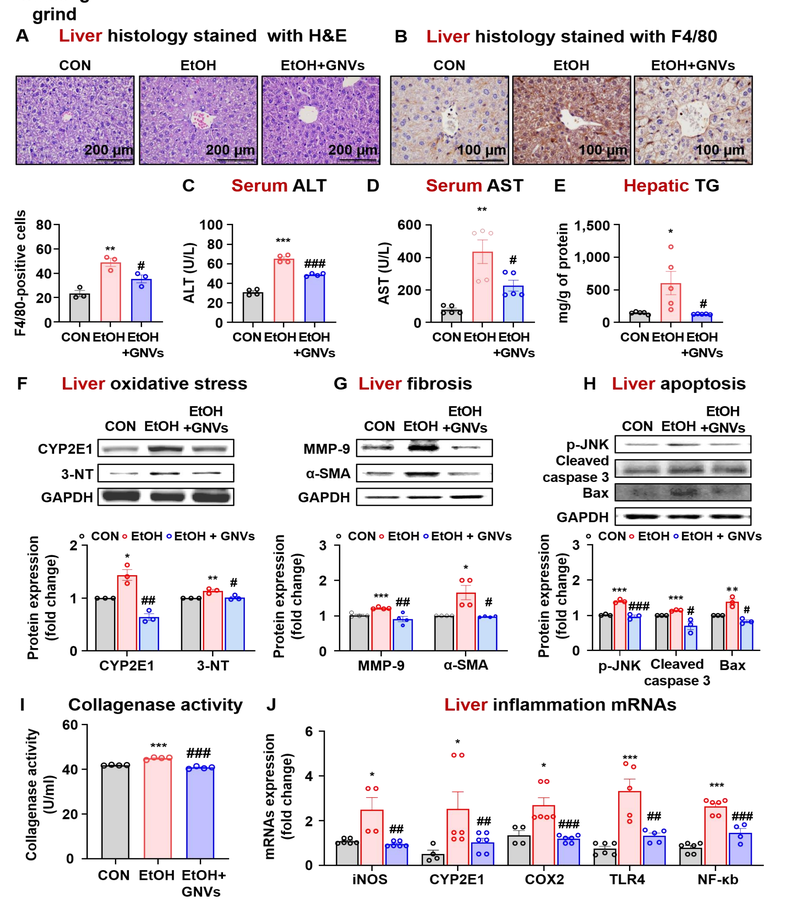


Fig. 6. GNVs attenuate alcohol-induced liver injury in ALD mice. (A, B) H&E and F4/80 staining. (C–E) Serum ALT/AST and hepatic TG levels. (F–H) Western blot analysis of indicated hepatic protein(I) Hepatic collagenase activity. (J) RT-PCR analysis of indicated hepatic genes. Data are mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001 vs. CON; #p < 0.05, ##p < 0.01, ###p < 0.001 vs. EtOH.

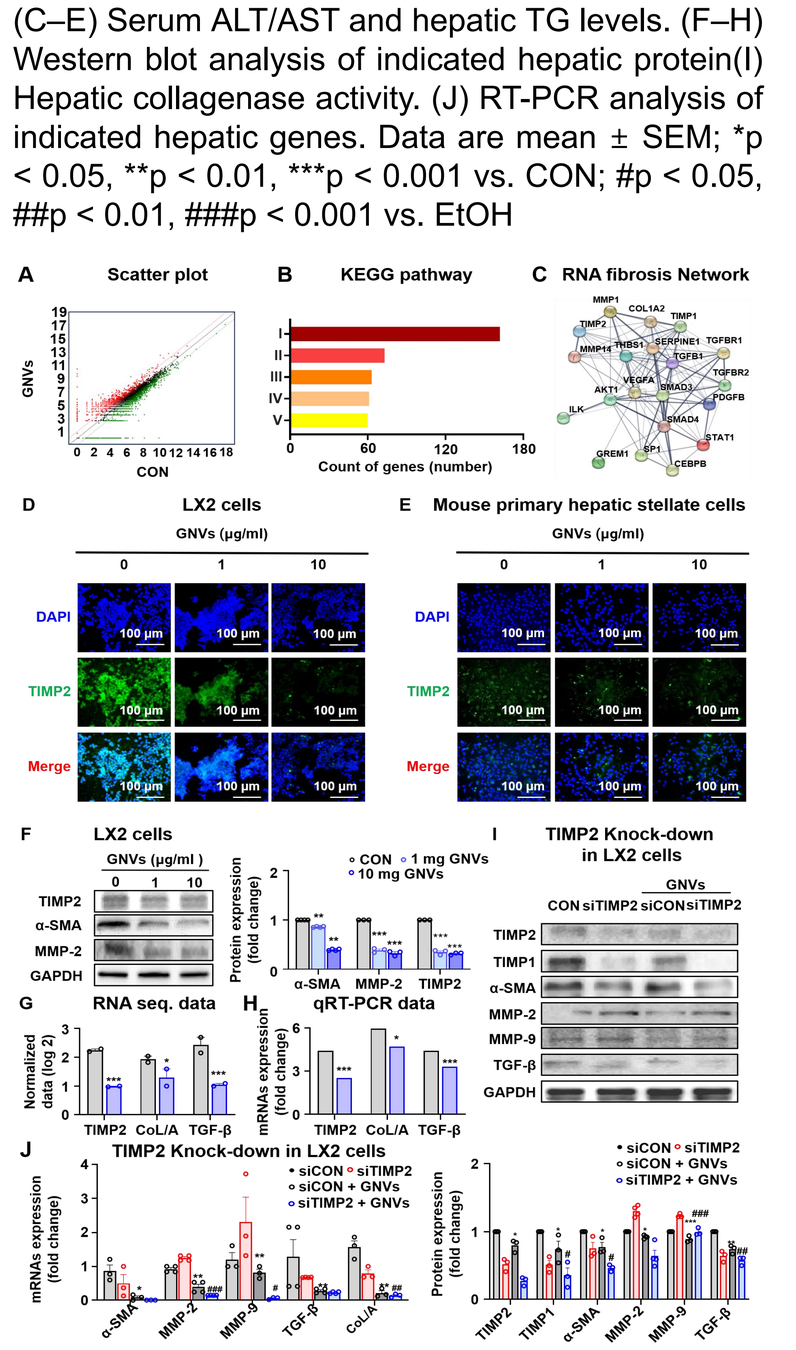


Fig. 7. GNVs attenuate hepatic fibrosis via TIMP2-dependent regulation. (A–C) RNA-seq scatter plot, KEGG pathway analysis, and liver fibrosis-related RNA interaction network in GNV-treated LX-2 cells. (D, E) TIMP2 expression in LX-2 cells and primary hepatic stellate cells. (F–H) Western blot, RNA-seq, and qRT-PCR analyses of fibrosis-related markers. (I, J) Protein and mRNA expression of fibrosis markers in TIMP2-knockdown LX-2 cells ± GNVs. Data are mean ± SD/SEM; *p < 0.05, **p < 0.01, ***p < 0.001; #p < 0.05, ##p < 0.01, ###p < 0.001.

Conclusion

Orally administered GNVs protected against MASLD- and ALD-associated gut barrier dysfunction, liver injury, and hepatic fibrosis. These effects were associated with restoration of intestinal junction proteins, modulation of gut microbiota, reduction of hepatic oxidative stress and inflammation, and TIMP2-dependent suppression of fibrogenic signaling in hepatic stellate cells. Therefore, edible GNVs may represent a promising nanovesicle-based therapeutic strategy targeting the gut–liver axis in chronic liver diseases.

Reference: Kim, Ji-Su, et al. "Ginseng-derived exosome-like nanovesicles protect against liver fibrosis by regulating TIMP2 pathways and gut dysbiosis." *Asian Journal of Pharmaceutical Sciences* (2025): 101105.