EDP-297, a novel and potent FXR agonist, exhibits robust anti-fibrotic effects with significant liver function improvement in a rat model of non-alcoholic steatohepatitis (NASH)

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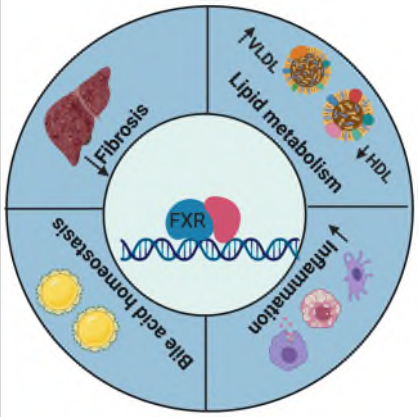
INTRODUCTION

Farnesoid X receptor (FXR) is a nuclear receptor that has emerged as a key regulator in the maintenance of bile acid homeostasis. FXR agonists are currently under clinical investigation for the management of various liver diseases such as primary biliary cholangitis (PBC) and nonalcoholic steatohepatitis (NASH). However, most preclinical studies have examined the effects of FXR agonists in mouse models where fibrosis progression to cirrhosis does not resemble that observed in humans. Here, we investigate the anti-fibrotic effects of the FXR agonist EDP-297 in a rat model of NASH cirrhosis.



METHODS

Adult male Wistar rats (175-200 g) were fed either normal chow (NC) or a choline-deficient, L-amino acid-defined, high fat diet with 60 kcal% fat and 0.1% methionine (CDAHFD) for 12 weeks. Rats were randomized to receive either vehicle control (0.5% methylcellulose (MC)), 0.1 mg/kg EDP-297, or 0.3 mg/kg EDP-297 by once-daily oral gavage at the first signs of fibrosis (5 weeks, n = 8 per group).

RESULTS

Treatment with EDP-297 significantly reduces liver fibrosis progression

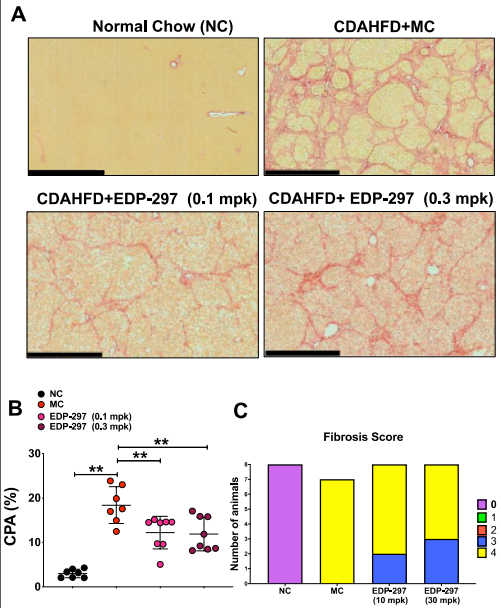
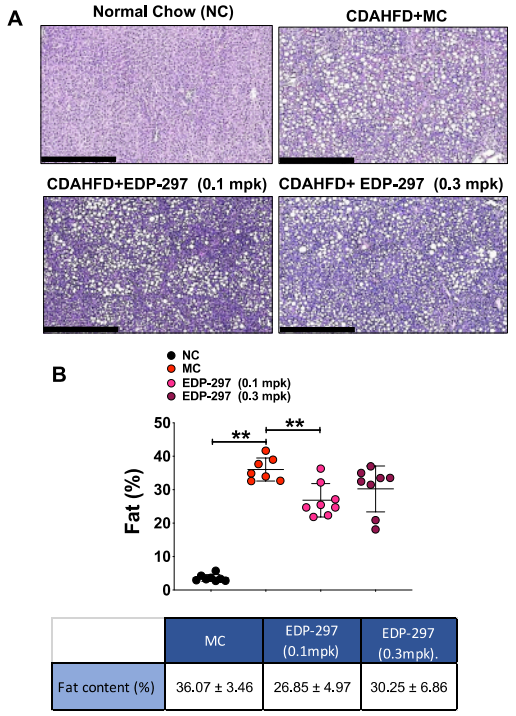


Figure1: A) Collagen Sirius Red staining on Normal Chow and CDAHFD-fed rats without drug (MC) and treated with EDP-297 (0.1 and 0.3 mpk). (B) EDP-297 treated rats have less fibrosis as measured by Collagen proportional area (CPA%). N=8, mean ±SD, One-way ANOVA, **p < 0.01. (C) Brunt fibrosis scores show improvement in histopathology of livers treated with EDP-297.

EDP-297 significantly decreased the liver fat contents in CDAHFD-fed rats



	MC	EDP-297 (0.1mpk)	EDP-297 (0.3mpk).
Fat content (%)	36.07 ± 3.46	26.85 ± 4.97	30.25 ± 6.86

Figure2: (A) H&E staining on Normal Chow and CDAHFD-fed rats without drug (MC) and treated with EDP-297 (0.1 and 0.3mpk). (B) EDP-297 (0.1 mpk). treated rats have less fat content as measured by Image J analysis. N=8, mean ±SD, One-way ANOVA, **p < 0.01.

EDP-297 improves liver functions significantly

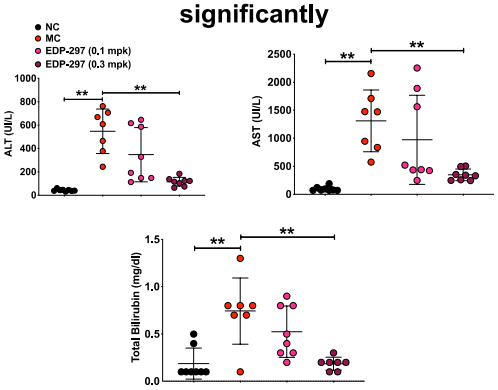


Figure3: Serum levels of Alanine transaminase (ALT), Aspartate transaminase (AST) and Total Bilirubin have improved significantly in CDAHFD-fed rats that received EDP-297 (0.3 mpk). N=8, mean ±SD, One-way ANOVA, **p < 0.01.

CONCLUSIONS

In a rat model of NASH cirrhosis that more closely resembles the human disease progression, EDP-297 at a remarkably low dose significantly reduced fibrosis progression and improved liver functions. These results suggest that EDP-297 may have potent anti-fibrotic effects in NASH patients with late-stage F3/4 fibrosis. Since the effective dose is quite low, it is possible that fewer side effects would be encountered in clinical trials.

REFERENCES

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