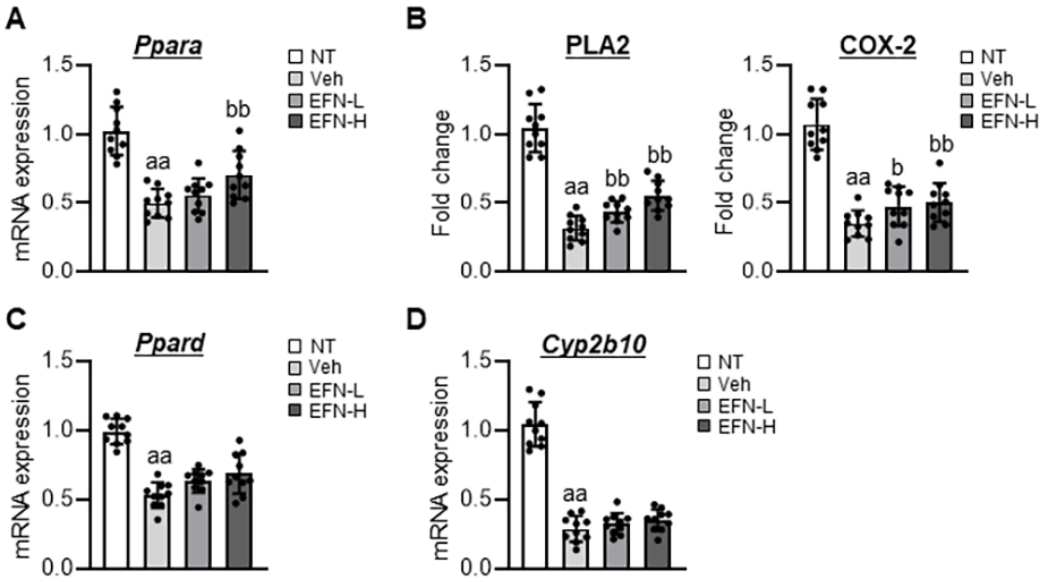
Supplementary methods

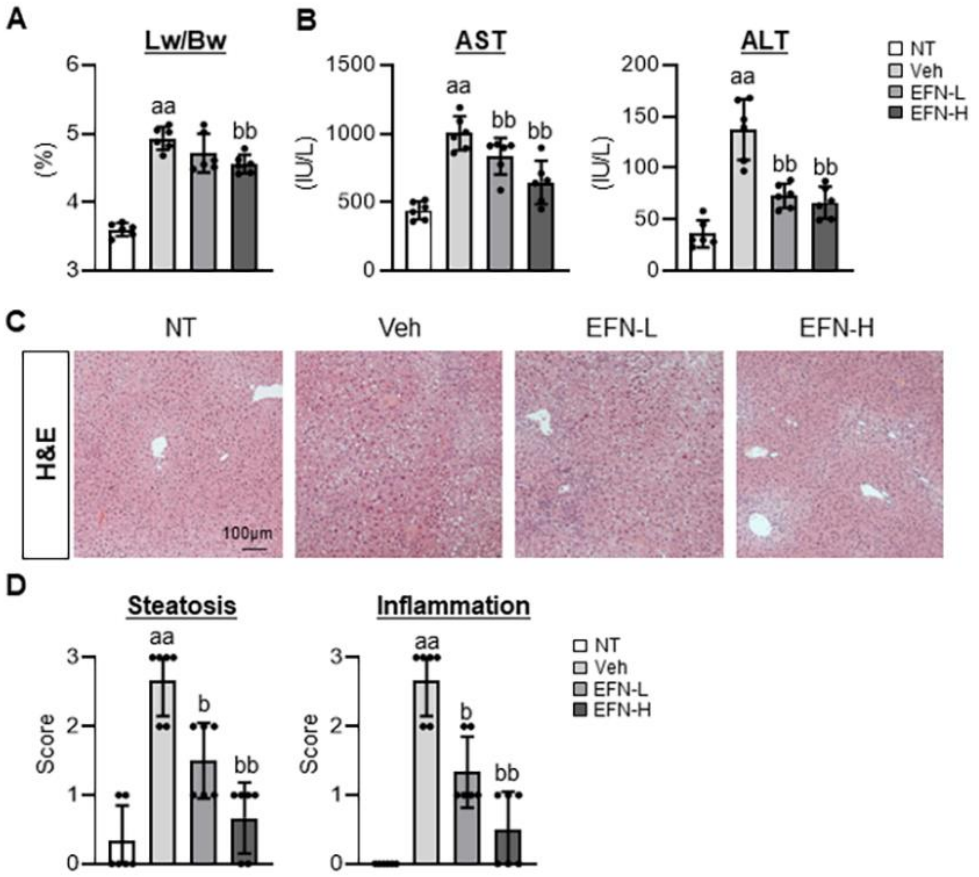
Hepatic levels of phospholipase A2 (PLA2) and cyclooxygenase (COX)-2

The levels of the PLA2 and COX-2 in mouse liver tissue were measured using a Mouse cytosolic PLA2 ELISA Kit (LSBio, Seattle, WA) and Mouse COX-2 ELISA Kit (CUSABIO, Houston, TX), respectively, following the manufacturers' instructions.

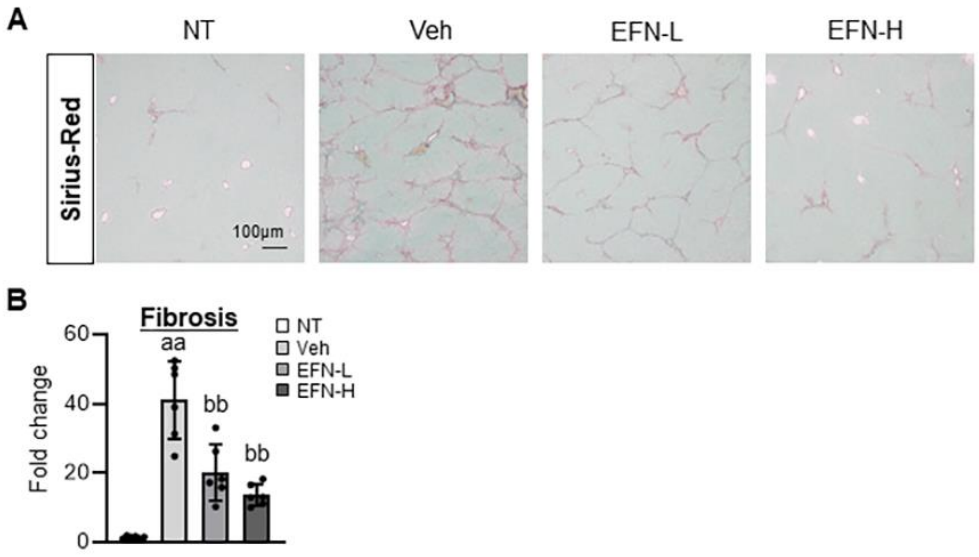
Supplementary figures



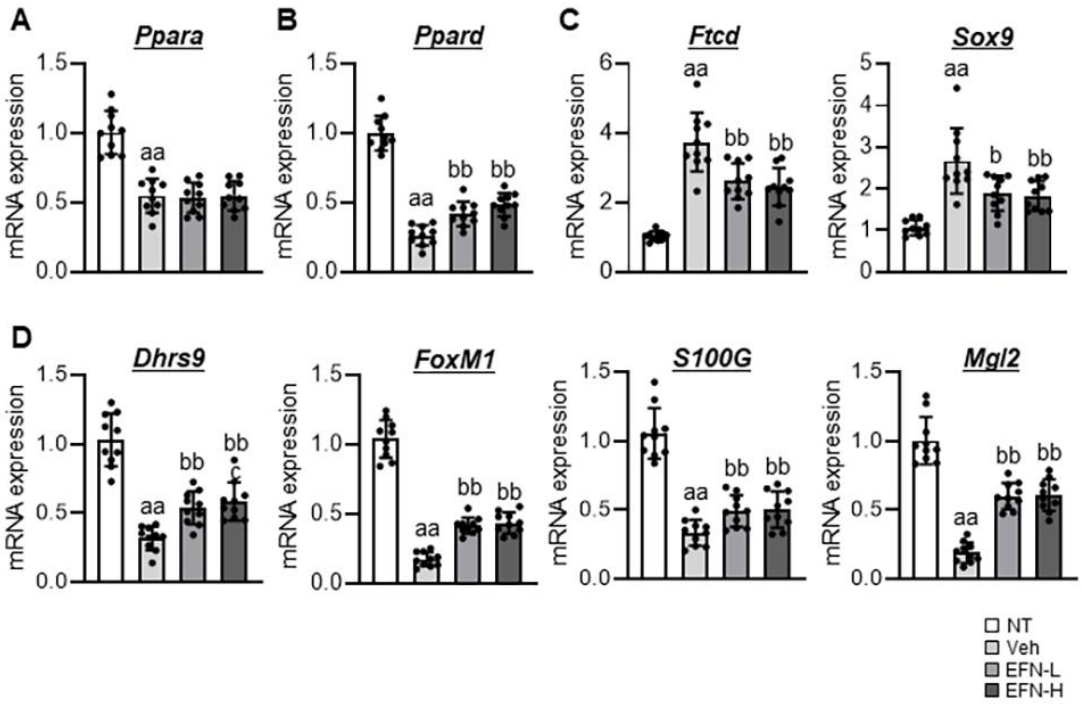
Supplementary figure 1. Effect of elafibranor on PPARα and PPARδ signaling in the liver of ALD mice. (A) Hepatic mRNA expression of *Ppara* in the experimental mice. (B) Hepatic levels of phospholipase A2 (PLA2) and cyclooxygenase (COX)-2 in the experimental mice. (C and D) Hepatic mRNA expression of *Ppard* (C) and *Cyp2b10* (D) in the experimental mice. *Gapdh* was used as an internal control for qRT-PCR. Quantitative values are indicated as fold changes to the values of NT group. Data are the mean ± SD (n = 10). $^{a, aa}$: $P < 0.05, 0.01$ vs NT group, $^{b, bb}$: $P < 0.05, 0.01$ vs Veh group, significant difference between groups by Student's t-test. NT, non-therapeutic group; Veh, vehicle-treated ALD group; EFN-L, elafiblanor (3mg/kg/day)-treated ALD group; EFN-H, elafibranor (10mg/kg/day)-treated ALD group.



Supplementary figure 2. Effect of elafibranor on ALD-induced steatohepatitis in male mice. (A) Liver/body weight at the end of experiment. (B) Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). (C) Representative microphotographs of hematoxylin and eosin (H&E) of the livers in the experimental mice. (D) Hepatic pathological scores for steatosis and inflammation. Data are the mean ± SD (n = 6; A, B and D). a, aa: $P < 0.05$, 0.01 vs NT group, b, bb: $P < 0.05$, 0.01 vs Veh group, significant difference between groups by Student's t-test. NT, non-therapeutic group; Veh, vehicle-treated ALD group; EFN-L, elafiblanor (3mg/kg/day)-treated ALD group; EFN-H, elafibranor (10mg/kg/day)-treated ALD group.



Supplementary figure 3. Effect of elafibranor on ALD-induced liver fibrosis in male mice. (A) Representative microphotographs of sirius-red staining of the livers in the experimental mice. (B) Quantification of sirius-red stained fibrotic area in high-power field. Quantitative values are indicated as fold changes to the values of NT group. Data are the mean ± SD (n = 6; B). [a, aa]: $P < 0.05$, 0.01 vs NT group, [b, bb]: $P < 0.05$, 0.01 vs Veh group, significant difference between groups by Student's t-test. NT, non-therapeutic group; Veh, vehicle-treated ALD group; EFN-L, elafiblanor (3mg/kg/day)-treated ALD group; EFN-H, elafibranor (10mg/kg/day)-treated ALD group.



Supplementary figure 4. Effect of elafibranor on PPARα and PPARδ signaling in the liver of ALD mice. (A−D) Intestinal mRNA expression of *Ppara* (A), *Ppard* (B), *Ftcd* and *Sox9* (C), *Dhrs9*, *FoxM1*, *S100G* and *Mgl2* (D) in the experimental mice. *Gapdh* was used as an internal control for qRT-PCR. Quantitative values are indicated as fold changes to the values of NT group. Data are the mean ± SD (n = 10). [a, aa]: $P < 0.05$, 0.01 vs NT group, [b, bb]: $P < 0.05$, 0.01 vs Veh group, significant difference between groups by Student's t-test. NT, non-therapeutic group; Veh, vehicle-treated ALD group; EFN-L, elafiblanor (3mg/kg/day)-treated ALD group; EFN-H, elafibranor (10mg/kg/day)-treated ALD group.

Supplementary Table 1. List of primary antibodies

Antibody	Source (catalog number)	Application (Dilution)
α-SMA	Abcam (ab5694)	IHC (1:100)
F4/80	Abcam (ab111101)	IHC (1:100)
Ki-67	Abcam (ab15580)	IHC (1:100)
ZO-1	Invitrogen (61-7300)	IHC (1:200)
Occludin	Abcam (ab216327)	IHC (1:200)
Claudin2	Abcam (ab53032)	IHC (1:200)
β-Actin	Cell signaling (4967)	WB (1:1000)
LC3	Proteintech (14600-1-AP)	WB (1:1000)
Mcl-1	Cell signaling (5453)	WB (1:1000)
Bcl-2	Abcam (ab182858)	WB (1:2000)
IκBα	Cell signaling (4812)	WB (1:1000)
NF-κB p65	Cell signaling (8242)	WB (1:1000)
p-NF-κB p65	Cell signaling (3033)	WB (1:1000)

Supplementary Table 2. List of primers used in q-PCR.

Gene	Sense (5′-3′)	Antisense (5′-3′)
	Mouse	
Acta2	CTGACAGAGGCACCACTGAA	CATCTCCAGAGTCCAGCACA
Tgfb1	TTGCTTCAGCTCCACAGAGA	TGGTTGTAGAGGGCAAGGAC
Col1a1	GAGCGGAGAGTACTGGATCG	GCTTCTTTTCCTTGGGGTTC
Gapdh	CTGCGACTTCAACAGCAACT	GAGTTGGGATAGGGCCTCTC
PPARα	ATGCCAGTACTGCCGTTTTC	TTGCCCAGAGATTTGAGGTC
PPARδ	GGACCAGAACACACGCTTCCTT	CCGACATTCCATGTTGAGGCTG
Srebf1	CGACTACATCCGCTTCTTGCAG	CCTCCATAGACACATCTGTGCC
Fasn	CTGAGATCCCAGCACTTCTTGA	GCCTCCGAAGCCAAATGAG
Scd1	TTCTTGCGATACACTCTGGTGC	CGGGATTGAATGTTCTTGTCGT
Lipe	GCTCATCTCCTATGACCTACGG	TCCGTGGATGTGAACAACCAGG
Plin2	GACAGGATGGAGGAAAGACTGC	GGTAGTCGTCACCACATCCTTC
Mgll	GACACCATCCAGAAGGACTACC	GATTGGCAAGGACCAGAGGTGA
Acaa1b	GGAGAATGTGGCTGAGCGGTTT	AGGACAGTGGTTGTCACAGGCA
Acox1	GCCAAGGCGACCTGAGTGAGC	ACCGCAAGCCATCCGACATTC
Cpt1b	ATGTATCGCCGCAAACTGGACC	CTCTGAGAGGTGCTGTAGCAAG
Cpt2	GATGGCTGAGTGCTCCAAATACC	GCTGCCAGATACCGTAGAGCAA
P62	ACACCTGCTTCTGGAGGAACAG	TTGGAGGTGCTGCCACTTGAGA
Atg7	TGCCTATGATGATCTGTGTC	CACCAACTGTTATCTTTGTCC
Atg5	GACAGATTTGACCAGTTTTGGGC	GGGTTTCCAGCATTGGCTCTATC
Beclin1	GTGCGCTACGCCCAGATC	GATGTGGAAGGTGGCATTGAA
Tnfa	ACGGCATGGATCTCAAAGAC	AGATAGCAAATCGGCTGACG
Nos2	GAGACAGGGAAGTCTGAAGCAC	CCAGCAGTAGTTGCTCCTCTTC
Arg1	CATTGGCTTGCGAGACGTAGAC	GCTGAAGGTCTCTTCCATCACC
Ccl2	AGGTCCCTGTCATGCTTCTG	TCTGGACCCATTCCTTCTTG
Il1b	GCCCATCCTCTGTGACTCAT	AGGCCACAGGTATTTTGTCG
IL6	GAGCCCACCAAGAACGATAG	TCCACGATTTCCCAGAGAAC
Lbp	GGCTGCTGAATCTCTTCCAC	GAGCGGTGATTCCGATTAAA
Cd14	GTCAGGAACTCTGGCTTTGC	TGGCTTTTACCCACTGAACC
Tlr4	GGCAGCAGGTGGAATTGTAT	AGGCCCCAGAGTTTTGTTCT
Zo1	GCTAAGAGCACAGCAATGGA	GCATGTTCAACGTTATCCAT
Ocln	ACTGGGTCAGGGAATATCCA	TCAGCAGCAGCCATGTACTC
Cldn2	CAACTGGTGGGCTACATCCTA	CCCTTGGAAAAGCCAACCG
Cyp2b10	AAAGTCCCGTGGCAACTTCC	TTGGCTCAACGACAGCAACT
Ftcd	ATGCCAGTGGACTCCATCAT	GGTGCTGTCCTTCTTGAAGG

Sox9	CACACGTCAAGCGACCCATGAA	TCTTCTCGCTCTCGTTCAGCAG
Dhrs9	GGATGTCACTGACCCAGAGAATG	GTAGTCGTCCACTGTCAACCAG
FoxM1	GTCTCCTTCTGGACCATTCACC	GCTCAGGATTGGGTCGTTTCTG
S100G	CTCTCCAAGGAGGAGCTAAAGC	CTCCATCGCCATTCTTATCCAGC
Mgl2	CGAGACTTGAGCCAGAAGGTGA	GCCTTCAAGTCTGTCTCCAGCT
	Human	
ZO-1	CAACATACAGTGACGTTCACA	CACTATTGACGTTTCCCCACTC
OCLN	TCCTATAAATCCACGCCGGTTC	CTCAAAGTTACCACCGCTGCTG
CLDN-2	ATGGCCTCTCTTGGCCTCCAA	TCACACATACCCTGTCAGGCT
TGFB1	GGGACTATCCACCTGCAAGA	CCTCCTTGGCGTAGTAGTCG
COL1A1	GATTCCCTGGACCTAAAGGTGC	AGCCTCTCCATCTTTGCCAGCA
SREBF1	ACTTCTGGAGGCATCGCAAGCA	AGGTTCCAGAGGAGGCTACAAG
CPT1B	TGTATCGCCGTAAACTGGACCG	TGTCTGAGAGGTGCTGTAGCAC
CPT2	GCAGATGATGGTTGAGTGCTCC	AGATGCCGCAGAGCAAACAAGTG
Beclin1	CTGGACACTCAGCTCAACGTCA	CTCTAGTGCCAGCTCCTTTAGC
Atg5	GCAGATGGACAGTTGCACACAC	GAGGTGTTTCCAACATTGGCTCA
Atg7	CGTTGCCCACAGCATCATCTTC	CACTGAGGTTCACCATCCTTGG
LC3	AAGGCGCTTACAGCTCAATG	CTGGGAGGCATAGACCATGT
P62/ SQSTM1	TGTGTAGCGTCTGCGAGGGAAA	AGTGTCCGTGTTTCACCTTCCG
GAPDH	AGGGCTGCTTTTAACTCTGGT	CCCCACTTGATTTTGGAGGGA