

Metabolic, biochemical, histopathological, and transcriptomic effects of Seladelpar in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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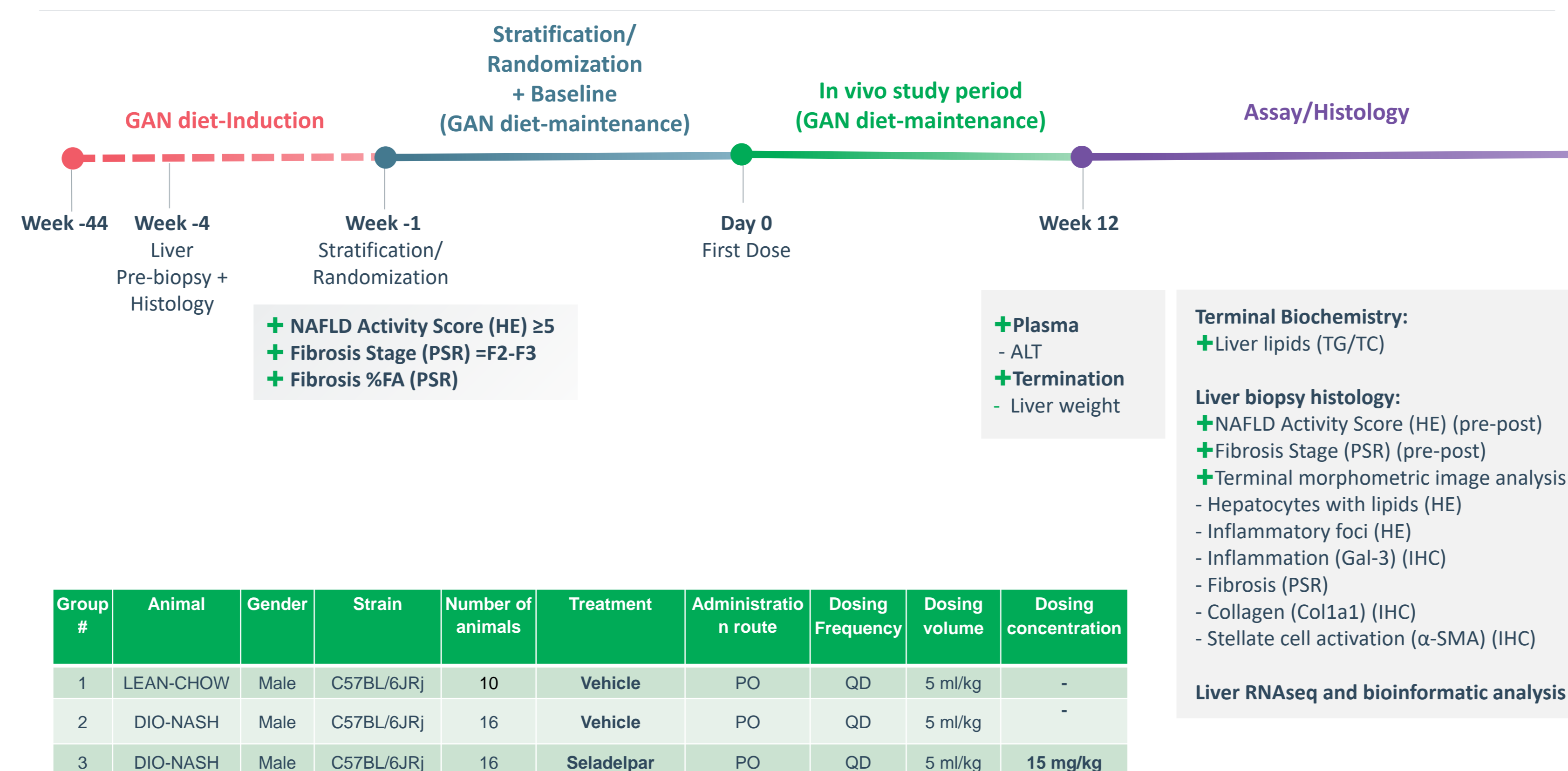
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Background & Aim

Seladelpar, a PPAR-delta agonist, is currently in late-stage clinical development for liver disease including non-alcoholic steatohepatitis (NASH). The present study aimed to evaluate the metabolic, biochemical, histopathological and transcriptomic effects of seladelpar treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH.

Study outline



Improvement in metabolic and biochemical parameters

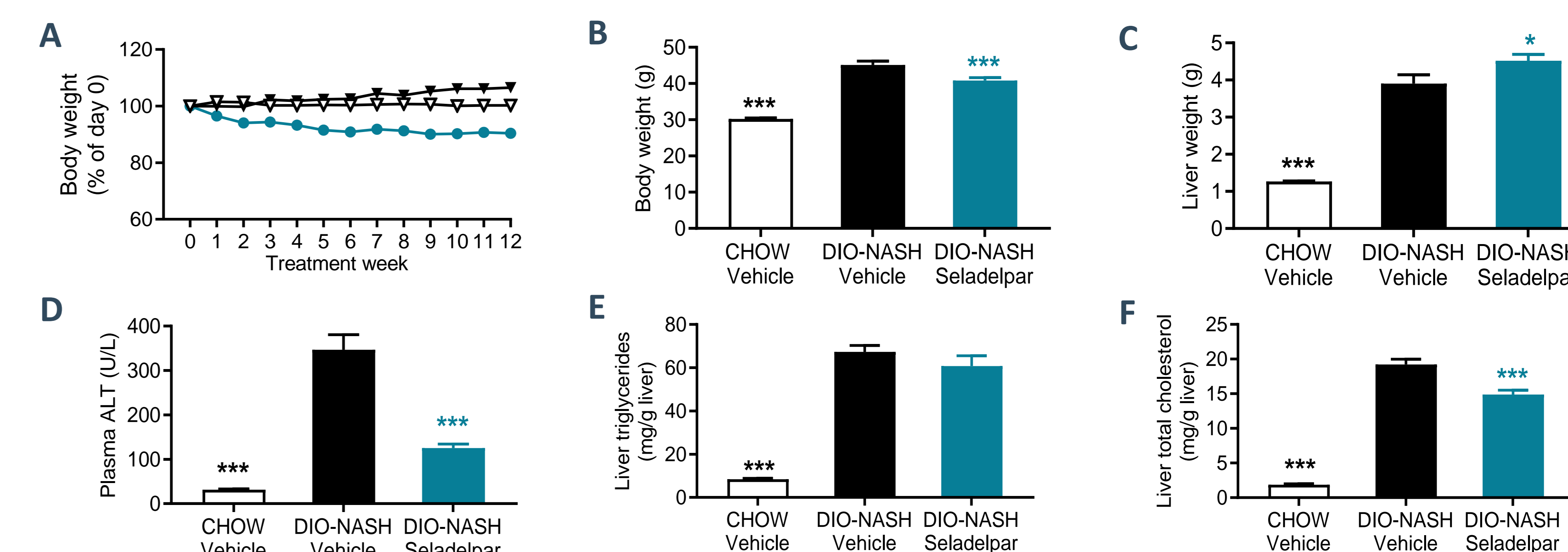


Figure 1. Seladelpar improves body weight and biochemical parameters in GAN DIO-NASH mice. (A) Body weight change relative to baseline (day 0). (B) Terminal body weight (g). (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver triglycerides. (F) Terminal liver total cholesterol. (H) *** $p < 0.01$, **** $p < 0.001$ compared to corresponding DIO-NASH vehicle control (Dunnett's test one-factor linear model).

Improvement in NAFLD Activity Score

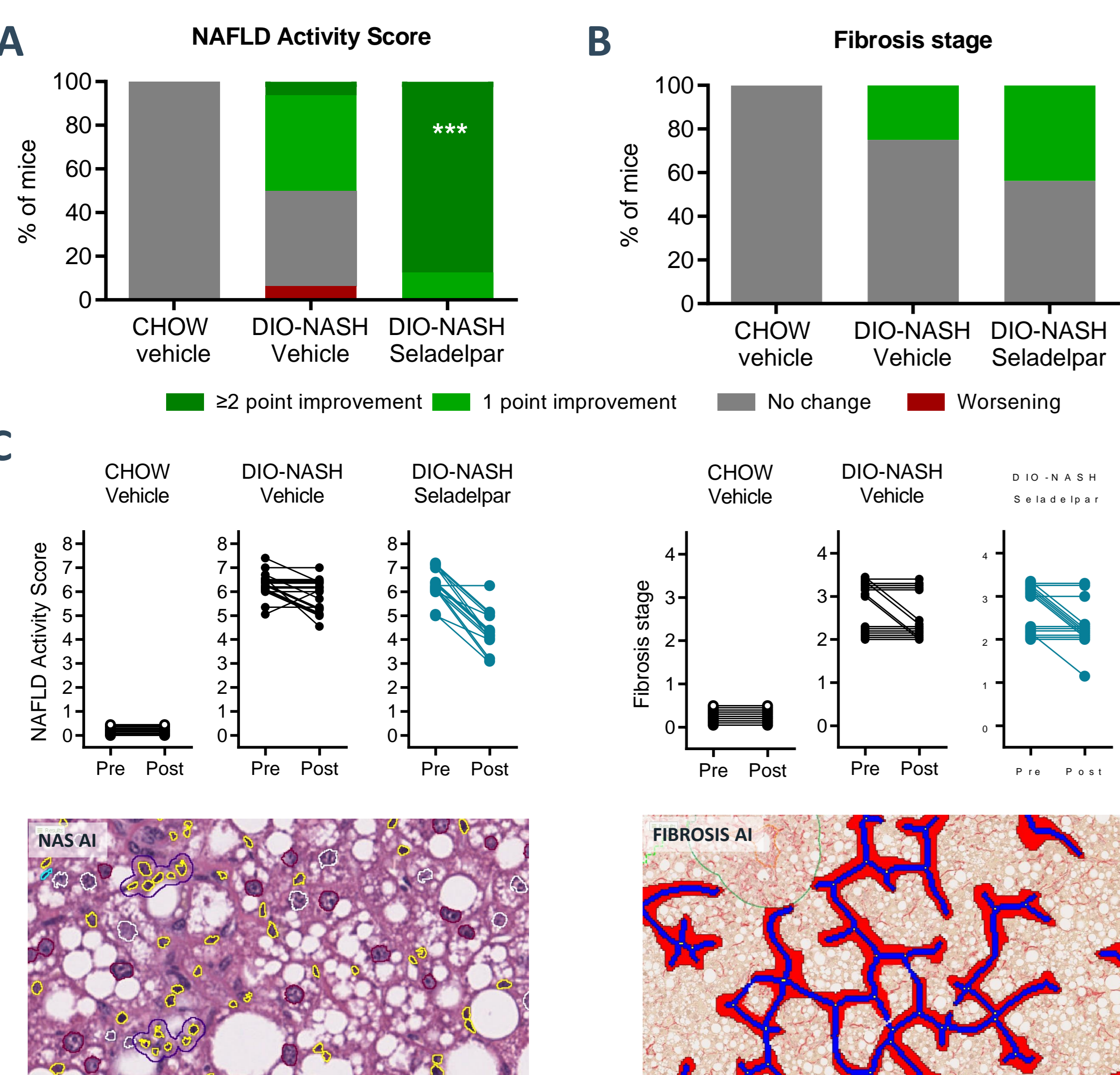


Figure 2. Seladelpar improves liver histopathological scores in GAN DIO-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C) Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. **** $p < 0.001$ to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

Improvement in quantitative histology of steatosis, inflammation and fibrosis

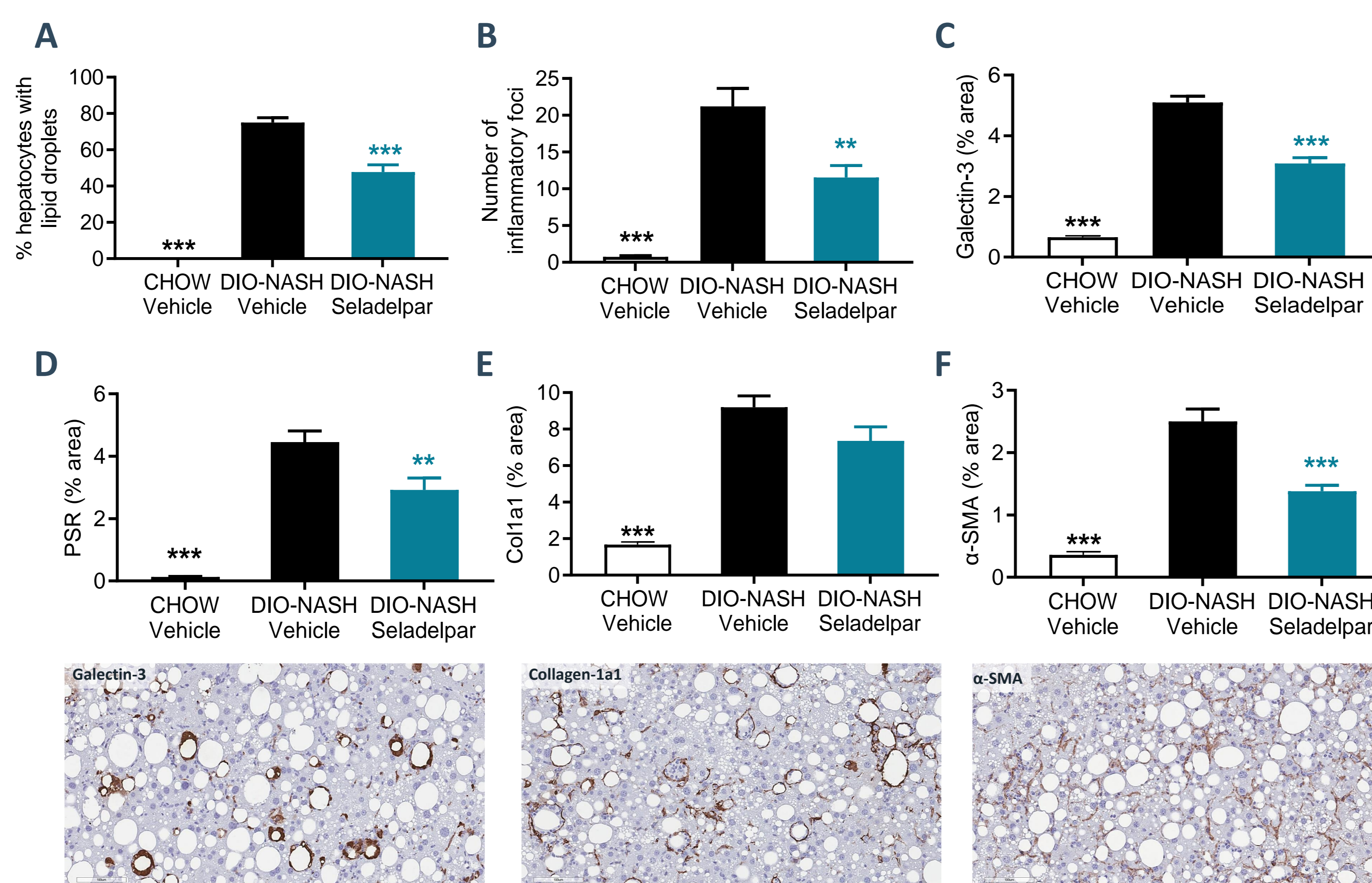


Figure 3. Seladelpar improves quantitative liver histological markers in GAN DIO-NASH mice. Histomorphometric terminal assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of galectin-3. (D) % area of PSR. (E) % area of collagen-1a1. (F) % area of alpha-smooth muscle actin (α -SMA) as marker for stellate cell activation. Mean \pm SEM. **** $p < 0.01$, **** $p < 0.001$ to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α -SMA photomicrographs (scale bar, 100 μ m).

Hepatic transcriptomic profile for fibrosis and inflammation

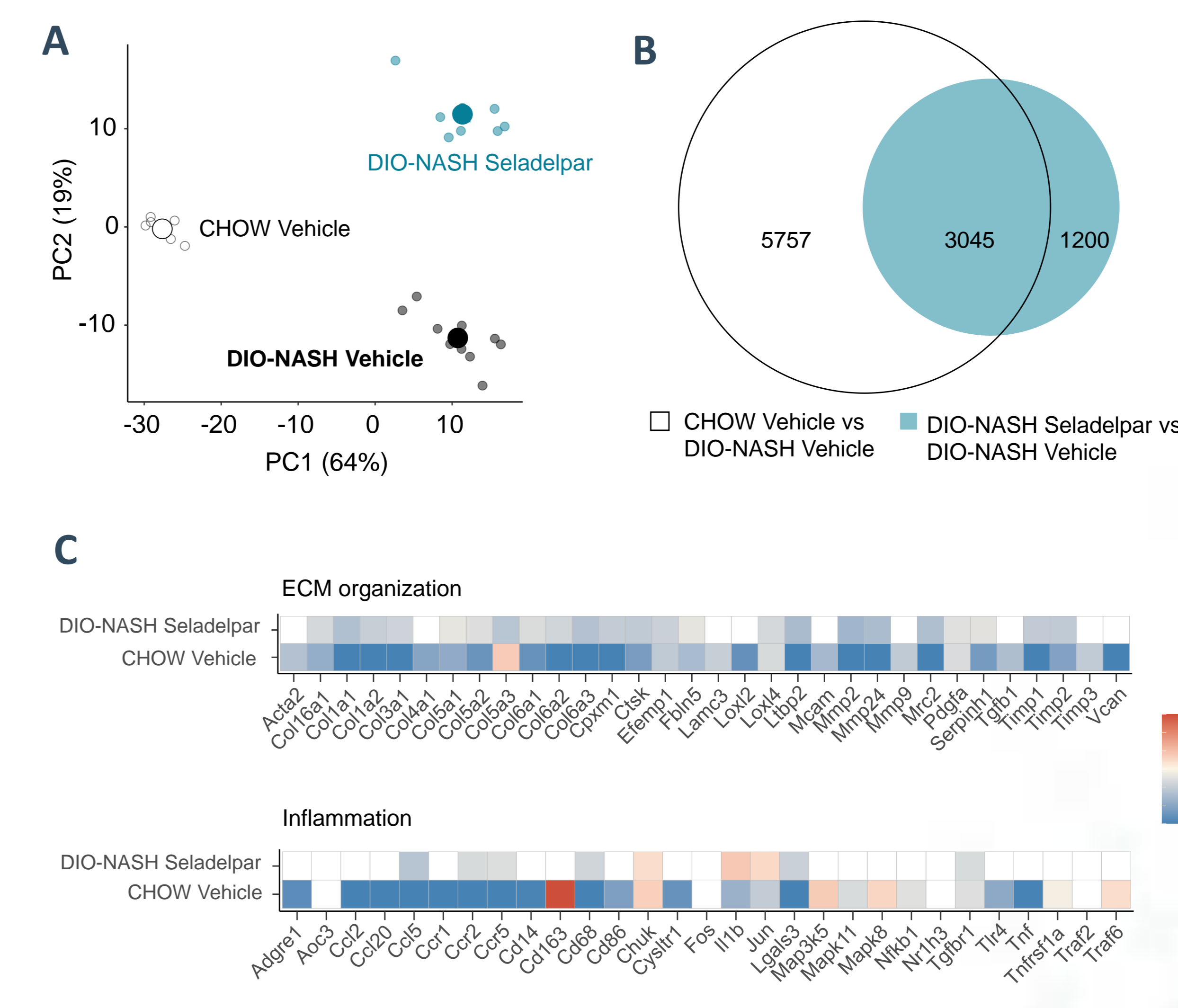


Figure 4. Seladelpar suppress fibrosis-associated genes in GAN DIO-NASH mice. (A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. (B) Venn diagram depicting shared and separate differentially expressed genes in treatment groups. (C) Regulation of hepatic extracellular matrix (ECM) and inflammation candidate genes (log2-fold change compared to DIO-NASH vehicle mice). Blue and red colour gradients indicate significantly ($p < 0.05$) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not significantly regulated ($p > 0.05$) compared to DIO-NASH vehicle mice.

CONCLUSION

- + Seladelpar reduces body weight, plasma ALT and liver total cholesterol levels.
- + Seladelpar promotes ≥ 2 -point significant improvement in NAFLD Activity Score.
- + Fibrosis stage was unaffected by Seladelpar.
- + Seladelpar reduces quantitative histological markers of steatosis, inflammation, fibrosis and stellate cell activation.
- + Seladelpar demonstrated transcriptomic effects on fibrosis-associated gene expression.
- + These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model