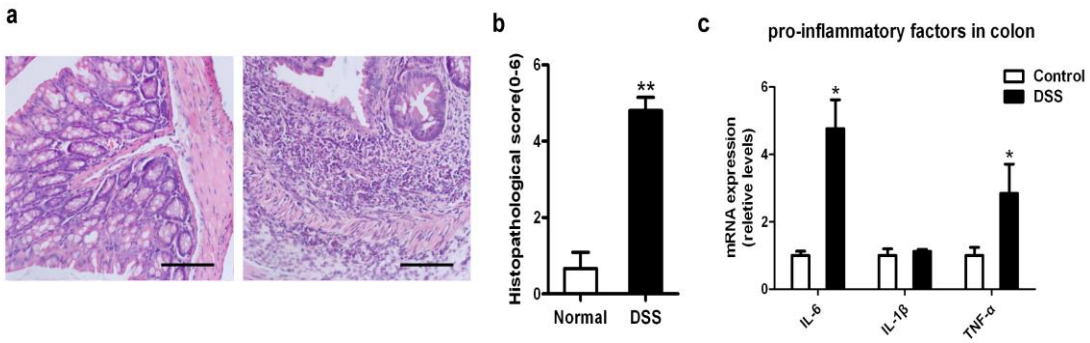
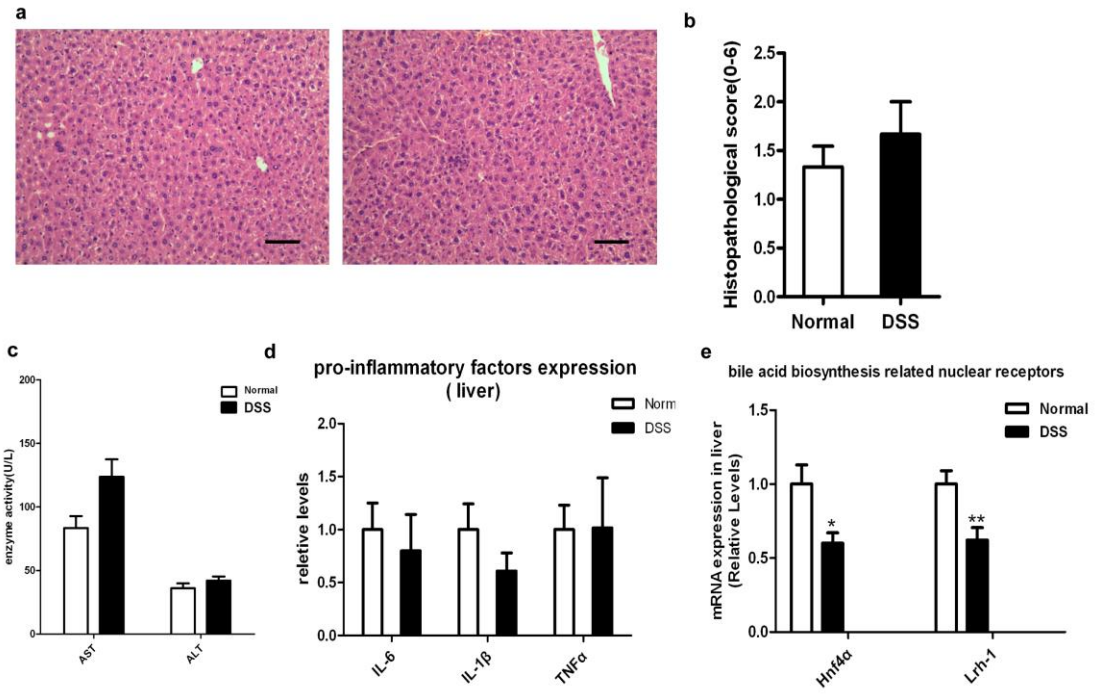
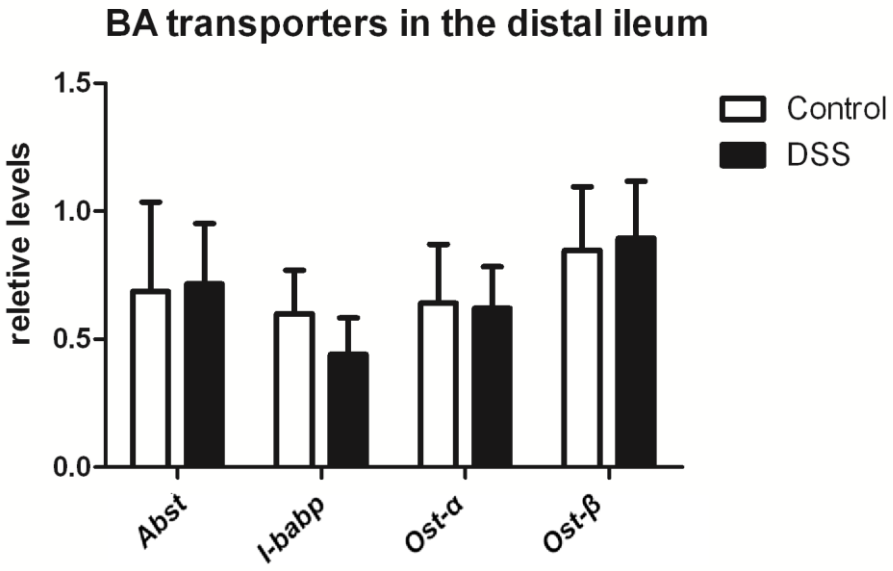


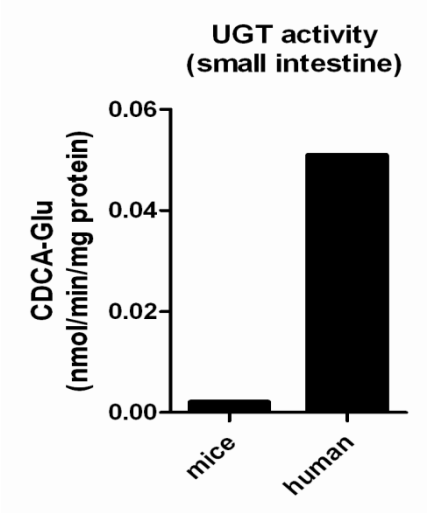
Supplementary Fig. 1. DSS induced chronic colitis model. (a) Hematoxylin and eosin staining of colon tissues (Scale bar, 100 μm). (b) Histopathological scores. (c) The mRNA expression of *IL-6, IL-1β, and Tnf-α* in colon. Results are mean ± s.e.m (n=6; * *P*<0.05; ** *P*<0.01; VS control, Student's *t* test.



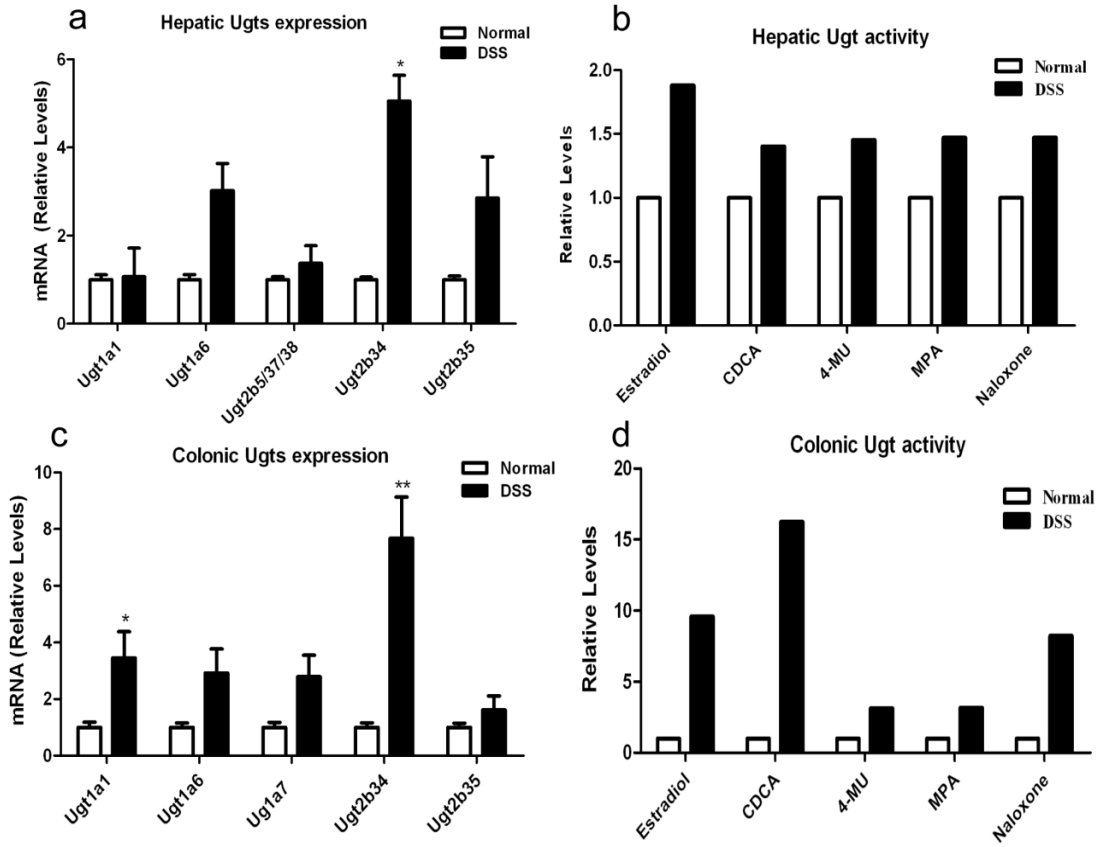
Supplementary Fig. 2. Characterization of *Cyp7a1* positive transcriptional factors in liver. (a) Hematoxylin and eosin staining of liver (Scale bar, 100 μm). (b) Histopathological scores. (c) Analysis of biochemical parameters indicative of liver damage (serum AST, and ALT activities). (d) The mRNA expression of *IL-6*, *IL-1β*, and *Tnf-α* in liver. (e) The expression of genes in the transcriptional activation pathway of bile acids synthesis, as quantified by qRT-PCR. Results of quantitative analysis values are expressed as mean ± s.e.m (n=6) and are plotted as fold change. **P*<0.05, ***P*<0.01, VS normal control, Student's *t* test.



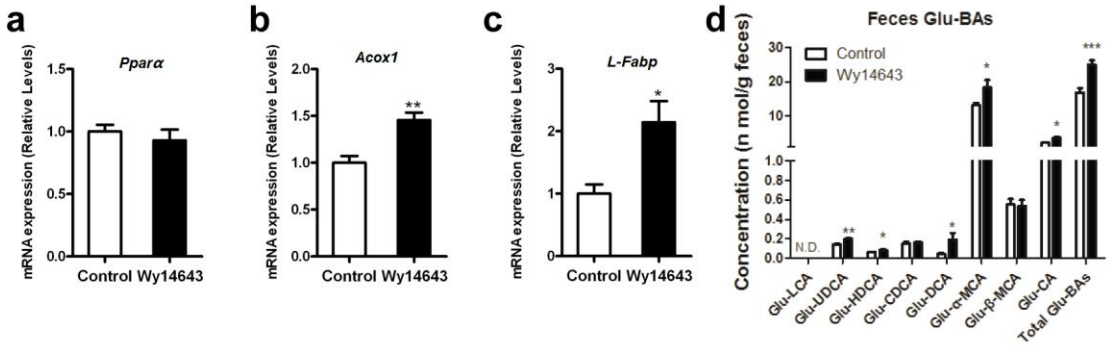
Supplementary Fig.3. Characterization of intestinal transporters of bile acids. The mRNA expression of *Asbt*, *Ostα*, and *Ostβ* and the intracellular bile acids binding protein *Ibabp* in distal ileum. Results are mean ± s.e.m (n=6).



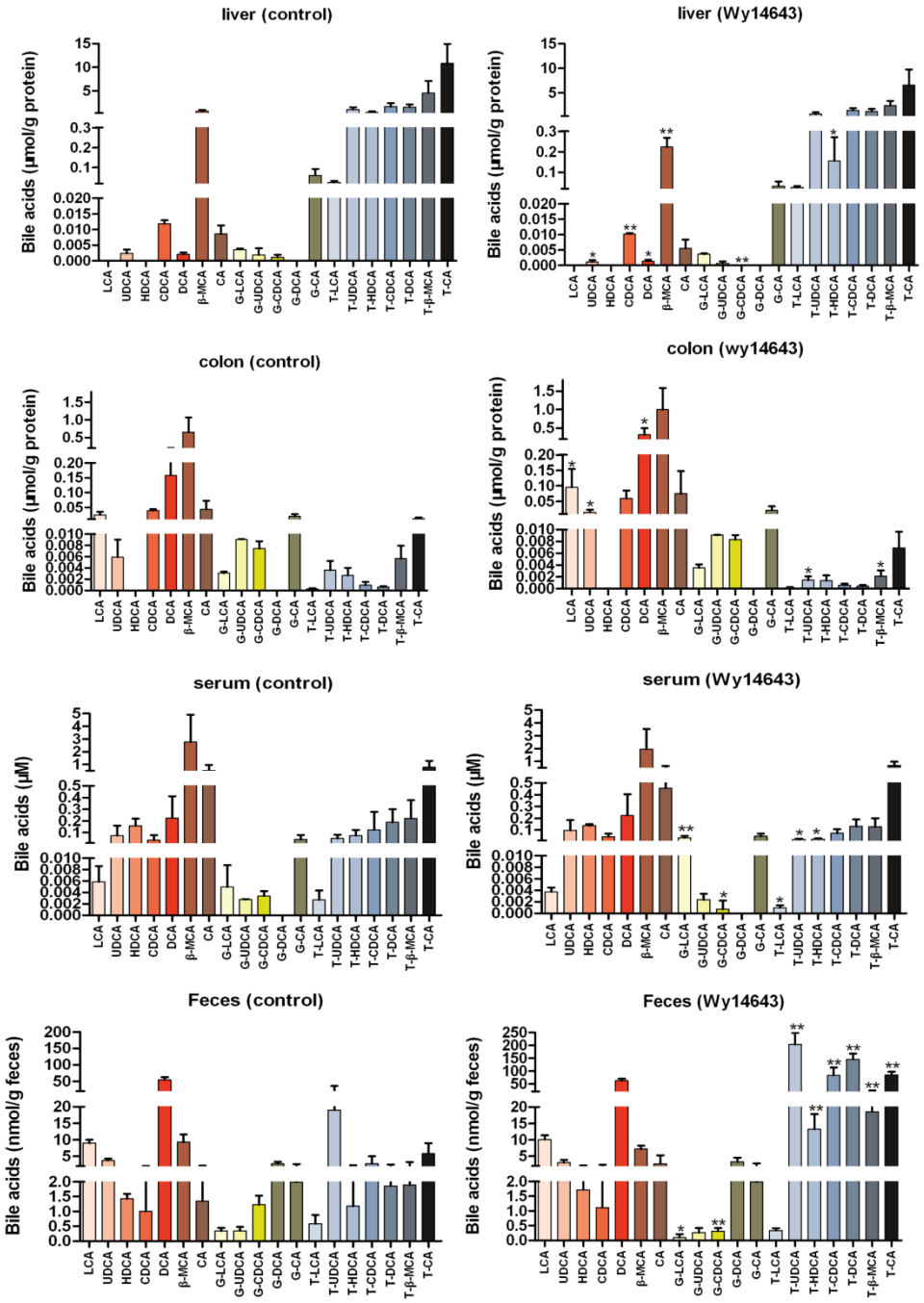
Supplementary Fig. 4. Glucuronidation of CDCA in human intestinal S9. Intestinal UGT activities toward CDCA were determined in pooled mice intestinal S9 (n=6) and pooled human intestinal S9 (BD Biosciences, Bedford, MA, USA). Results represent the mean of triplicate determinations.



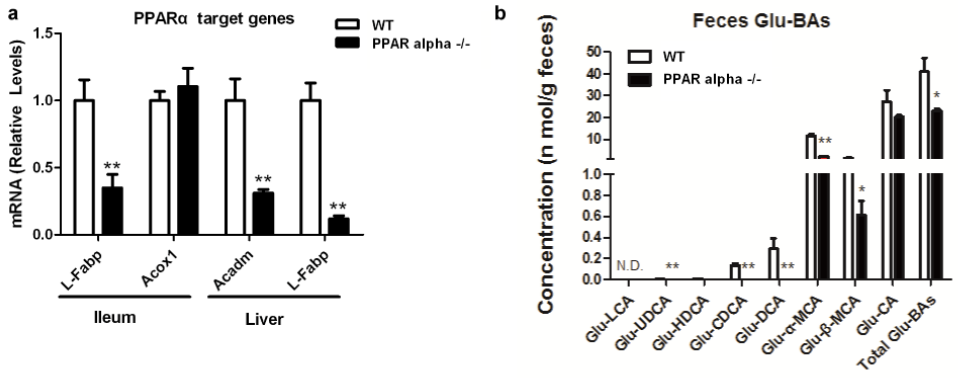
Supplementary Fig. 5. Disturbance of hepatic and colonic UGTs in colitis mice. The mRNA expression and activity of *Ugt1a1, Ugt1a6, Ugt1a7, Ugt2b34, and Ugt2b35* in mice liver (a, b) and colon (c, d). Results of mRNA expression are mean ± s.e.m and are plotted as fold change (n=6; *, P<0.05; **, P<0.01; VS control, Student's t test). UGT activities toward each substrate were determined in pooled S9 (n=6). Results represent the mean of triplicate determinations.



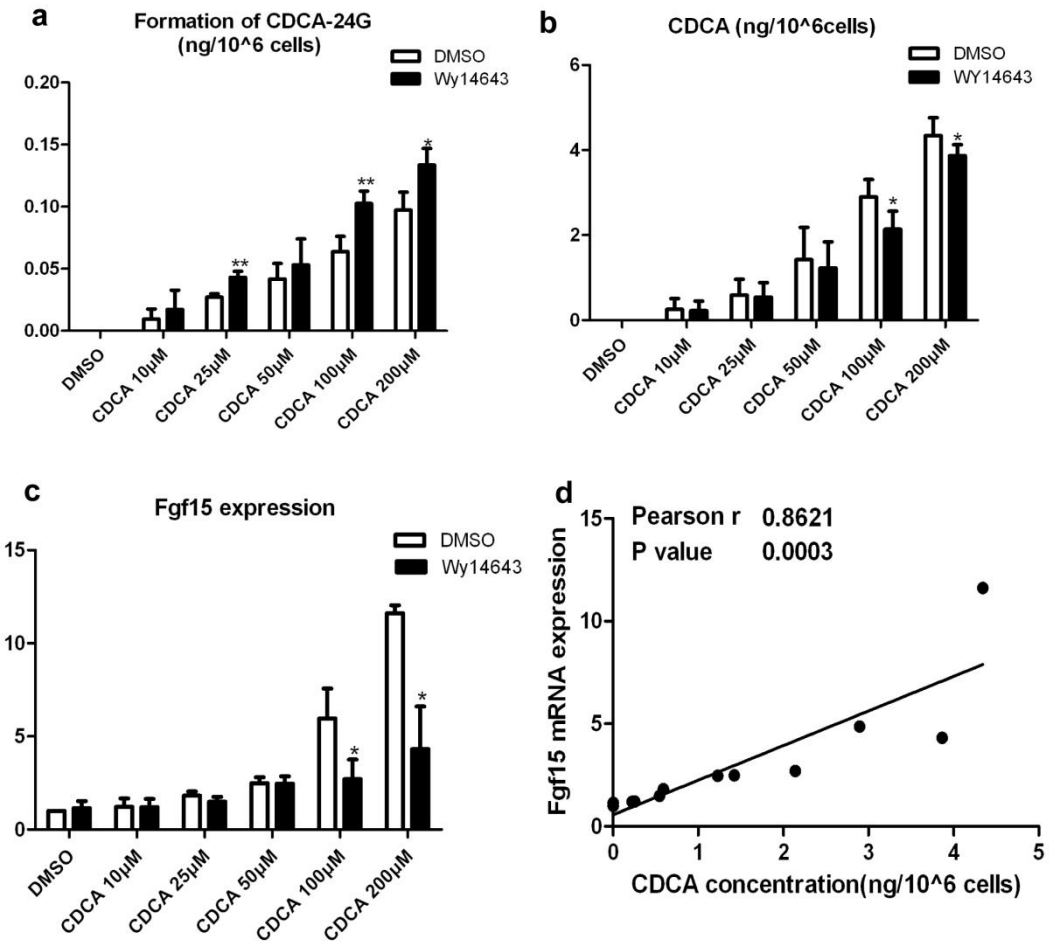
Supplementary Fig. 6. Wy14643 activates PPARα and promotes bile acid glucuronidation. (a)-(c) The mRNA expression of *Ppara*, *Acox1,* and *L-Fabp* in the distal ileum of control and Wy14643-treated mice;(d) Bile acid glucuronides in feces. Results are mean ± s.e.m of 8 mice. **P*<0.05, ***P*<0.01 VS control, Student's *t* test.



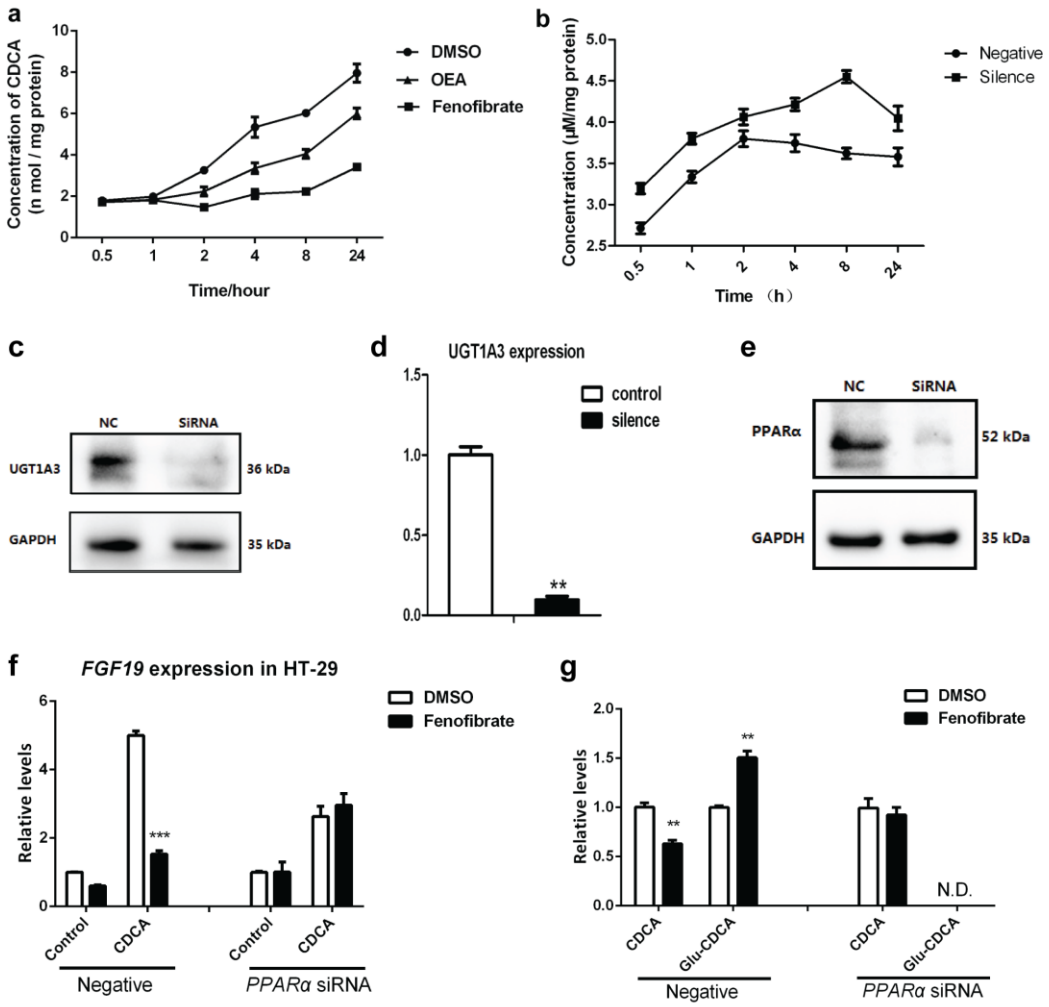
Supplementary Fig. 7. PPARα activation by Wy14643 disrupts bile acid homeostasis. Compartmental bile acid profiles of control and Wy14643-treated mice using UFLC-Triple-TOF analysis. Results are mean ± s.e.m of 8 mice, **P*<0.05, ***P*<0.01 VS control, Student's *t* test. CA, cholic acid; LCA, lithocholic acid; HDCA, hyodeoxycholic Acid; UDCA, ursodeoxycholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; MCA, muricholic acid; T, tauro-conjugated species; G, glyco-conjugated species.



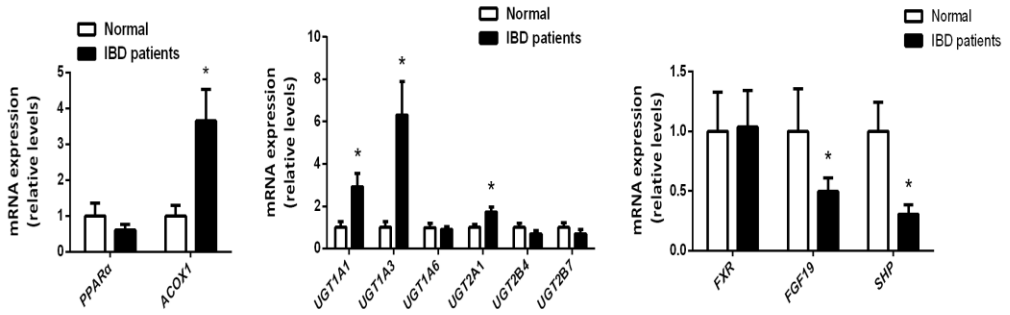
Supplementary Fig. 8. *Pparα*-null mice show reduced glucuronidation of bile acids. (a) The mRNA expression of *Acox1*, *L-Fabp* in the ileum and *Acadm* and *L-Fabp* in the liver of control and *Pparα*-/- mice. (b) Bile acid glucuronides in feces. Results of quantitative analysis values are expressed as means ± s.e.m (n=6) and are plotted as fold change. **P*<0.05, ***P*<0.01 VS WT, Student's *t* test.



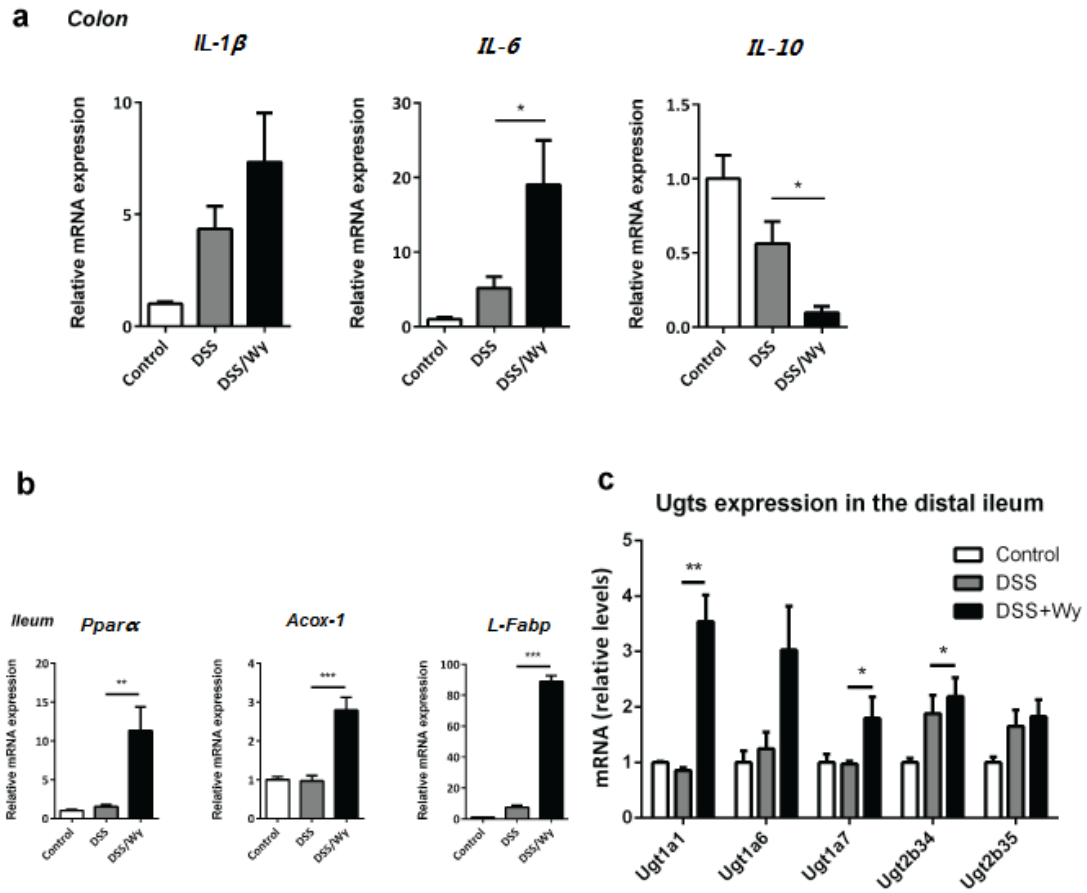
Supplementary Fig. 9. Cellular disposition of CDCA and FXR-FGF15 signaling in IEC-6 cells. (a) Formation of CDCA-24G in IEC-6 cell line treated with different concentrations of CDCA. (b) Intra-cellular concentration of CDCA in IEC-6 cell line treated with different concentrations of CDCA. (c) The mRNA expression of *Fgf15* in the IEC-6 cell line treated with different concentrations of CDCA. (d) The correlation of CDCA concentration and the expression of *Fgf15*. Results are the mean ± s.e.m of three independent experiments and are plotted as fold change, **P*<0.05, ***P*<0.01 VS DMSO, Student's *t* test.



Supplementary Fig. 10. PPARα-UGT1A3 determines the cellular disposition of CDCA in HT29 cells. (a-b) HT29 Cells were incubated with 50 μM CDCA in the absence or presence of PAPRα agonist (a) or UGT1A3 Stealth RNAi (b) for 0.5, 1, 2, 4, 8, and 24 hours. (c-d) Verification of the transfection efficiency of *UGT1A3* stealth RNAi in HT29 cells. (c) Western Blot and (d) qRT-PCR analysis of *UGT1A3*. (e-g) HT29 cells were transfected with PAPRα siRNA or negative control siRNA. (e) Western Blot analysis of PAPRα. (f) PAPRα-dependent effect of fenofibrate in *FGF19* expression. (g) PAPRα-dependent effect of fenofibrate in CDCA cellular disposition. The intracellular accumulation of CDCA and its glucuronide was detected using LC-MS analysis. Results are mean ± s.e.m of three independent experiments and are plotted as fold change. ***P*<0.01 VS control, Student's *t* test.



Supplementary Fig. 11. Colon biopsies from IBD patients show upregulated intestinal PPARα-UGTs and deceased FXR-FGF19 signaling. RNA extracts were prepared from the colon biopsies of 8 healthy humans and 13 IBD patients (5 ulcerative colitis and 8 Crohn's disease patients). (a) The mRNA expression of *PPARα* and *ACOX1*. (b) The mRNA expression of *UGTs.* (c) The mRNA expression of *FXR, FGF19* and *SHP.* Data represent the mean ± s.e.m. **P*<0.05, ***P*<0.01 VS normal control, Student's *t* test.



Supplementary Fig. 12. Wy14643 treatment aggravates DSS-induced colitis. (a) The mRNA expression of cytokines in colon. (b) The mRNA expression of *Pparα*, *Acox-1* and *L-Fabp*. (c) The mRNA expression of *Ugts in the distal ileum.* Results are means ± s.e.m of 6 mice. **P*<0.05, ***P*<0.01, VS DSS, Student's *t* test.

Fig 2b.

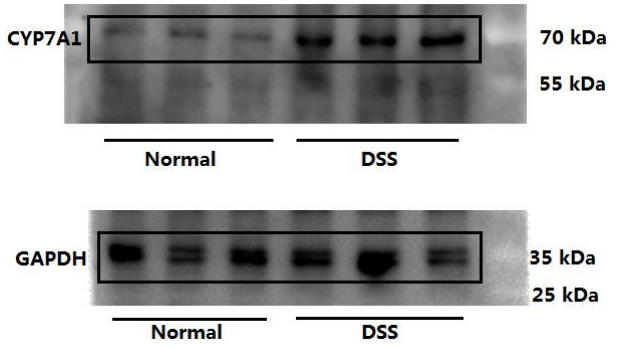


Fig 4e.

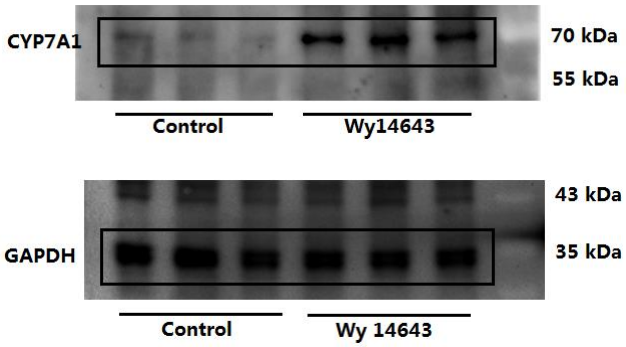
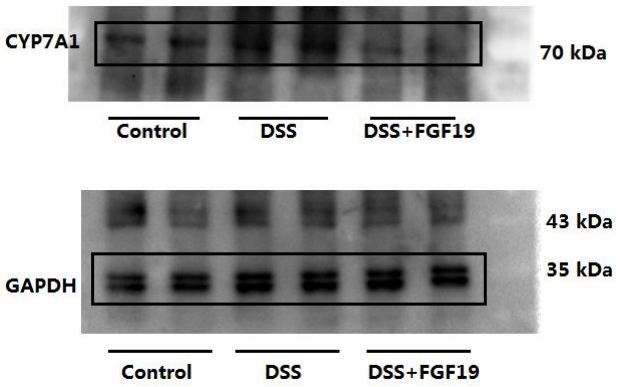


Fig 8f.



Supplementary Fig. 13. Unedited immunoblotting images in this study.

Supplementary Table 1. Incubation conditions and UGT activities of normal and DSS-treated mice

Substrates	Incubation Conditions			UGT activities (nmol/min/mg protein)					
	S9	Time	Substrate	Liver		Small intestine		colon	
	(mg/ml)	(min)	(μM)	Normal	DSS	Normal	DSS	Normal	DSS
Estradiol	0.4	30	20	0.10	0.19	0.0024	0.0074	0.0017	0.016
CDCA	1	60	50	0.142	0.20	0.0020	0.0080	0.0022	0.035
4-MU	0.1	15	100	13.6	19.8	3.90	11.07	2.50	7.85
MPA	0.2	30	200	1.61	2.37	0.13	0.24	0.12	0.39
Naloxone	0.5	60	20	0.28	0.41	0.00022	0.00071	0.00025	0.0020

Colitis was induced by administration of 2.5% (w/v) DSS in drinking water for 7 days and a 14 days washout with drinking water for 3 cycles. Results of UGT activity were determined toward various substrates in pooled mice S9 (n=6) and are presented as the mean of triplicate determinations.

Supplementary Table 2. Primer sequences for qRT-PCR (mice)

Gene	Sequence
Cyp7a1	TACTAGATAGCATCATCAAGGAGGCTC CCATCCTCAAGGTGCAGAGTG
Cyp7b1	GAGCCTATCTACTTCTACAA TTCTGTGTTCCAATCTGT
Cyp8b1	GATAGGGGAAGAGAGCCACC TCCTCAGGGTGGTACAGGAG
Cyp27a1	GAAGCCATCACCTATATC ATAGACTGAGTTCTGGAA
Fgf15	CAGTCTTCCTCCGAGTAGCG TGAAGACGATTGCCATCAAG
Fxr	GCACGCTGATCAGACAGCTA CAGGAGGGTCTGTTGGTCTG
Hnf4α	GCTGTCCTCGTAGCTTGACC TTAAGAAGTGCTTCCGGGCT
I-Babp	CCTTCAGTGGCAAATATG GACCTCTGTGATGATCTT
Lrh-1	TCAAGAGCTCACTCCAGCAG TTGAGTGGGCCAGGAGTAGT
Shp	GTACCTGAAGGGCACGATCC GTGAAGTCTTGGAGCCCTGGT

Il-6	ATCCAGTTGCCTTCTTGGGACTGA TAAGCCTCCGACTTGTGAAGTGGT
IL-1β	CCTCGTGCTGTCGGACCCAT TCCAGCTGCAGGGTGGGTGT
TNF-α	AGGGTCTGGGCCATAGAACT CCACCACGCTCTTCTGTCTAC
Fgfr4	GTACCCTCGGACCGCGGCACATAC GCCGAAGCTGCTGCCGTTGATG
β-Klotho	CGAGCCCATTGTTACCTTGT CTCCAAAGGTCTGGAAGCAG
Ugt1a1	ATGGCTTTCTTCTCCGGAAT TCAGAAAAAGCCCCTATCCC
Ugt1a6	CACCGGAACTAGACCATCGAA GCATCATCACCATCGGAACTC
Ugt1a7c	TGCAATGGAGTTCCGATGGT CTGGAGAGGCGCATGATGTT
Ugt2b34	GGAGAATGCCATGCGGTTAT CTGCCACACGAAGATGCTTG
Ugt2b35	GTGGCGCGAATGGACTCTAT TCTCAGGTGCTTGGCTCCTT
Ugt2b5/37/38	TGGCCGATGGAATTCAGTC GTTTCAAACTTAAGGCCAGGTG

Acox1	TGAGGCGCCAGTCTGAAATC CCGTCTGCAGCATCATAACA
L-Fabp	GCAGAGCCAGGAGAACTTTGAG TTTGATTTTCTTCCCTTCATGCA
Pparα	CAGTGGGGAGAGAGGACAGA AGTTCGGGAACAAGACGTTG
Asbt	GGAACTGGCTCCAATATCCTG GTTCCCGAGTCAACCCACAT
Ostα	GTCTCAAGTGATGAACTGCCA TTGAGTGCTGAGTCCAGGTC
Ostβ	GTATTTTCGTGCAGAAGATGCG TTTCTGTTTGCCAGGATGCTC
Gapdh	TTGATGGCAACAATCTCCAC CGTCCCGTAGACAAAATGGT

Supplementary Table 3. Primer sequences for qRT-PCR (human)

Genes	Sequence
PPARα	ATGGTGGACACGGAAAGCC CGATGGATTGCGAAATCTCTTGG
ACOX-1	ACTCGCAGCCAGCGTTATG AGGGTCAGCGATGCCAAAC
FXR	GACTTTGGACCATGAAGACCAG GCCCAGACGGAAGTTTCTTATT
FGF19	ATCTCCTCCTCGAAAGCACA CAGCGTGCGGTACCTCTG
UGT1A1	TTGTCTGGCTGTTCCCACTTA GGTCCGTCAGCATGACATCA
UGT1A3	GATTTTGCCCAAAGCATCAG TGCCAACAGGAAGCCACTAT
UGT1A6	TGCCCAACATGGTCTTCATT CCACAATTCCATGTTCTCCA
UGT2A1	AACCACTCTTGGTGGGAATGT AGATGGGTTAGAGGTTGGTGT
UGT2B4	ACTCAATGCACTGAAGACAGTAAT GATCAAGGGGCTTCACTGGT
UGT2B7	GGTGTTTTCTCTGGGGTCAA TCCCATCAAATCTCCACAGA
GAPDH	AATGAAGGGGTCATTGATGG AAGGTGAAGGTCGGAGTCAA

Supplementary Table 4. Primer sequences for qRT-PCR (rat)

Genes	Sequence
Fgf15	ACGGGCTGATTCGCTACTC TGTAGCCCAAACAGTCCATTTCCT
Gapdh	TGACTTCAACAGCAACTC CCATATTCATTGTCATACCAG

Supplementary Table 5. Stealth RNAi (*Ugt1a3*) and siRNA (*Pparα*) sequences

Genes	Sequence
Ugt1a3	CAGGCACCUGAAUGCUACUUCCUUU AAAGGAAGUAGCAUUCAGGUGCCUG
Pparα	GCGUAUGGAAAUGGGUUUATT UAAACCCAUUUCCAUACGCTT

Supplementary Table 6. Chromatographic and mass spectrometric parameters for the quantification of bile acids

Bile acids	Retention time (min)	$[M-H]^-$	Fragment ions at Q3
LCA	27.83	375.291	375.291, 279.2335
UDCA	16.21	391.285	391.285, 373.274, 345.2805
HDCA	17.68	391.285	391.285, 373.274
CDCA	25.55	391.285	391.285, 345.2805
DCA	25.81	391.285	391.285, 345.2805
α-MCA	6.75	407.281	407.281, 389.2699, 371.2595
β-MCA	7.30	407.281	407.281, 389.2699, 371.2595
CA	18.82	407.281	407.281, 343.2638,
G-LCA	26.61	432.312	432.312, 74.025, 388.322
G-UDCA	17.55	448.307	448.307, 74.025, 386.3057
G-CDCA	25.48	448.307	448.307, 74.025, 386.3057
G-DCA	25.70	448.307	448.307, 74.025, 404.3167, 345.28
G-CA	21.35	464.301	464.301, 74.025, 402.301
T-LCA	26.83	482.295	482.295, 79.957, 106.981, 124.007
T-UDCA	20.55	498.289	498.289, 79.957, 106.981, 124.007
T-HDCA	23.17	498.289	498.289, 79.957, 106.981, 124.007
T-CDCA	25.73	498.289	498.289, 79.957, 106.981, 124.007
T-DCA	25.93	498.289	498.289, 79.957, 106.981, 124.007
T-β-MCA	12.48	514.284	514.284, 79.957, 106.981, 124.007
T-CA	23.99	514.284	514.284, 79.957, 106.981, 124.007
Glu-LCA	26.68	552.320	552.320, 375.289, 175.028, 113.028
Glu-UDCA	20.62	567.313	567.313, 391.284, 175.028, 113.028
Glu-HDCA	23.19	567.313	567.313, 391.284, 175.028, 113.028
Glu-CDCA	25.79	567.313	567.313, 391.284, 175.028, 113.028
Glu-DCA	26.08	567.313	567.313, 391.284, 175.028, 113.028
Glu-α-MCA	13.26	583.312	407.279, 175.028, 113.028
Glu-β-MCA	13.46	583.312	407.279, 175.028, 113.028
Glu-CA	24.80	583.312	407.279, 175.028, 113.028
dhCA (IS)	4.00	401.233	249.233