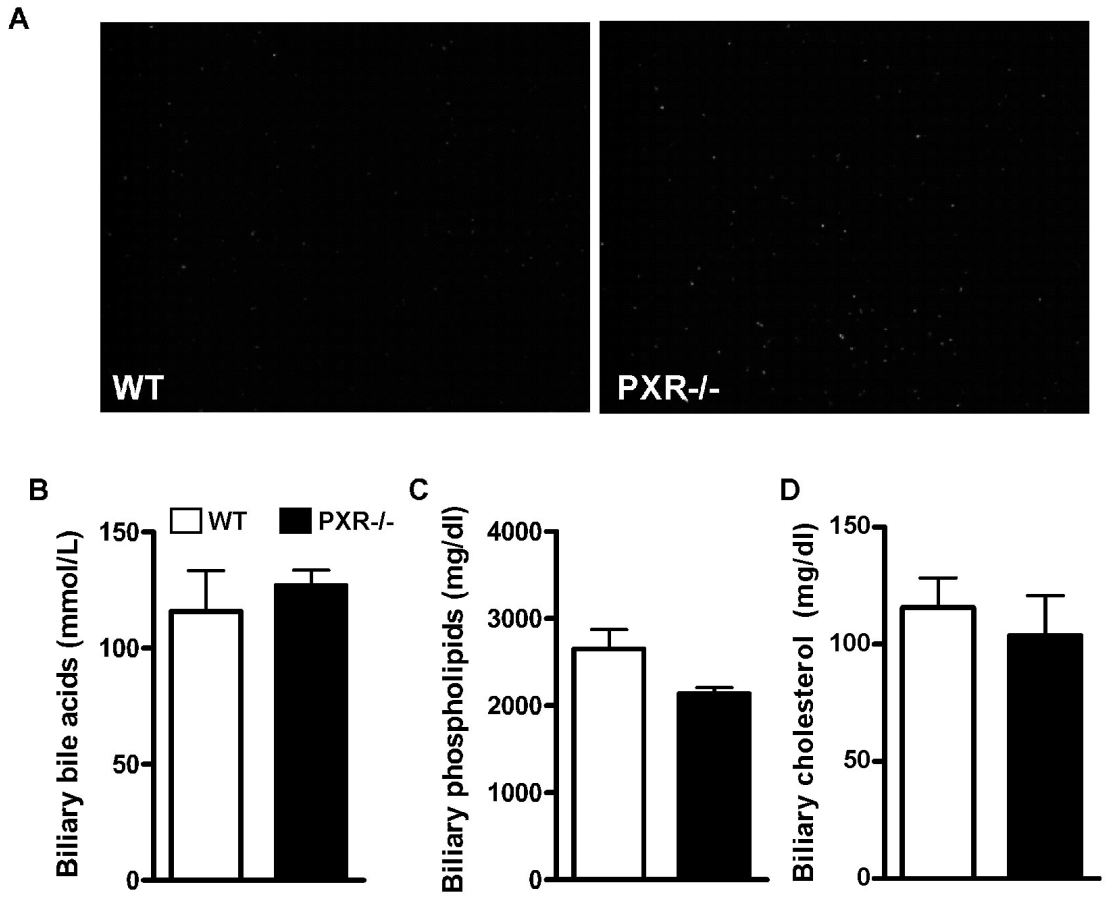
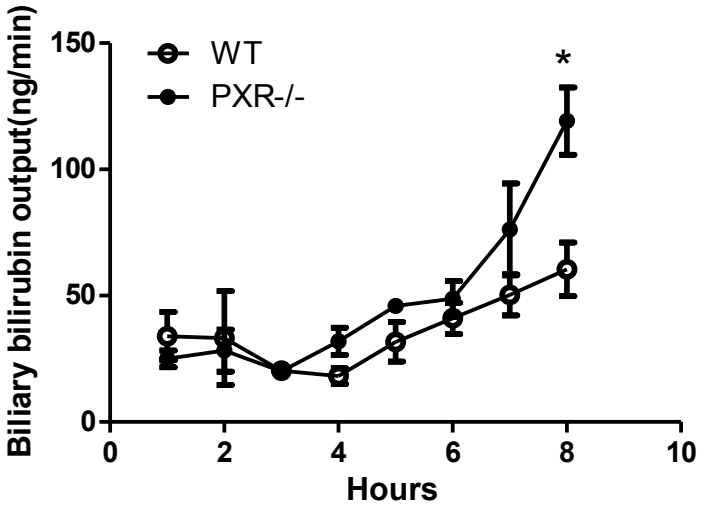
He et al., Supplementary Figure 1



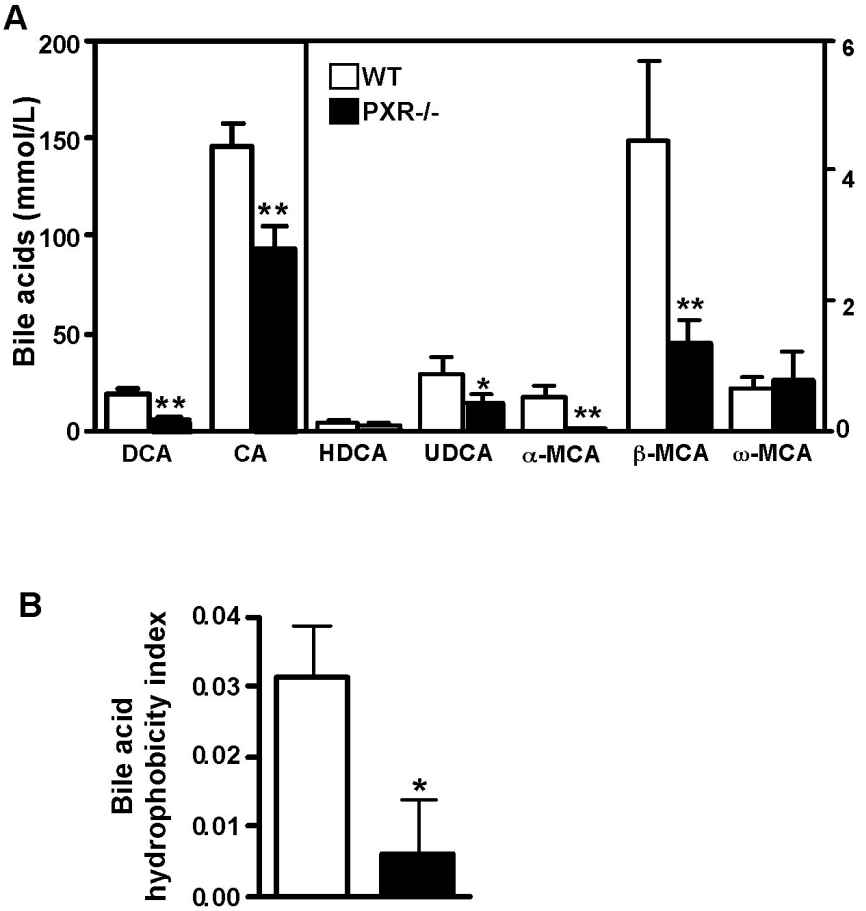
Supplementary Figure 1. PXR-/- mice were free of CGD in the absence of lithogenic diet. (A) No cholesterol crystals were observed in the bile of WT and PXR-/- mice maintained under chow diet. **(B-D)** Measurement of biliary bile acid (B), phospholipid (C), and cholesterol (D) levels.

He et al., Supplementary Figure 2



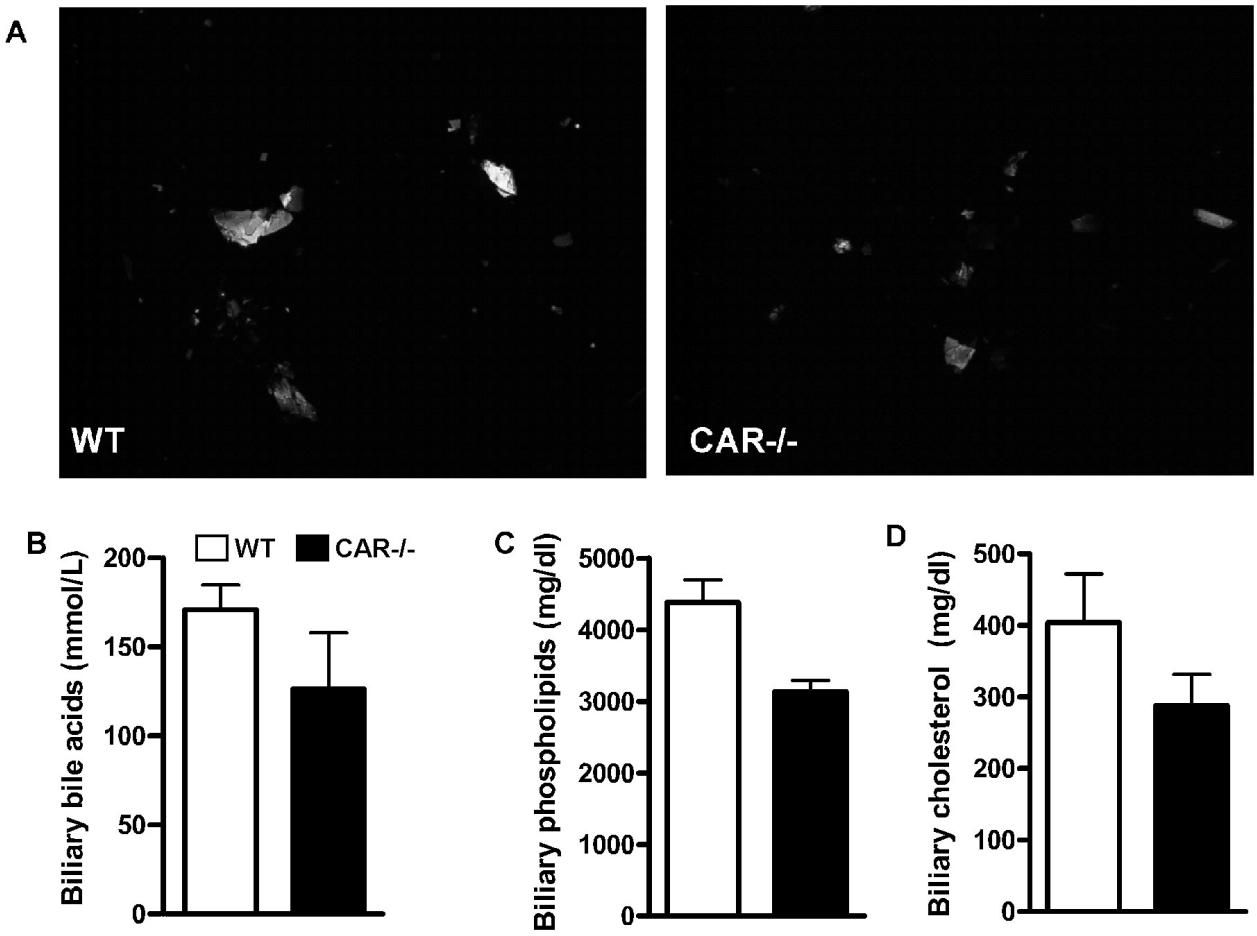
Supplementary Figure 2. Biliary bilirubin output in lithogenic diet-fed WT and PXR-/- mice. Samples are the same as those used in Fig. 2C. *, P<0.05.

He et al., Supplementary Fig. 3



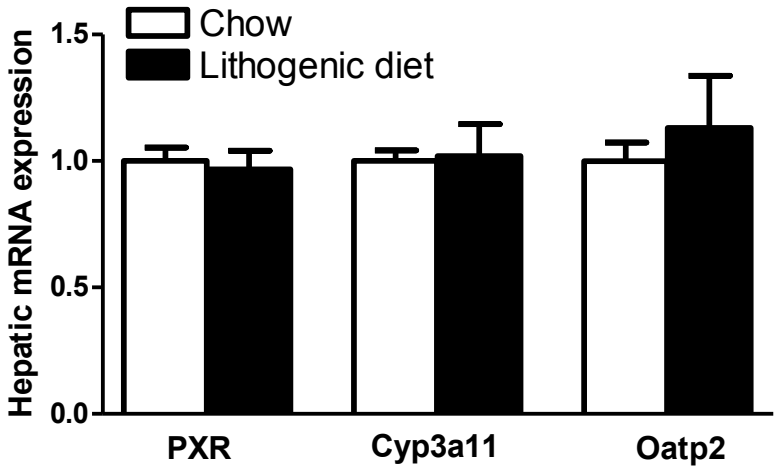
Supplementary Figure 3. Profiles of bile acid species in WT and PXR-/- mice fed with lithogenic diet for 4 weeks. (A) Biliary bile acid species profiled by GC-MS. **(B)** Bile acid hydrophobicity index calculated based on the species profile. DCA, deoxycholate; CA, cholate; HDCA, hyodeoxycholate; UDCA, ursodeoxycholate; MCA, muricholate.

He et al., Supplementary Figure 4



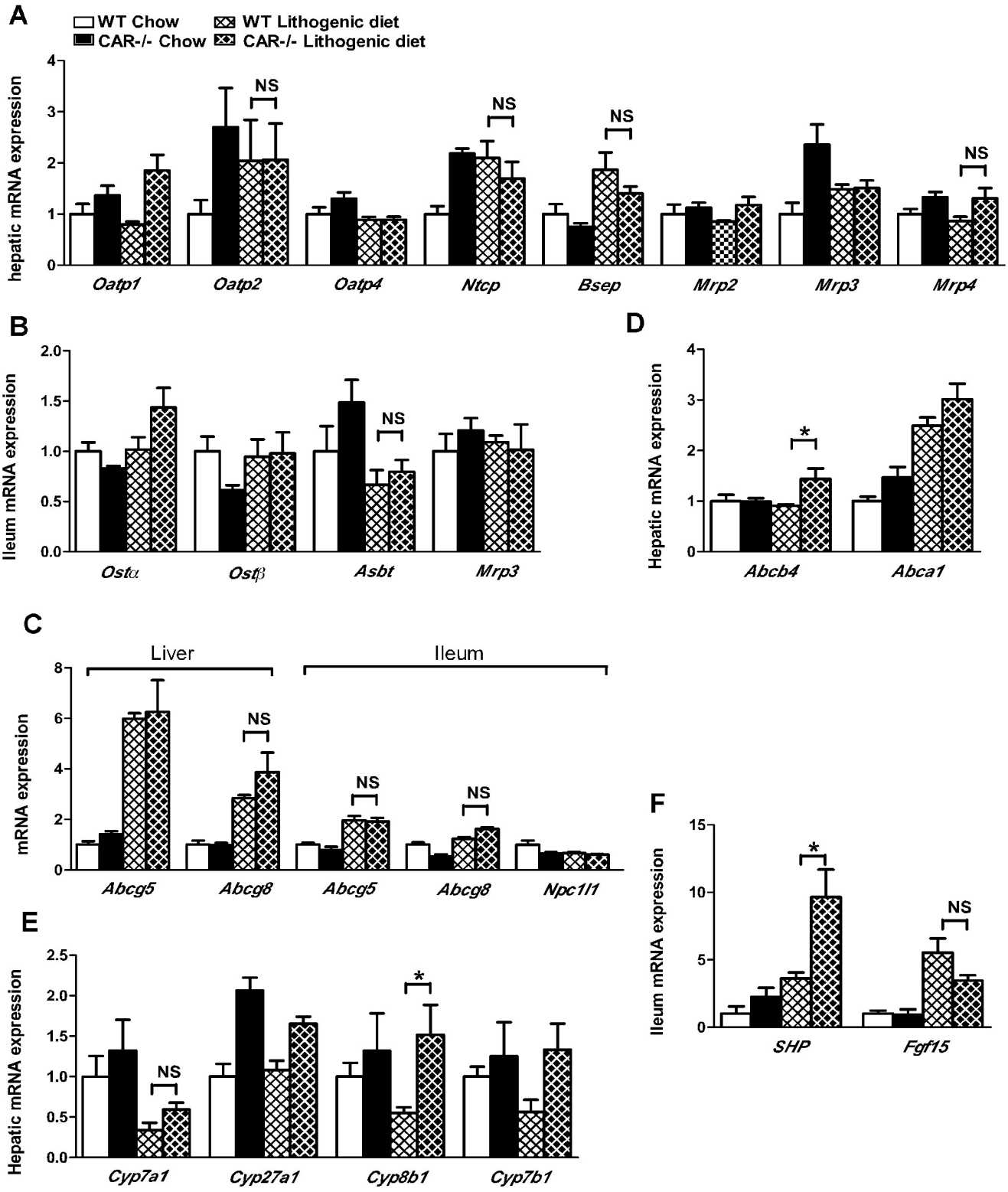
Supplementary Figure 4. Loss of CAR failed to sensitize mice to CGD. WT and CAR-/- mice were fed with lithogenic diet for 4 weeks before being analyzed for cholesterol crystals **(A)**, as well as the biliary levels of bile acids **(B)**, phospholipids **(C)**, and cholesterol **(D)**.

He et al., Supplementary Figure 5



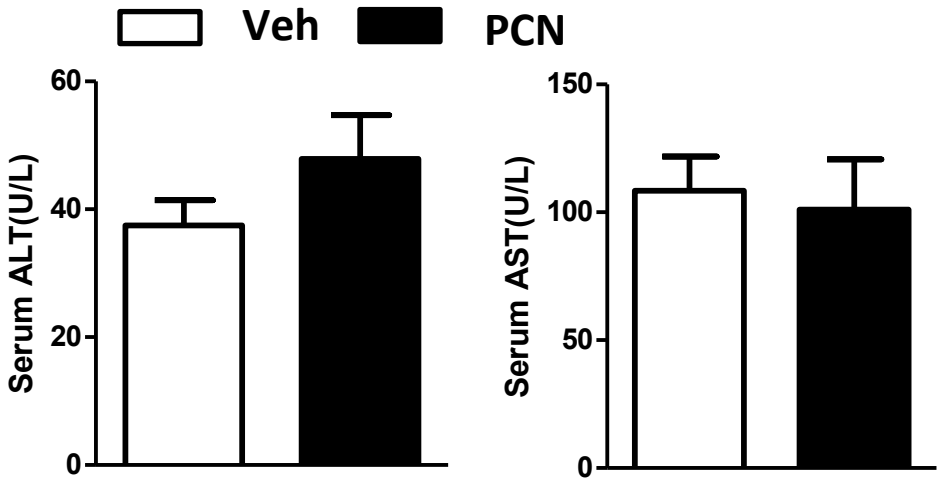
Supplementary Figure 5. The lithogenic diet had little effect on the expression of PXR and its target genes Cyp3a11 and Oatp2 in WT mice. The mRNA expression was measured by real-time PCR analysis.

He et al., Supplementary Figure 6



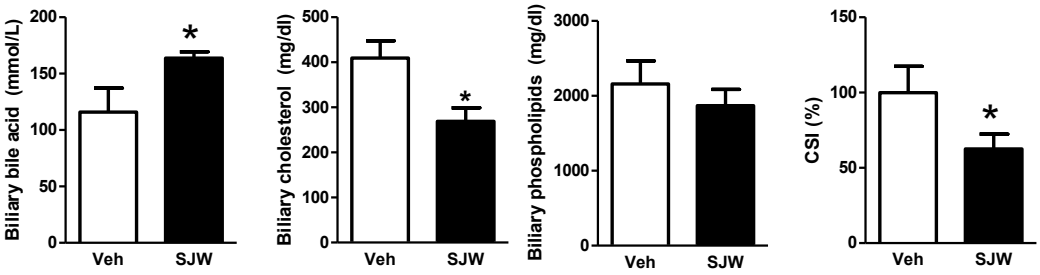
Supplementary Figure 6. Gene expression profiles in CAR-/- mice. The mRNA expression was measured by real-time PCR analysis. **(A and B)** Expression of hepatic (A) and ileal (B) bile acid transporters. **(C)** Expression of hepatic and ileal cholesterol transporters. **(D)** Expression of hepatic phospholipid transporters. **(E)** Expression of hepatic bile acid synthesis genes. **(F)** Ileal expression of Fgf15 and SHP. N=5 for each group. * $P<0.05$; NS, statistically not significant.

He et al., Supplementary Figure 7



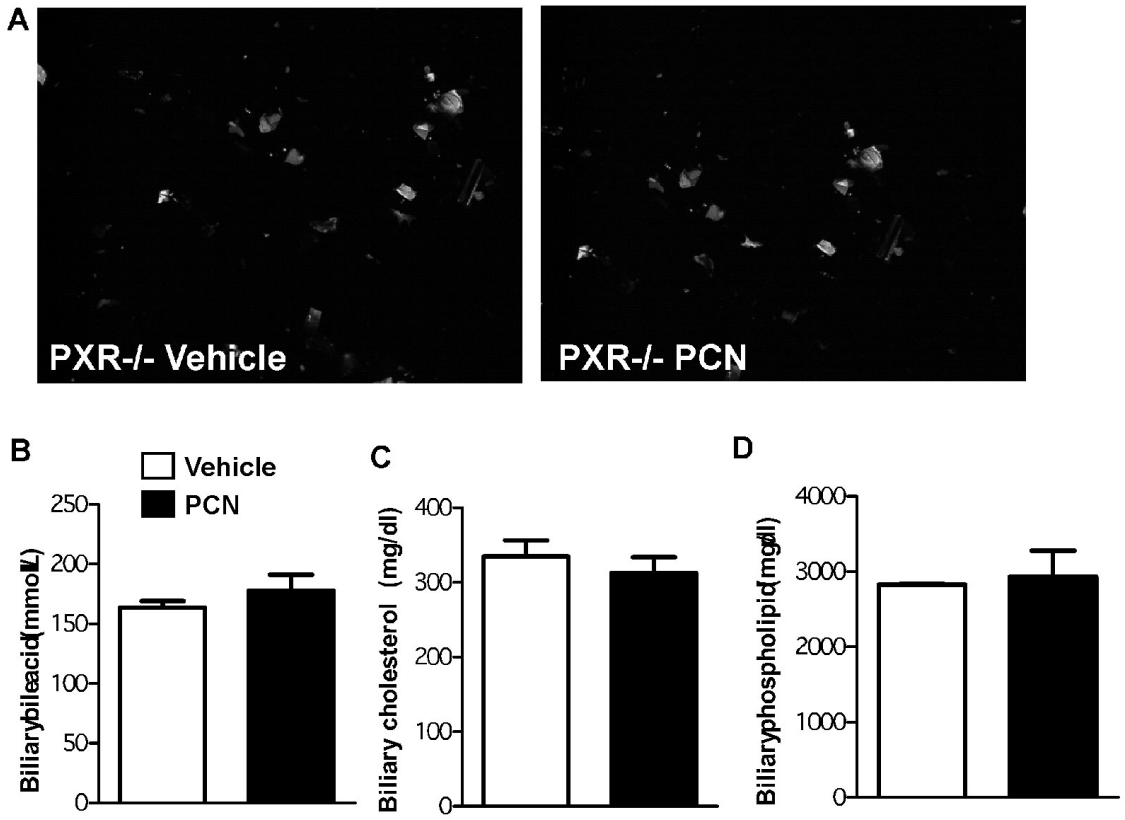
Supplementary Figure 7. PCN did not cause appreciable hepatotoxicity in C57L mice. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

He et al., Supplementary Figure 8



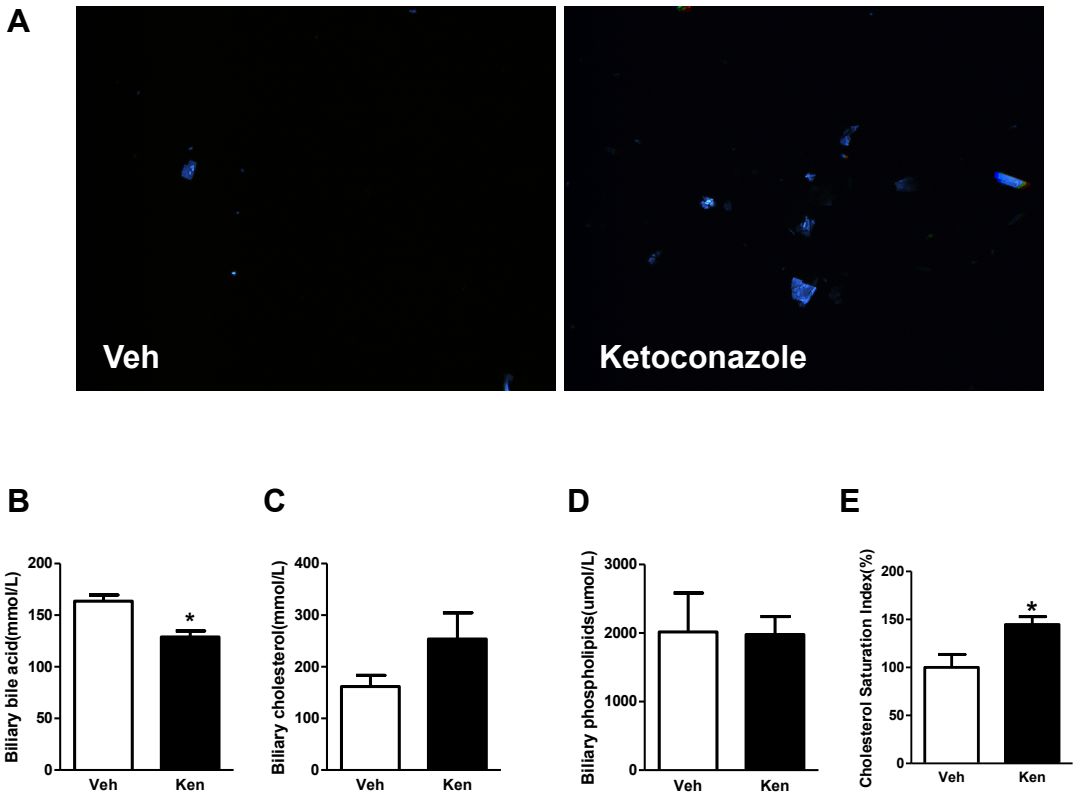
Supplementary Figure 8. Biliary biochemistry in vehicle and St. John‘s wort (SJW) treated and lithogenic diet-fed PXR-/- mice. *, P<0.05.

He et al., Supplementary Figure 9



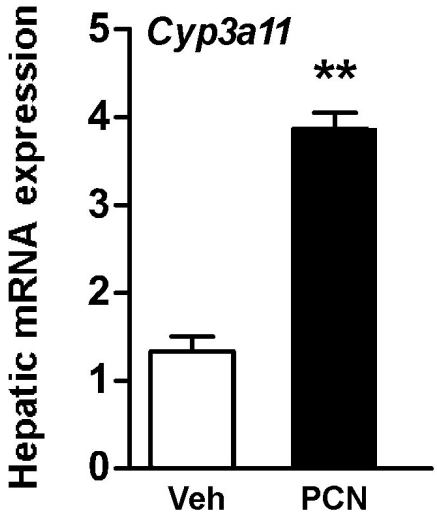
Supplementary Figure 9. PCN failed to inhibit lithogenesis in PXR-/- mice. (**A**) Microscopic examination of cholesterol crystals in male PXR-/- mice treated with vehicle (Veh) or PCN. All mice were fed with lithogenic diet for 10 days. **(B-D)** Biliary concentrations of bile acids (B), cholesterol (C), and phospholipids (D). N=5 for each group.

He et al., Supplementary Figure 10



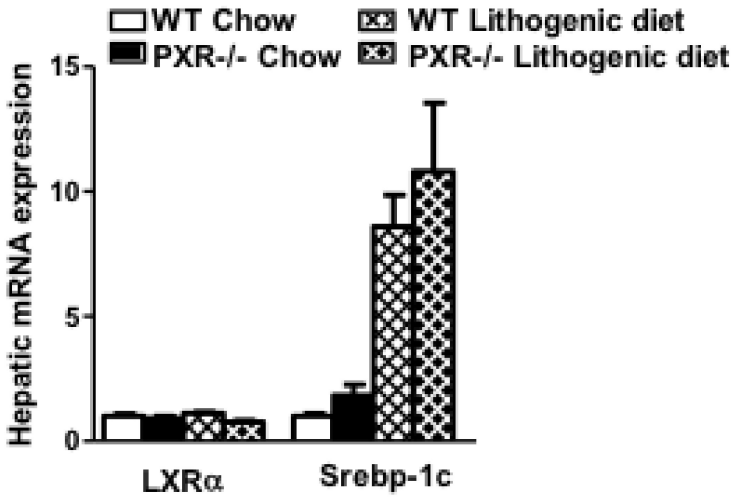
Supplementary Figure 10. Treatment with ketoconazole sensitized WT mice to CGD. Male mice received daily i.p. injection of ketoconazole (50 mg/kg) or vehicle for 4 days before treatment of lithogenic diet for 10 days. The drug treatment continued until the completion of the experiment. (A) Microscopic examination of cholesterol crystals. (B-E) Biliary concentrations of bile acids (B), cholesterol (C), phospholipids (D), and the calculated CSI (E). N=5 for each group. * $P<0.05$.

He et al., Supplementary Figure 11



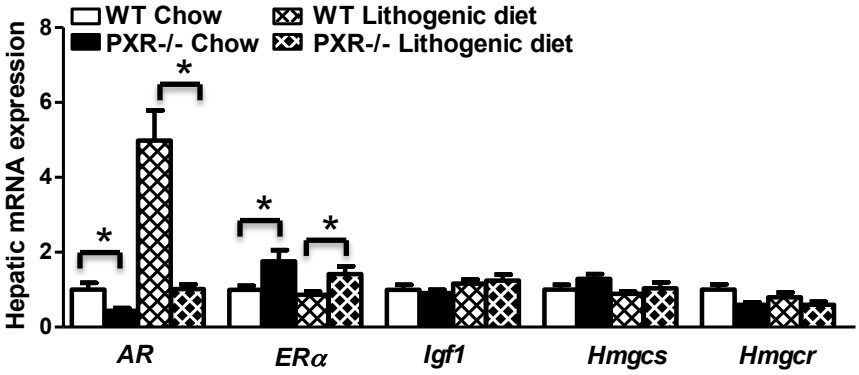
Supplementary Figure 11. PCN efficiently induced Cyp3a11 gene expression in the liver in C57L mice. The mRNA expression was measured by real-time PCR analysis. **, $P<0.01$.

He et al., Supplementary Figure 12



Supplementary Figure 12. Expression of LXRα and it target gene Srebp-1c in WT and PXR-/- mice. The mRNA expression was measured by real-time PCR analysis.

He et al., Supplementary Figure 13



Supplementary Figure 13. Expression of AR and ERα and their responsive genes in WT and PXR-/- mice. The mRNA expression was measured by real-time PCR analysis. *, $P<0.05$.

He *et al.*, Supplementary Table 1: List of real-time PCR primers

Gene name	Sequence
Abca1 forward	5'-TCCTCATCCTCGTCATTCAAA-3'
Abca1 reverse	5'-GGACTTGGTAGGACGGAACCT-3'
Abcb4 forward	5'-GGTTGCTGATGCTGCCTAGT-3'
Abcb4 reverse	5'-CTTGAGGCAGCGAGAAATG-3'
Abcg5 forward	5'-TCAATGAGTTTTACGGCCTGAA-3'
Abcg5reverse	5'-GCACATCGGGTGATTTAGCA-3'
Abcg8 forward	5'-TGCCCACCTTCCACATGTC-3'
Abcg8 reverse	5'-ATGAAGCCGGCAGTAAGGTAGA-3'
Asbt forward	5'-TGGGTTTCTTCCTGGCTAGACT-3'
Asbt reverse	5'-TGTTCTGCATTCCAGTTTCCAA-3'
Bsep forward	5'-AAGCTACATCTGCCTTAGACACAGAA-3'
Bsep reverse	5'-CAATACAGGTCCGACCCTCTCT-3'
Cyp27a1 forward	5'-GCCTCACCTATGGGATCTTCA-3'
Cyp27a1 reverse	5'-TCAAAGCCTGACGCAGATG-3'
Cyp3a11 reverse	5'-TCCAGGTATTCCATCTCCATCAC-3'
Cyp7a1 forward	5'-AGCAACTAAACAACCTGCCAGTACTA-3'
Cyp7a1 reverse	5'-GTCCGGATATTCAAGGATGCA-3'
Cyp7b1 forward	5'-TAGCCCTCTTTCCTCCACTCATA-3'
Cyp7b1 reverse	5'-GAACCGATCGAACCTAAATTCCT-3'
Cyp8b1 forward	5'-AGTGCCCTGAAACACACTCC-3'
Cyp8b1 reverse	5'-TCCTCCTGTACCACCCTGAG-3'
Cypa11 forward	5'-AAACTGCAGGATGAGATCGATGA-3'
Fgf15 forward	5'-AGACGATTGCCATCAAGGAC-3'
Fgf15 reverse	5'-CAGTCCATTTCCTCCCTGAA-3'
Fgfr4 forward	5'-AGTCAAATGGATGGCTCCAG-3'
Fgfr4 reverse	5'-GAGGGTGAAGATTTCCCACA-3'
β-Klotho forward	5'-TCCCCTGTGATTTCTCTTGG-3'
β-Klotho reverse	5'-GAGCAATCTGTTGCCAGTGA-3'
Mrp2 forward	5'-CGACCATCCGGAACGAGTT-3'
Mrp2 reverse	5'-GCAGCCTGTGTGCGATAGTG-3'
Mrp3 forward	5'-TGGCCCGAGCTGTTTATAGTG-3'
Mrp3 reverse	5'-CAGCCGACAGTGGGTCATC-3'
Mrp4 forward	5'-CAAAGACATCGGACACATGG-3'
Mrp4 reverse	5'-CACACTTACGACGAGGAGCA-3'
Ntcp forward	5'-AAATCGGATGGTTTGACTGC-3'
Ntcp reverse	5'-GGCAATGGCTTCATCAATTT-3'
Oatp1 forward	5'-TCCCCGCAGTCTTCATTCTAA-3'
Oatp1 reverse	5'-TGGATGTCGCCAGGGAAAT-3'
Oatp2 forward	5'-ATTAGGTGGTATTCCAGCACCTATTT-3'
Oatp2 reverse	5'-CTGGCTCACCACATTTTAGAGTTC-3'
Oatp4 forward	5'-CAAACTCAGCATCCAAGCAA-3'
Oatp4 reverse	5'-GGCTGCCAAAAATATCCTGA-3'
OSTα forward	5'-TACAAGAACACCCTTTGCCC-3'
OSTα reverse	5'-CGAGGAATCCAGAGACCAAA-3'
OSTβ forward	5'-GTATTTTCGTGCAGAAGATGCG-3'
OSTβ Reverse	5'-TTTCTGTTTGCCAGGATGCTC-3'
SHP forward	5'-CTCATGGCCTCTACCCTCAA-3'
SHP reverse	5'-GGTCACCTCAGCAAAAGCAT-3'

He *et al*., Supplementary Table 2. Hepatic lipid profile

	Chow diet		Lithogenic diet	
	WT	**PXR-/-**	**WT**	**PXR-/-**
Cholesterol (mg/g tissue)	**1.09±0.09**	**1.37±0.28**	**34.27±6.15**	**32.37±2.77**
Phospholipids (mg/g tissue)	**9.56±1.76**	**14.98±2.36***	**19.42±1.55**	**22.65±1.77***
Bile acids (nmol/g tissue)	**263.00±87.36**	**352.98±106.91**	**403.49±55.47**	**596.53±128.92***

*, $P<0.05$

He *et al*., Supplementary Table 3. Serum biochemistry

	Chow		Lithogenic diet	
	WT	**PXR-/-**	**WT**	**PXR-/-**
Cholesterol (mg/dl)	**105.05±3.48**	**51.43±2.56****	**111.50±3.31**	**95.60±5.21**
Phospholipids (mg/dl)	**294.98±5.85**	**176.15±3.37****	**202.42±5.27**	**142.30±4.58***
Bile acids (μmol/L)	**46.01±5.5**	**29.60±3.02**	**27.71±2.56**	**125.20±1.97***
Total bilirubin (mg/dl)	**0.84±0.44**	**0.76±0.52**	**0.77±0.27**	**0.64±0.41**
ALT (U/L)	**53.15±5.91**	**47.95±3.53**	**53.83±3.11**	**55.65±4.086**
AST (U/L)	**80.53±7.11**	**66.69±4.29**	**77.86±3.82**	**83.2±5.04**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; *, $P<0.05$; **, $P<0.01$. Note the serum samples were collected after the mice were fasted overnight.