The essential oil of raw and vinegar processed Rhizoma Curcumae suppresses rat liver fibrosis by inhibiting TGF-β/Smads and PI3K/AKT pathways based on network pharmacology and transcriptomic analysis

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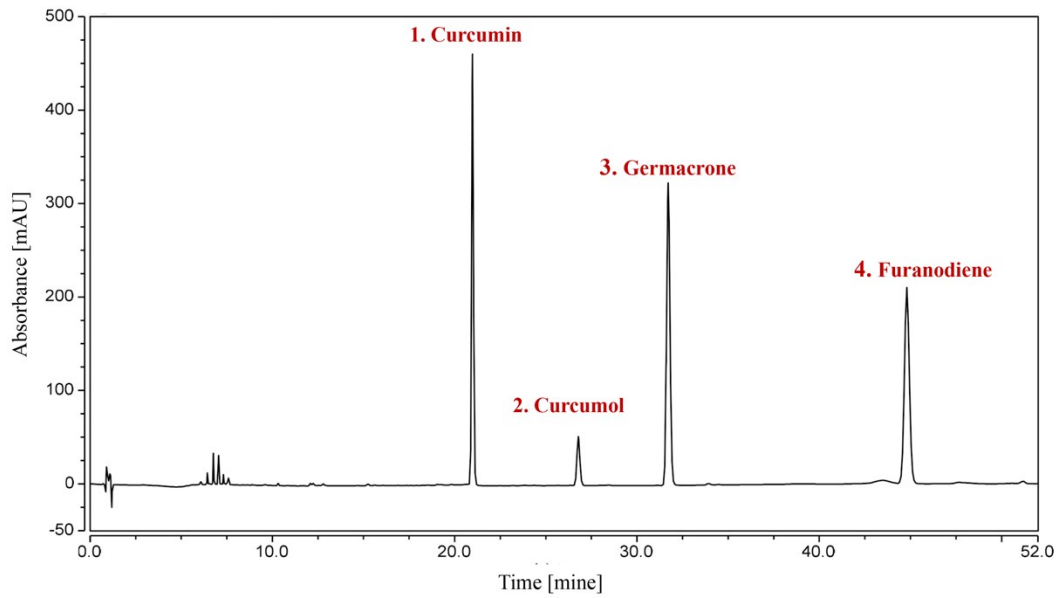
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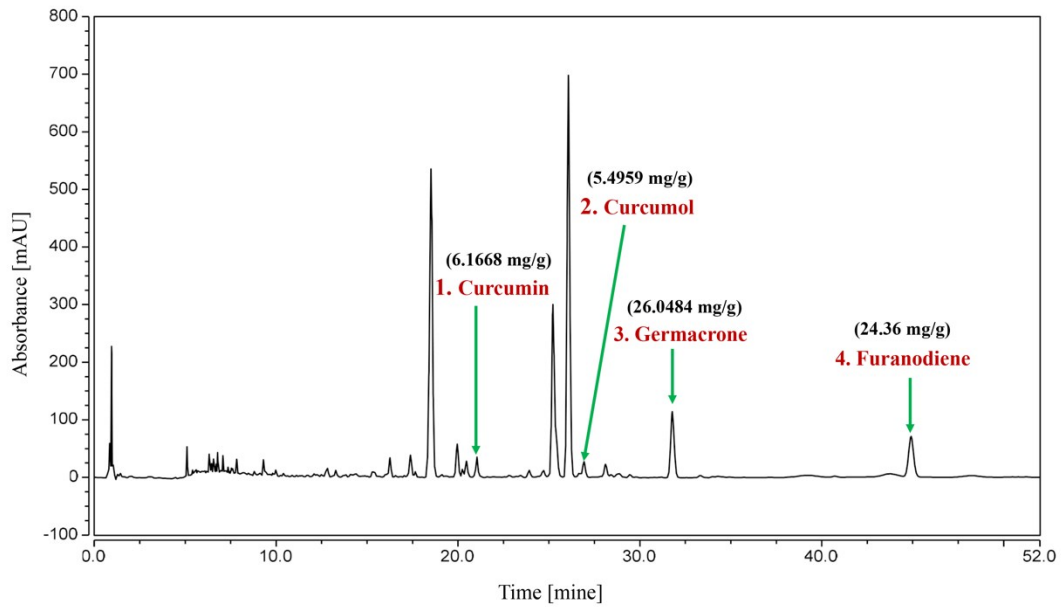Electronic supplementary information (ESI) available.

1.Supplementary Figures

Supplementary Figure S1

A

B

Supplementary Figure 1. UPLC Chromatogram of reference substances(A) and Rhizoma Curcumae sample(B)

2. Supplementary Tables

Supplementary Table S1:

Table S1 Potential Targets Obtained through Molecular Similarity Match

Molecule Name	Target
α-Pinene	PPARA, CNR2, ACHE, FAAH, TRPV1, AR, CYP19A1, ESR1, CHRM2, SLC6A2, SLC6A4, CYP2C19, BCHE, PTPN1
(+)-Camphene	CHRM2, CHRNA2, GABRA1, CHRM3, CHRM1, ADRA1B, HSD11B1, SLC5A7
β-pinene	CHRM1, CHRM2, GABRA1, PTGS1, PTGS2, RXRA, RXRG, MAOB, NCOA2, SLC6A2
Eucalyptol	CYP19A1, SHH, CYP51A1, ACHE, GABRA1, PTGS2, ADH1B, ADH1C, CHRNA2
2-Nonanol	CA2, CA1, CA4, TRPM8, AR, SHBG, UGT2B7, ESR2, ESR1, CDC25A, SHH, HSD11B1, IDO1, CDC25B, PGR, JAK1, JAK2, NR3C1, DRD2, SIGMAR1, NR3C2, PTGS2, KCNH2, JAK3, TYK2, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, CNR1, AKR1C3, NPC1L1, NR1I3, NR1H4, HMOX1, PRKCG, PRKCD, PRKCA, CCNB3, CDK1, CCNB1, CCNB2, SLC6A3, ADORA3, GSK3B, CDK1, MAPK3, CYP19A1, HSD17B2, TRPV3, TRPV1, HMGCR, SLC6A4, EPHX2, CYP17A1, F2RL3, PRKCB, PRKCE, PRKCH, PRKCQ, RASGRP1, OPRM1, CHRM4, CHRM5, CHRM2, CHRM1, CHRM3, CYP2C9, CYP2C19, CHEK1, CYP11B1, EGFR, CYP11B2, PARP1
Camphor	NR1I3, CYP19A1, CA2, CA1, CA4, AR, ADH1A, ADH1C, SERPINA6, SHBG, G6PD, GABBR1, CES1, CES2, CTSK, VDR, NPC1L1, NR1H4, GABRA2, GABRB2, GABRG2, GPBAR1, AKR1B10, POLB, CHRM1, CHRM2
(+)-borneol	CA2, CA1, CA4, TRPM8, CDC25A, CDC25B, NR1I3, AR, NR1H4, GPBAR1, SHH, ESR2, ESR1, UGT2B7, SHBG, POLA1, NPC1L1, HSD11B1, NR1H3, G6PD, GABBR1, NR3C1, DRD2, SIGMAR1, GABRA2, GABRB2, GABRG2, AKR1B10, POLB, CYP19A1, CHRM2, GABRA1, PTGS1, PTGS2, SLC6A2, MAOB, NCOA2
endo-borneol	CA2, CA1, CA4, TRPM8, CDC25A, CDC25B, NR1I3, AR, NR1H4, GPBAR1, SHH, ESR2, ESR1, SHBG, UGT2B7, POLA1, NPC1L1, HSD11B1, NR1H3, G6PD, GABBR1, NR3C1, DRD2, SIGMAR1, GABRA2, GABRB2, GABRG2, AKR1B10, POLB, CYP19A1, GABRA1
4-Terpinenol	AR, CYP19A1, CA2, CA1, CA4, RORC, SREBF2, NPC1L1, NR1H3, HMGCR, ESR2, TRPM8, CHRM2, CYP17A1, PTPN1, DRD2,

	RORA, SQLE, CYP51A1, PPARA, PPARD, SLC6A4, G6PD, ACHE, ESR1, ADRA2C, HSD17B2, NR3C1, SHBG, SLC6A2, NR3C2, BCHE, PTPRF, PTPN2, PLA2G1B, ACP1, AKR1B10, GABRA1
α-Terpineol	AR, CYP19A1, CA2, CA1, CA4, CHRM2, SLC6A4, SMAD7, TRPM8, NR1H3, PTPN1, NR1I3, SREBF2, NPC1L1, BCHE, ACHE, SQLE, ESR1, SLC6A2, CYP51A1, DRD2, ESR2, CYP17A1, CYP2C19, NR3C2, PTPRF, PTPN2, PLA2G1B, ACP1, AKR1B10, SIGMAR1, TRPV3, NR3C1, ATP12A, PTPN6, SMAD3, SHBG, FABP4, PPARA, FABP3, FABP5, PPARD, FABP1, RORA, HMOX1, HMGCR, PGR, CD81, G6PD, SCD, ADRA2C, HSD11B1, SLC6A3, CHRM3, CHRM1, SLC6A2, ADRA1A, CHRM2, ADRA1B, SLC6A3, GABRA1, MAOB, MAOA, ADRB1, RXRA, ADRB2, SLC6A4, SMAD4
2-Decanol	AR, SHBG, CA2, CA1, CA4, ESR2, ESR1, HSD11B1, CDC25A, CDC25B, GPBAR1, SHH, NR1I3, TRPM8, HMGCR, UGT2B7, JAK3, JAK1, TYK2, PTGS2, PGR, KCNH2, NR3C1, CNR1, JAK2, IDO1, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, GLUL, CYP17A1, NPC1L1, KCNA3, EPHX2, CNR2, TRPA1, CCNB3, CDK1, CCNB1, CCNB2, GSK3B, CDK1, EPHX1, PRKCG, PRKCD, PRKCA, PRKCB, PRKCE, PRKCH, PRKCQ, RASGRP1, PER2, GABRB3, GABRG2, GABRA5, POLA1, CYP19A1, SRD5A1, SRD5A2, EGFR, TRPV1, CYP11B1, CYP11B2, ADA, EDNRA, PIM1, C5AR1, PIM3, SLC6A3, SERPINA6, FAAH, SIGMAR1, ADH1B, ADH1C
2-Undecanone	CA2, CA1, CYP19A1, CES1, CA4, ADH1A, ADH1C, CES2, AR, NR1I3, HLCS, MGLL, MTNR1A, MTNR1B, GRM1, SRD5A1, ACHE, PARP1, DBF4, CDC7, AKR1B1, TSPO, PTGS1, PTGS2, NAAA, CYP11B2, MAOA, MAOB, EPHX2, ABCG2, PPARG, THRB, EPHX1, HSP90AA1, GRK2, HTR2C, MAPK14, GRM5, NQO2, CYP11B1, CNR1, CNR2, MMP13, JAK1, MMP1, ICMT, SLC18A3, CYP27A1, PAOX, MMP9, MMP2, SIRT2, HTR2B, CYP2C19, PTGDR2, ITK, TNKS2, PPARA, PPARD, SRD5A2, THRA, CHRM1, PARP2, HSD11B1, CHRM2, DRD2, DRD3 , HSD17B1, P2RX7, GRM2, BRD4, BRD2, BRD3, PGR, CTSK, ICAM1, ADH1B, SELE, JAK2, GCK, DHODH, NR3C2, NR3C1, PIM1, DYRK1A, CCR1, CSNK1G2, CSNK1D, SIGMAR1, CLK4, CLK1, CLK2, CLK3, CSNK1E, CSNK1G3, PIM3, DYRK1B, MAP3K19, FABP1, OXTR, ADH1C
δ-elemene	PPARA, CNR2, NR1H3, CXCR3, PTGS1, CHRM3, CHRM1, PTGS2, RXRA, SLC6A2, ADRA1A, CHRM2, ADRA1B, GABRA1, NCOA2, HJV
β-elemene	PTGS2, RXRA, SLC6A2, CHRM2, GABRA1, PTGS1, CHRM3, CHRM1, ADRA1A, NCOA2, BCL2, CDKN1A, EIF6 RB1, TP63, TEP1, RUNX1T1, CCNB1, RHOA
β-Caryophyllene	PPARA, CNR2, FAAH, TRPV1, PTGS1, CHRM3, CHRM1, PTGS2, RXRA, CHRM2, ADRA1B, CHRNA2, GABRA1, NCOA2, SLC6A2, ADRA1A, SLC6A3, IL6
γ-elemene	PPARA, CNR2, CXCR3, NR1H3, PTGS1, CHRM3, PTGS2, RXRA, SLC6A2, ADRA1A, CHRM2, GABRA1

(-)-isoledene	PPARA, CNR2, NR1I3, FAAH, TRPV1, CHRM2, CHRM3
germacrene D	PPARA, CNR2, ADORA1, ADORA2A, ADORA3, AR, CYP19A1, ESR1, ESR2, PTGS1, PTGS2, SLC6A2, NCOA2
β-selinene	PTGS1, CHRM3, CHRM1, PTGS2, RXRA, SLC6A2, CHRM2, ADRA1B, GABRA1, NCOA2
Curzerene	DRD4, NR3C1
(-)-alpha-Gurjunene	PPARA, CNR2, NR1I3, FAAH, TRPV1, CHRM3, CHRM1, PTGS2, ADRB2, SLC6A4, GABRA1
Caryophyllene Oxide	SQLE, LSS, SLC6A4, SLC6A3, CHRM3, CHRM1, PTGS2, ACHE, CHRM2, GABRA1, CHRM3, CHRM1, PTGS2, ACHE, CHRM2, ADRA1B, GABRA1, CHRM3, CHRM1, ACHE, CHRM2, ADRA1B, NCOA2
(+)-Calarene	PPARA, CNR2, BCHE, AR, CYP19A1, ESR1, CHRM2, SLC6A2, SLC6A4, CYP2C19, PTPN1, NR1I3, CHRM3, CHRM1, GABRA1, GRIA2, SLC6A2, CHRM2
β-elemenone	SRD5A1, CYP19A1, SRD5A2, TRPA1, SERPINA6, SHBG, FABP1, HSD17B3, AR, SIGMAR1, CHRM2, CHRM1, ADH1A, GRM5, MTNR1A, MTNR1B, CYP17A1, CTSK, CTSL, CTSB, P2RX7, EPHX1, PARP1, PTGS1, DRD4, ADH1C, NR1I3, HTR2B, EPHX2, NR1H3, TYMS, GABRB3, GABRA3, GABRG2, GABRA1, GABRA5, GABRA2, GABRA6, TSPO, NR3C1, PGR, HTR7
Epicurzerenone	SLC6A4, SLC6A3, PTGS2, PABPC1, PREP, CTSK, CTSL, CTSB, HSD17B2, EPHX1, NLRP3, MDM2, HCRTR1, PTGS1, NOS2, AR, HTR6, CYP17A1, CTSC, CTSF, CTSS, CTSV, CDC25B
Curzerenone	SLC6A4, SLC6A3 , PTGS2, PABPC1, HSD17B2, PREP, MDM2, CTSK, CTSL, CTSB, EPHX1, NLRP3, PTGS1, HTR6, HCRTR1, NOS2, MTNR1A, AR, CYP17A1, CTSC, CTSF, CTSS, CTSV, ACHE, GABRA1, PGR, NR3C1, RXRA, NR3C2
Isospathulenol	CYP19A1, NR1H3, AR, SREBF2, NPC1L1, CYP51A1, CYP17A1, SHBG, HMGCR, SLC6A4, ESR1, ESR2, PPARA, PPARD,RORA, UGT2B7, ACHE, RORC, G6PD, CHRM2, PTGER2 , TRPM8, SLC6A2, PTPN1, SERPINA6, CHRM3, CHRM2
ar-turmerone	MGLL, DRD2, DRD4, SRD5A1, CHRM1, GRM1, HTR2C, PREP, P2RX7, CYP19A1, OPRL1, HCRTR2, CACNA1B, GRM5, EPHX2, MPO, C5AR1, AKR1C3, HCRTR1, MTNR1A, MTNR1B, HSD17B2, KCNN4, KCNA3, MC4R, EPHX1, LTA4H, PTGDR2, TGFBR1, FCGR1A, CRHR1, CHRM4, HTR2B, ADRA2A, HTR1B, ADRA2C, HRH2, ADRA2B, HTR1D, CHRM5, DRD1, CHRM2, ADRA1D, ADRA1A, HRH1, DRD3, CHRM3, HTR6, TACR3, GABRB3, GABRA3, GABRG2, GABRA1, GABRA5, GABRA2, GABRA6, PIK3CB, PIK3CA, TSPO, DNMT3A, SIRT2, BRD4, PABPC1, PDE4B, ADH1A, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, TDO2, CCNE2, CDK2, CCNE1, STAT3, CHRM1, ESR1, ADRB1, PTGS2, ADRA2A, RXRA, ACHE, SLC6A2, CHRM2, SLC6A3, ADRB2, SLC6A4, MAOB, PTGS1, ADRA1A, PPARG, BMP2, BMP6
Germacrone	GLI2, GLI1, CYP19A1, ADH1A, ALOX5, ACHE, CHRM2, CHRM1, TRPV1, GRM5, P2RX7, EPHX1, MTNR1A, MTNR1B, HTR7,

	GABRA1, PTGS1, CHRM1, PTGS2, SLC6A2, GRIA2, TNF, TGFB2, TGFB3
Spathulenol	UGT2B7, HSD11B1, IDO1, PTGS1, PGR, NR1H3, ICMT, CHRM3, CHRM1, CHRM2
Curcumenol	SLC6A2, SLC6A4 , PARP1, SIGMAR1, P2RX7, TRPV3, MDM2, GSK3A, PTK2B, CHRM4, ADRA2A, ADRA2C, ADRA2B, CHRM2, ADRA1B, OPRM1, OPRD1, OPRK1, FADS1, PTAFR, ABAT, AKR1B1, GABRA1, CTSD, BCHE, PRSS1, GATM, AKT1, AKT2, AKT3
Furanodienon	CTSK, CTSL, CTSB, HSD11B1, PABPC1, NLRP3, CHRM2, CHRM1, PREP, PTGS2, NOS2, BRD4, SLC6A4, SLC6A3, APP, CTSC, CTSF, CTSS, CTSV, ACHE, CHRM2, GABRA1, GRIA2
Isofuranodienone	NLRP3, PTGS2, NOS2, HSD11B1, CTSK, CTSL, CTSB, HCRTR1, PREP, APP, PABPC1, HSD17B2, SLC6A4, SLC6A3, CHRM2, CHRM1, CTSC, CTSF, CTSS, CTSV
Curcumenone	AR, CYP19A1, PGR, SRD5A1, SRD5A2, TRPA1, SIGMAR1, SERPINA6, SHBG, HSD17B3, TRPV1, NR1I3, NR3C2, NR3C1, NR1I2, PTGS2, FAAH, PARP1, CYP17A1, CTSK, CTSS, CTSB, MTNR1A, MTNR1B, EPHX2, P2RX7, NQO2, GABRA1, F2, PRSS1, GABRA5, DUSP3, SIRT2, FLT1, PDGFRB, CCNB3, CDK1, CCNB1, CCNB2, CDK2, CCNA1, CCNA2, CCND1, CDK6, LCK, CDK2, CDK4, FGFR1, FABP1, CACNA1B, ACE, MME, PTGS1, HTR2B, MAOA, MAOB, OPRM1, ITK, HDAC6, CHRM1, HTR2C, BRD4, DPP4, CYP11B2, PSMB5, CCR5, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, PARP3, PARP2, PARP4, TNKS, GABRA1, GABRB2, GABRG2, TACR1, CCND2, EPHX1, CSF1R, PGGT1B, FNTA, PDE7A, MMP9, MMP1, CTSL,DBF4, CDC7, HTR2A, ICAM1, ADH1A, HLCS, CTSC, ADH1C, CDK5R1, CDK5, PIM1, KCNJ5, KCNJ3, KCNJ6, KCNJ3, FAP, PDE7B, ADORA2B, CMA1, S1PR1, CCR1, CTSG, HRH1, PTAFR, MAPK14, GSK3B, GPR139
Furanodiene	CHRM2, CHRM1, CHRM5, CHRM3, HSD11B1, CHRM4, SLC6A4, SLC6A3, CHRM3, CHRM1, PTGS2, SLC6A3, ADRB2, SLC6A4, CHRM3, CHRM1, PTGS2, SLC6A2, ADRA1A, ADRA1B, SLC6A3, ADRB2, SLC6A4, GABRA1, ERK, Ras
Curcumol	SLC6A3, SLC6A2, SLC6A4, SIGMAR1, PARP1, MDM2, CHRM4, CHRM2, OPRM1, OPRD1, OPRK1, ADRA2C, TRPV3, HSD17B2, PTK2B, NR3C1, KCNA5, IDO1, NR3C2, PGR, P2RX7, HCRTR2, HCRTR1, HRH3, HRH4, PGR, NR3C1, CHRM3, CHRM2, Bcl2, SMAD1
Curdione	CYP19A1, CTSD, PTGS1, CCR5, TRPV1, FAAH, MTNR1A, MTNR1B, CTSK, CTSS, CTSB, SIGMAR1, SMAD5, AR, CTSL, ACE, P2RX7, EPHX2, PARP1, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, GABRA3, GABRG2, GABRB3, GABRG2, GABRA1, GABRB3, GABRA5, GABRA2, GABRA6, PIN1, CHRM1, CTSC, NQO2, CYP17A1, SERPINA6, SHBG, NR1I2, FABP1, MAOB, MC4R, CYP51A1, PPARG, HTR2B, SRD5A1, EPHX1, F2, PRSS1, FAP, CHRM4, CHRM5, CHRM3, BRD4, GABRA1, GABRB2, CDC25A, GRM5, SMAD6, MAP2K1, PDE7A, PPARA, FABP5, PPARD, MPO, SRD5A2, HMOX1, SIRT2, GPR139, KCNA5, PDE4B, HTR6,

| | TNKS2, FKBP1A, CYP11B2, HSD17B3, TLR9, PGR, ADH1A, CNR1, PTPN1, PABPC1 |

Supplementary Table S2:

Table S2 Candidate Target Relating to Liver Fibrosis

Target Name
TERT, HFE, INS, IL10, NR1H4, IL1B, ABCB4, TP53, ALB, SERPINA1, IFNG, GPT, PKD1, RTEL1, TMEM67, ABCB11, CCN2, CAV1, SLC25A13, FAS, TERC, ABCC2, FASLG, MIR21, RPGRIP1L, GGT1, SERPINE1, HLA-DRB1, ATP8B1, CDH1, CXCL8, PPARG, CC2D2A, EGF, JAG1, MUC1, SLC17A5, CD40LG, PNPLA3, CTNNB1, NPHP4, CCR6, MUC5B, NPHP1, KRT18, NPHP3, PARN, MIR122, SEC63, PRKCSH, HGF, SFTPC, F2, G6PC, CP, HAMP, FAH, INVS, PTPRC, NEK8, TTC21B, APOB, PKD2,IL13, OFD1, MET, INSR, MBL2, HNF1A, WDR19, RBP4, TF, HNF4A, TIMP1, IL1RN, TLR4, RETN, WRAP53, AFP, APC, GYS2, MARS1, PHKA2, NHP2, CRP, EGFR, IRS1, TINF2, CEP290, FOXP3, MKS1, ICAM1, IFT140, CEP164, CTLA4, KRAS, MTTP, ENG, MIR130A, APOA1, CYP2E1, MTOR, SMPD1, MIRLET7D, NOTCH1, PRTN3, TCTN2, SLC40A1, PIK3CA, IFT122, WDR35, PHKG2, KIT, IFT80, VEGFA, MMP9, NOP10, AGL, STAT3, CYP3A4, TJP2, TTR, GANAB, SMAD4, PDGFB, ANKS6, MMP2, CDKN3, TFR2, B9D1, IFT172, MYC, TNF, AHI1, ABCG5, HADHA, ACTC1, ADIPOQ, IGF2, ACE, SDCCAG8, GPC3, IFT43, TMEM216, FBN1, STN1, PTEN, SCNN1A, DGUOK, NOS2, ASS1, TSC2, GBE1, NR1H3, MAPK8, HMOX1, KIAA0586, APOE, IL4, INPP5E, IQCB1, IRS2, DKC1, PPARA, ELANE, FECH, DYNC2H1, ATP11A, LEP, CCL2, CDKN2A, TRAF3IP1, TRMU, IRF5, CCND1, NFKB1, CPT2, RELA, POLG, ATP7B, EDN1, B9D2, HLA-DQB1, DNAH8, TGFBR2, CEP120, BBS2, IL12RB1, CD36, MIR223, MIR17, HRAS, SPP1, MIR34C, FARSB, ABCB1, ELN, UGT1A1, IGF2R, HP, TMEM231, BRAF, JAK2, HSD3B7, STAT1, KRT8, IL1A, IFNL3, KIF21A, PRSS1, CYP7A1, NDUFS1, SMAD3, THPO, IL17A, TCF4, FAM111B, PDGFRB, FADD, IGF1, SMAD3, WDR60, CASP8, LPL, ALDOB, LIPA, HNF1B, NFE2L2, MIR34A, FGF2, AKR1D1, PDGFRA, DCDC2, MIR181B1, ABCA3, CYP1A2, SPINK1, ASL, FABP1, BBS4, ARL13B, MIR16-1, KRT19, WT1, FN1, JUN, ALG9, ERBB2, TLR2, PMM2, LBR, ALMS1, MPO, ABCD3, FGFR1, NEK1, OTC, SREBF1, EPCAM, ALG8, BBS1, HLA-DQA1, MIR200B,

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Supplementary Table S3:

Table 3S Primer sequences used in Real-Time PCR analyses

Target gen	Primer sequence(5'→3')
TGF-β1	Forward: AACAATTCCTGGCGTTACCTT
	Reverse: GCCCTGTATTCCGTCTCCTT
Smad3	Forward: CAGGGCTTTGAGGCTGTCTA
	Reverse: CATCTGGGTGAGGACCTTGTC
Smad4	Forward: GCGGGTTGTCTCACCTGGAA
	Reverse: CCGTGGGTAAGGATGGCTGT
Smad7	Forward: TCGGAAGTCAAGAGGCTGTG
	Reverse: CATCGGGTATCTGGAGTAAGGA
PI3K	Forward: CAGAGCACGGTGGGTAACAC
	Reverse: ACGAACCTTTCCACTGCTGC
AKT	Forward: CCTTTCAAGCCCCAGGTCAC
	Reverse: GGAGAACTGGGGAAAGTGCG
CDK	Forward: CACAAAACTACAGGTCAAGTGG
	Reverse: GAGAAATTTCCCGAATTGCAGT
JAK1	Forward: GTTTATTGTAGAGCTTCGGCAG
	Reverse: GGAACACTGTAAACACCAACTC
Actin	Forward: TGTCACCAACTGGGACGATA
	Reverse: GGGGTGTTGAAGGTCTCAAA