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A review of edible plant-derived natural compounds for the therapy of liver fibrosis

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Effects of natural compounds derived from edible plants in *in vitro* cell models

1. Phenolic compounds

1.1 Capsaicin

Capsaicin suppresses the activation and proliferation of mouse GRX cells or rat HSC-T6 cells, two immortalized HSCs, and promotes the rat HSCs apoptosis, supporting its antifibrotic effect [1, 2]. The action mechanisms of capsaicin in HSCs are particularly associated with the inhibition of PPARγ-mediated TGF-β1/Smad pathway and Notch-mediated TNF-α secretion [1-4].

1.2 Chlorogenic acid

Chlorogenic acid inhibits HSCs proliferation and profibrotic factor expression in immortalized rat HSC-T6 cells and human LX2 cells through the inhibition of oxidative stress and IL-13/miR-21/TGF-β1/Smad7 signaling, respectively [5-8]. Chlorogenic acid also alleviates fatty acids or palmitic acid-induced hepatocyte toxicity in primary or non-transformed cultured hepatocytes, and the mechanism is related to activating silent information regular 1 (SIRT1) signaling and inhibiting endoplasmic reticulum (ER) stress [9, 10]. In mouse macrophage cell lines RAW264.7 and Ana-1, chlorogenic acid enhances lipopolysaccharide (LPS) and interferon-γ (IFN-γ)-induced M1 polarization [11, 12]. In addition, ECM production induced by HMGB1 reduces in primary human LSECs (liver sinusoidal endothelial cells) after treatment with chlorogenic acid [8]. The above studies in *in vitro* models support that chlorogenic acid is beneficial for the treatment of liver fibrosis and injury. Additionally, chlorogenic acid decreases the replication of hepatitis B virus (HBV) and hepatitis C virus (HCV) in HBV or HCV-infected cells and HBV-infected duck, proving that chlorogenic acid may be useful for treating hepatitis B and C liver diseases [13, 14].

1.3 Curcumin

Numerous studies confirm that curcumin reduces activation, proliferation and migration of HSCs, and promotes apoptosis of activated HSCs in primary or immortalized HSCs, which supports its anti-fibrosis effect [15-17]. The mechanism is correlated with inhibition of DNA methylation, AMPK-mediated glycolysis, wnt/β-catenin pathway, hedgehog signaling, cannabinoid receptor type-1, DLK1 expression,

connective tissue growth factor (CTGF) expression, succinate/HIF-1α signaling pathway, CXCL12/CXCR4 biological axis, or MyD88 pathway, as well as increase of PPARγ expression, AMPK/PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1α) axis-activated superoxide dimutase-2 (SOD2) expression or Plin5 gene expression [15-32]. Moreover, curcumin inhibits epithelial-mesenchymal transition (EMT) and differentiation of hepatocytes in BNL CL.2 cells (mouse embryonic hepatocytes), supporting its anti-liver fibrosis effect, which is mediated by oxidative stress and autophagy [33]. Curcumin also alleviates EMT of human intrahepatic biliary epithelial cells by reducing Smad and hedgehog signaling, and increasing CD109 expression [34]. Another study in RAW264.7 cells (a mouse macrophage cell line) shows that curcumin inhibits activated RAW264.7 toward to M1 macrophages and reduces monocyte infiltration by lowering phosphorylation levels of ERK1/2 and p38 [35]. In addition, Curcumin suppresses HCV replication in Huh7.5 cells expressing the HCV genotype by modulating heme oxygenase-1 (HO-1) and PI3K-AKT signaling [36].

1.4 Ellagic acid

Ellagic acid could beneficially regulate the differentiation of primary rat HSCs in culture, supporting its antifibrotic effect [37]. Ellagic acid also reduces vitamin k3 (VK3)-induced hepatocyte damage by inhibiting reactive oxygen species (ROS) productions in Chang human liver (CHL) cells [38]. Additionally, ellagic acid relieves host immune tolerance in HBeAg transgenic mice and HBV-infected cells, and inhibits HCV replication in HCV-infected cells, supporting the protective property of ellagic acid against HBV and HCV-elicited diseases [39-41].

1.5 Epigallocatechin-3-Gallate

It has been reported that EGCG inhibits the HSCs proliferation, promotes the HSCs apoptosis, or reduces fibrosis markers expression in primary culture HSCs or stable human HSCs (LI90, TWNT-4 and LX-2 cells), supporting its anti-liver fibrosis effect [42-50]. The mechanism of EGCG in above *in vitro* liver fibrosis models may be related to decreasing PDGF receptor activation and oxidative stress, inhibiting Rho signaling, or regulating PI3K/Akt/Smads pathway [42, 43, 45-48]. EGCG also alleviates stimulant-induced primary hepatocyte injure by attenuating oxidative stress, apoptosis and

autophagy, promoting FGF21-AMPK pathway, or reducing JNK/IRS1/AKT/GSK pathway [51-54]. In isolation lymphocyte and primary mouse Kupffer cells, EGCG induces M1-to-M2 polarization of infiltrating macrophages, further demonstrating its hepatoprotection [55, 56]. In addition, data obtained from HBV or HCV-infected cells have shown that EGCG could inhibit virus infection and replication by promoting farnesoid X receptor (FXR), and inhibiting ERK1/2-HNF4α (hepatocyte nuclear factor 4α) axis or CD81 receptor, supporting protection of EGCG against HBV or HCV-induced hepatopathy [57-60].

1.6 Resveratrol

Resveratrol inhibits the activation of HSCs in mouse GRX cell model via modulating inflammatory cytokines and PPARγ/SIRT1 ratio, in rat HSC-T6 cell model via regulating NFκB and the PI3K/Akt signaling, and in human LX-2 cell model via suppressing Akt/NFκB and Hippo pathways, which supports its anti-liver fibrotic effects [61-66]. Resveratrol also attenuates TGF-β1, cytokine or hydroquinone-induced primary hepatocytes toxicity and apoptosis by modulating miR-190a-5p/HGF axis or inhibiting oxidative stress damage [67-70]. In human hepatocyte Chang cell line, resveratrol decreases alcohol-induced hepatocyte apoptosis through suppressing ER stress-mediated caspase-12 activation and phosphodiesterase activity [71]. In addition, resveratrol could mitigate HBV-induced hepatocellular carcinoma in HBV-infectious hepatoma cells or transgenic mice [72, 73]. However, some reports show that resveratrol increases HBV or HCV replication in virus-infectious cells or mice, signifying that resveratrol should be cautious as a medicine or dietary supplement when treating hepatitis B or C patients [74, 75].

1.7 Sinapic acid

Sinapic acid mitigates alcohol-induced hepatocyte damage in AML-12 cells by reducing oxidative stress and bromodomain-containing protein 4 (BRD4)-mediated pyroptosis [76].

1.8 Syringic acid and Vanillic acid

Syringic acid and vanillic acid inhibit the expression of collagen I (COL1) and α smooth muscle actin (α-SMA) in the primary rat HSCs, supporting their antifibrosis [77].

1.9 Vitamin E

Vitamin E suppresses the proliferation of activated primary rat HSCs, enhances the viability of silver nanoparticle-impaired primary mouse hepatocytes, ameliorates the apoptosis and pyroptosis of H_2O_2-induced primary sheep hepatocytes, mitigates fructose-induced human hepatic L02 cell injury by activating Nrf2/CES1 pathway, supporting the anti-liver fibrosis effects of vitamin E [78-81].

2. Flavonoid compounds

2.1 Genistein

The results obtained from fatty acid-induced hepatic steatosis models in primary human hepatocytes or rat liver cell line BRL cells, supports the protection of genistein against NAFLD, which is related to activating AMPK pathway or enhancing PPARα expression [82, 83]. In addition, genistein significantly inhibits the proliferation and fibrosis markers expression of primary cultured or immortalized rat HSCs through upregulating the SIRT1 expression or inhibiting Akt/p38-mediated peroxidation [84-86].

2.2 Hesperidin and Hesperetin

In fatty acid-induced human monocyte THP-1 cells, ER stress-induced inflammation could be inhibited by hesperidin, supporting that hesperidin could be used for the treatment of NAFLD [87]. Also, hesperidin improves tert-butyl hydroperoxide-induced hepatocytes injury in human hepatic L02 cells, which is related to the activation of Nrf2/HO-1 pathway [88].

In addition, hesperetin inhibits the HSCs proliferation and promotes the HSCs apoptosis, supporting its anti-liver fibrosis effect [89]. Hesperetin also attenuates palmitate or acetaminophen-induced apoptosis, oxidative stress and inflammation via activating GRP78 and upregulating HO-1 expression in primary rat hepatocytes or AML12 hepatocytes [90, 91].

2.3 Naringin and Naringenin

Naringin inhibits toxins-induced DNA fragmentation and apoptosis in primary hepatocytes, and the mechanism may involve the activation of AMPK pathway [92, 93].

In addition, in primary hepatocytes, Kupffer cells and immortalized macrophage RAW

264 cells, naringenin exhibits antifibrotic effects by suppressing NLRP3/NFκB pathway or reducing macrophage infiltration into adipose tissue [94, 95]. Moreover, naringenin decreases the accumulation of extracellular matrix in activated HSCs through the inhibition of Smad3 signaling, further supporting its anti-liver fibrosis [96, 97]. Naringenin also exhibits hepatoprotective effect against hepatic steatosis in HBV-transgenic mice, and HCV-infected mice, patient livers and Huh7.5.1 cells, which is related to modulating ER stress or PPAR signaling, and upregulating p53-dependent PTEN (phosphatase and tensin homolog) expression [98-102].

2.4 Quercetin

Quercetin could modulate the proliferation and apoptosis of HSCs by activating ER stress [103, 104]. In primary or immortalized hepatocytes, quercetin also mitigates oxidative damage and apoptosis caused by irritants via upregulating HO-1, SIRT or PGC1α signaling, activating Nrf2-keap1 pathway, or reducing ER stress or HMGB1, Nrf2 and NADPH oxidase expressions [105-111]. In macrophage Raw 264.7 cells, quercetin inhibits M1 polarization and promotes transformation to the M2 phenotype via modulating Notch1 or Nrf2-mediated HO-1 pathway [112, 113]. Quercetin also inhibited the migration of human THP-1 macrophage, and inflammation of infiltrating human macrophages MΦs [114, 115]. Evidence from these cell experiments supports the hepatoprotective and anti-fibrotic effects of quercetin. In addition, quercetin suppresses the replication of HBV and HCV in virus-expressing cells, implying that quercetin could protect liver against hepatitis B and C-induced liver damage [116-119].

3. Sulphur-containing compounds and other compounds

3.1 S-allylcysteine

S-allylcysteine (SAC) inhibits indomethacin or alcohol-induced hepatocytes apoptosis in rat liver cell line BRL□3A cells, supporting its liver protective effect [120, 121].

3.2 Lipoic acid

In primary human or rat hepatocytes, lipoic acid ameliorates toxins-induced apoptosis by suppressing ER stress, FFA (free fatty acid) oxidation and iNOS gene expression, enhancing pyruvate oxidation, or activating insulin receptor/PI3K/Akt pathway [122-125].

Moreover, in immortalized RAW 264.7 macrophages and primary rat Kupffer cells, lipoic acid inhibits LPS-induced nitric oxide (NO) and TNF-α production, supporting its hepatoprotective effects [126].

3.3 Sulforaphane

Oh CJ et al. report that sulforaphane markedly inhibits the expression of fibrosis markers in hTERT cell line (an immortalized human HSCs), supporting its reversible effect on liver fibrosis [127]. Ishida K et al. also find that sulforaphane shows liver protective effect by Nrf2-mediated antioxidation and inhibition of the LPS/TLR4 pathway in human LX-2 cells [128]. Another study by using LX-2 cell line suggests that the anti-liver fibrosis of sulforaphane may be also associated with the inhibition of miRNA-423-5p [129]. In immortalized human hepatocytes HHL5 cells, sulforaphane also reverses homocysteine-induced hepatocyte injure via reducing ER stress and increasing Nrf2 translocation [130]. In addition, sulforaphane inhibits HCV replication via upregulating PI3K/Nrf2 Pathway-mediated HO-1 expression in HCV-infectious cells, representing its protection against viral-induced liver injure [131].

3.4 Betaine

Betaine reduces cycloheximide-induced primary rat hepatocyte damage by activating heme oxygenase HO-1 expression, mitigates the injury of isolated hepatocytes from ethanol-fed rats by decreasing methylation-related s-adenosylhomocysteine levels, and alleviates LPS or polyinosinic-polycytidylic acid-induced injury in RAW 264.7 macrophage cells by inhibiting oxidative stress and inflammation, supporting the liver protection of betaine [132-134]. In addition, betaine could suppress hepatitis B virus (HBV) and hepatitis C virus (HBV) in virus-containing cells or HBV-positive ducklings, representing that betaine protects liver against HBV and HCV damages [135, 136].

3.5 Caffeine

The studies in HSCs support the anti-fibrosis effects of caffeine. In LX2 cells, an immortalized human HSCs, caffeine suppresses cell proliferation and adhesion, and promotes cell apoptosis, which is mediated by endoplasmic reticulum stress-associated autophagy through the IRE1-α pathway [137, 138]. In HSC-T6 cells, an immortalized rat HSCs, caffeine inhibits the cell proliferation via acting on adenosine A2A receptor and

subsequently suppressing the cAMP-PKA-Src-ERK1/2/p38 MAPK signal pathway [139]. Caffeine also exhibits anti-fibrosis in primary cultured rat or mouse HSCs, through inhibiting the cAMP/PKA/CREB pathway or Akt1 signaling, respectively [140-142]. Moreover, caffeine inhibits CTGF expression induced by TGF-β in hepatocytes, and reduces ROS and TNF-α expression in Kupffer cells isolated from ALD mice [143, 144]. Some studies show that caffeine inhibits the PGE2 Synthesis of hepatocytes or the replication of HCV in in HBV or HCV-transfected liver cells, respectively, supporting that caffeine is beneficial to HBV or HCV-induced liver injure [145, 146].

3.6 Lycopene

Lycopene alleviates stimulants-induced cellular damage by inhibiting oxidative stress or promoting M2 polarization in hepatocytes or Raw 264.7 macrophages, respectively, supporting the protective effects of lycopene on the liver [147-150]. Moreover, lycopene could also reduce the expression of the fibrosis markers or proliferation of HSCs in two rodent HSCs cell lines (GRX cell, mice; RI-T cell, rats) [151, 152].

3.7 α-Mangostin and γ-Mangostin

α-mangostin and γ-mangostin also ameliorate free fatty acid-induced hepatocyte damage by stimulating SIRT1/LKB1/AMPK pathway in immortalized human L02 liver cells, supporting their potentials for NAFLD treatment [153, 154]. Moreover, another research group finds that α-mangostin significantly suppresses the proliferation and migration of HSCs by inhibiting the activation of TGF-β/Smads, ERK1/2 and Akt pathways in LX-2 cell model [155, 156]. In addition, Wang et. al report that γ-mangostin also produces significant liver fibrosis reversal in LX-2 cells, which involves SIRT3-HMGB1 signaling axis [157].

3.8 Ursolic acid

In primary or immortalized rat HSCs, ursolic acid reduces proliferation and migration, promotes apoptosis, and downregulates the expressions of fibrogenesis markers α-SMA, COL1 and TIMP-1. The anti-fibrosis mechanism of ursolic acid in HSCs may be closely related to the inhibitions of ERK, PI3K/Akt, p38-MAPK, Hedgehog, NOX4/ROS and RhoA/ROCK1 signaling pathways [158-161]. Ursolic acid also induces the proliferation of rat primary hepatocytes, and prevented activation of rat primary Kupffer cells by

NOX4/ROS pathways [162-164]. In addition, ursolic acid could inhibit HCV replication or HBV-mediated autophagy in HCV or HBV-containing cells, exhibiting its protective effects against HCV or HBV-induced hepatitis [165, 166].

3.9 Vitamin C

Vitamin C inhibits the proliferation of LX-2 cells, and reduces COL1A1 expression in H_2O_2-induced stimulated human LX-2 cells and rat primary HSCs [167]. Vitamin C could also inhibit cypermethrin-induced cytotoxicity of rat primary hepatocyte, and the mechanism involves its antioxidation [168]. However, vitamin C promotes COL1 excretion and extracellular hydroxyproline level in TGF-β-stimulated human HSCs, which could be blocked by suppressing hydroxylase [169].

3.10 Yangonin

In human liver cell line L02 cells or mice primary and AML-12 cells, yangonin reverses irritants-induced hepatocyte injury and senescence by activating FXR or meditating hepatic transporters [170-173].

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Supplementary Table

Table S1 Summary of edible plant-derived natural compounds with anti-liver fibrosis effects in hepatic stellate cells (HSCs) and liver-resident cells models

Compounds	Models	Effects/Mechanisms	References
S-Allylcysteine	Hepatocytes: BRL□3A	↓ apoptosis, ER stress, p-eIF2α, CHOP, Bax, caspase 3; ↑ Bcl□2	120, 121
Betaine	Hepatocytes: Rat primary	↓ S-adenosylhomocysteine; ↑ HO-1	132, 133
	Macrophage cells: RAW264.7	↓ GCLM, NO, TNF-α, iNOS; ↑ GS, GCLC	134
Caffeine	Human HSCs: LX2 cells	↓ proliferation, adhesion, COL1, LC3II, α-SMA, FAK; ↑ apoptosis, IRE1-α, CHOP, p62	137, 138
	Rat HSCs: Primary, HSC-T6	↓ proliferation, COL1, COL3, A2AR, pERK1/2, p38, pCREB	139, 140
	Mouse HSCs: Primary	↓ α-SMA, pAkt1	141, 142
	Hepatocytes: Rat primary	↓ CTGF, Smad2/3; ↑ PPARγ	144
	Kupffer cells: Mice primary	↓ ROS, TNF-α	143
Capsaicin	Mouse HSCs: GRX	↓ proliferation, COL1, COX-2, TGF-β1; ↑ PPARγ	1
	Rat HSCs: HSC-T6	↓ proliferation, α-SMA, COL1, ROS, TIMP-1, TGF-β1, Bcl-2, N-cadherin, macrophage activation, M1 polarization, Notch1; ↑ Bax, caspase-3, PPARγ, E-cadherin	2, 4, 139
Chlorogenic Acid	Rat HSCs: HSC-T6	↓ viability, COL1, COL3, TIMP-1, NOX subunit, ROS, p-p38/p38, pERK/ERK	5
	Human HSCs: LX2 cells	↓ α-SMA, TIMP-1, TGF-β1, miR-21, CTGF, pSmad1, pSmad2/3; ↑ Smad7	6-8
	Hepatocytes: Rat primary, AML12	↓ Drp1, GRP78, CHOP, GRP94, oxidative stress; ↑ SIRT1, mitofusin 2	9, 10
	Endothelial cells: Primary human LSECs	↓ ECM production; ↑ mitochondrial biogenesis	8
	Macrophage cells: RAW264.7, Ana-1	↓ NO, TNF-α, iNOS, IL-1β, IL-6, STAT6, M2 phenotypic differentiation; ↑ STAT1, M1 phenotypic differentiation	11, 12
Curcumin	Human HSCs: LX2 cells	↓ PPARα; ↑ C/EBPα, PPARγ, RXRα, RARβ, Nrf2	30
	Rat HSCs: Primary, HSC-T6	↓ proliferation, migration, α-SMA, MMP-2, MMP-9, TNF-α, IL-1β, TGF-β1, TLR2, TLR4, CXCR4, RhoA, MyD88, NFκB, p38, MAT2B, LOX-1, wnt3a, β-catenin, hedgehog, DLK1, Cyclin D1, CTGF; ↑ apoptosis, PPARγ, p53, C/EBPα, PGC1α, pAMPK, LXRα, SOD2, CBR1, Bax	16-29
	Mouse HSCs: Primary	↓ COL1, COL3, fibronectin, TGF-β1, ROS, MAT2A, HIF-1α; ↑ Plin5, PPARγ, AMPK	15, 31, 32
	Hepatocytes: BNL CL.2 cells	↓ α-SMA, fibronectin, TGF-β, EMT, Smad2, Smad3, ROS, mTOR; ↑ LC3, Beclin-1, ATG7, PPARα, AMPK	33
	Biliary epithelial cells: HIBECs	↓ EMT, Smad2/3, hedgehog; ↑ Smad7, CD109	34
	Macrophage cells: RAW264.7	↓ CCL7, MCP-1, CD86, iNOS, pERK1/2, p-p38, $CD11b^{+}$ monocyte migration	35
Ellagic Acid	Rat HSCs: Primary	↓ activation	37
	Hepatocytes: Chang cell line	↓ ROS	38
Epigallocatechin-3-Gallate	Human HSCs: LI90, TWNT-4, LX-2	↓ proliferation, α-SMA, COL1A1, COL1A4, MMP-2, MMP-9, TIMP1, TGF-β1, pAkt, pMEK, PDGFR, Rho, FAK, pERK1/2, pJNK, p-p38, pSmad2/3; ↑ apoptosis	42-44, 48, 49
	Rat HSCs: Primary	↓ migration, invasion, α-SMA, TGF-β1, ROS, MMP-2, MT1-MMP, CTGF, PDGFR; ↑ GSH	45-47
	Mouse HSCs: Primary	↓ COL1, α-SMA, fibronectin, TIMP-1	50
	Hepatocytes: Rat, Mouse primary	↓ MDA, ROS, IL-6, JAK1, JAK2, p-STAT3, BNIP3, ACC1, FAS, SREBP1, PPARα, SCD1, FGF21; ↑ GSH, AKT, GSK, FGFR2, FGFR3,	51-54
	Immune cells: Primary Kupffer cells, lymphocyte	↓ TLR2, infiltrating macrophages; ↑ TLR3, IL-10, M2 polarization	55, 56
Genistein	Rat HSCs: Primary, HSC-T6, LX-2	↓ proliferation, α-SMA, c-Jun, cyclin D1, pSmad3, Akt, p38; ↑ SIRT1	84-86
	Hepatocytes: Human primary, BRL	↓ SREBP-1c; ↑ PPARα, AMPK	82, 83
Hesperidin	Hepatocytes: L02 cells	↓ ROS, ERK, MAPK; ↑ Nrf2, HO-1	88
	Macrophage cells: THP-1 cells	↓ ER stress, ATF6, ATF4, p-PERK, p-IRE1α, IL-1β, IL-6, TNF-α, GRP94	87
Hesperetin	Rat HSCs: HSC-T6	↓ proliferation, COL1, α-SMA; ↑ apoptosis	89
	Hepatocytes: Rat primary, AML12	↓ apoptosis, ROS, ER stress; ↑ GRP78, HO-1	90, 91
Lipoic Acid	Hepatocytes: Human, Rat primary	↓ ER stress, FFA oxidation, IL-1β, iNOS; ↑ CHOP, Nrf2, insulin receptor, PI3K, Akt	122-125
	Macrophage cells: RAW 264.7, primary rat Kupffer cells	↓ NO, TNF-α, NFκB, activator protein-1	126

Lycopene	Mouse HSCs: GRX cells	↓ proliferation; ↑ RXR-α, RXR-β, PPARγ	152
	Rat HSCs: RI-T cells	↓ α-SMA, TGF-β1, COL1A1	151
	Hepatocytes: Rat primary, AML12	↓ MDA, TNF-α, IL-6, LDH, TBARS, DNA damage; ↑ Nrf2, HO-1, GSH	148-150
	Macrophage cells: RAW 264.7	↑ pSTAT6, pAkt, M2 polarization	147
α-Mangostin	Human HSCs: LX2 cells	↓ COL1A1, α-SMA, TGF-β, TIMP1, TIMP3, pERK1/2, ROS, pAkt, PAI1, pSmad3; ↑ GPX	155, 156
	Hepatocytes: L02 cells	↑ SIRT1, LKB1, AMPK, ACC	153, 154
γ-Mangostin	Human HSCs: LX2 cells	↓ COL1, α-SMA, NOX, HMGB1, PI3K/Akt, p38-MAPK; ↑ SIRT3	157
	Hepatocytes: L02 cells	↑ SIRT1, LKB1, AMPK, ACC	153
Naringenin	Rat HSCs: HSC-T6	↓ viability, COL1A1, fibronectin, pSmad3, Smad3, PAI-1; ↑ uptake	96, 97
	Hepatocytes: Mouse primary	↓ NLRP3, IL□1β	95
	Macrophage cells: RAW 264, primary Kupffer cells	↓ infiltration, NLRP3, IL□1β	94, 95
Naringin	Hepatocytes: Rat, Mouse primary	↓ DNA fragmentation, apoptosis; ↑ AMPKα, IRS1	92, 93
Quercetin	Rat HSCs: Primary	↓ proliferation, α-SMA, Bcl-2; ↑ apoptosis, Bax, cleaved-caspase-9, cleaved-caspase-3, cleaved-PARP-1, calnexin, CHOP, cleaved-ATF6, pPERK, pIRE1	103, 104
	Hepatocytes: Rat primary, BRL-3A, HL-7702, L02 cells	↓ Nrf2, NQO1, ER stress, ROS, NADPH oxidase, HMGB1, NLRP3 inflammasome; ↑ Keap1, SIRT, PGC1α	105-111
	Macrophage cells: RAW264.7, human THP-1, MΦs	↓ migration, MCP-1, TNF-α, NOS2, IL-6, IL-8, IL-1β, COX-2, JNK, c-Jun, IκBα, ICAM-1, M1 polarization; ↑ HO-1, M2 phenotype	112-115
Resveratrol	Mouse HSCs: GRX cells	↓ migration, α-SMA, COL1, IL-6; ↑ apoptosis, PPARγ/SIRT1 ratio, GFAP, IL-10	61-63
	Rat HSCs: HSC-T6	↓ TLR4, MyD88, NFκB in the nucleus, pAkt, pPI3K; ↑ NFκB in the cytosol, LXRβ	64
	Human HSCs: LX-2 cells	↓ proliferation, α-SMA, COL1A1, NFκB, pAkt, Bcl-2, YAP, TAZ; ↑ apoptosis, Bax, IκBα	65, 66
	Hepatocytes: Rat primary, Mouse primary, Chang cell line	↓ apoptosis, miR-190a-5p, iNOS, caspase-12, PDE; ↑ HGF, Nrf2, catalase, SOD, GPX, NQO1, GST, Bax, SIRT1	67-71
Sinapic Acid	Hepatocytes: AML-12 cells	↓ BRD4	76
Syringic Acid	Rat HSCs: Primary	↓ COL1A1, α-SMA	77
Sulforaphane	Human HSCs: hTERT, LX2 cells	↓ proliferation, fibronectin, α-SMA, TIMP-1, PAI-1, Nrf2-mediated TGF-β/Smad, IL-6, miRNA-423-5p, NOX1, NOX4, NFκB; ↑ HMOX1, NQO1, GSTM3	127-129
	Hepatocytes: HHL5 cells	↓ ER stress, GRP78, PERK, ROS; ↑ Nrf2, NQO1	130
Ursolic Acid	Rat HSCs: Primary, HSC-T6	↓ proliferation, migration, COL1, α-SMA, TIMP-1, ROS, NOX, NOX subunits, pERK1, pERK2, p38-MAPK, pAkt, PI3K/Akt, RhoA, Rock1, Hedgehog; ↑ MMP-1, apoptosis	158-161
	Hepatocytes: Rat primary	↓ MDA, LPO, ROS, NOX, NOX subunits, Rac1	162-164
	Kupffer cell: Rat primary	↓ ROS, NOX, NOX subunits, Rac1	162
Vanillic Acid	Rat HSCs: Primary	↓ COL1A1, α-SMA	77
Vitamin C	Human HSCs: Primary, LX2 cells	↓ COL1A1 (stimulated with H_2O_2); ↑ COL1A1, HYP (stimulated with TGF-β1)	167, 169
	Rat HSCs: Primary	↓ COL1A1 (stimulated with H_2O_2)	167
	Hepatocytes: Rat primary	↓ GGT; ↑ GSH	168
Vitamin E	Rat HSCs: Primary	↓ proliferation	79
	Hepatocytes: Mouse, Sheep primary, L02 cells	↓ ROS, apoptosis, pyroptosis, lipid accumulation; ↑ viability, Nrf2	78, 80, 81
Yangonin	Hepatocytes: Mouse primary, L02, AML-12 cells	↓ injury and senescence, miR-194, NFκB, NTCP; ↑ FXR, BSEP	170-173

↓, represents downregulation or decrease compared with that before drug treatment; ↑, represents upregulation or increase compared with that before drug treatment.

A2AR, adenosine A2A receptor; ACC, acetyl-CoA carboxylase-1; ATF, activating transcription factor; ATG, autophagy-related protein; Bax, Bcl-2 associated X protein; Bcl-2, B-cell leukemia/lymphoma-2; BRD4, bromodomain-containing protein 4; BSEP, bile salt export pump; CBR, cannabinoid receptor; CHOP, C/EBP homologous protein; COL, collagen; C/EBPα, CCAAT enhancer binding protein alpha; CREB, cAMP-response element binding protein; DLK1, delta-like homolog 1; Drp1, dynamin-related protein 1; EMT, epithelial-mesenchymal transition; eIF2α, eukaryotic translation initiation factor 2alpha; ER, endoplasmic reticulum; FAK, focal adhesion kinase; FFA, free fatty acid; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate cysteine ligase modifier; GFAP, glial fibrillary acidic protein; GPX, glutathione peroxidase enzyme; GSTM3, glutathione S-transferase Mu 3; HMGB1, high mobility group box 1; HMOX1, heme oxygenase 1; ICAM-1, intercellular cell adhesion molecule-1; IRE1, inositol-requiring enzyme; IRE1α, inositol-requiring enzyme 1alpha; IRS1, insulin receptor substrate 1; LC3II, microtubule-associated protein light chain 3 II; LKB1, liver kinase B1; LSECs, sinusoidal endothelial cells; LXR, liver X receptor; MAT2, methionine adenosyltransferase 2; NLRP3, nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3; NOX, nicotinamide adenine dinucleotide phosphate-oxidase; NQO1, quinone oxidoreductase-1; Nrf2, NF-E2-related factor 2; NTCP, sodium

taurocholate cotransporting polypeptide; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PGC1, peroxisome proliferator-activated receptor gamma coactivator 1; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homolog gene family, member A; ROCK1, Rho kinase receptor 1; ROS, reactive oxygen species; RXR, retinoid X receptor; SIRT, silent information regulator; TAZ, transcriptional cofactor with PDZ-binding motif; YAP, Yes-associated protein.

Table S2 Summary of toxicity assessments of edible plant-derived natural compounds with anti-liver fibrosis effects

Compounds	Description	References
S-Allylcysteine	Minor acute/sub-acute toxicity in mice (LD_{50} > 54.7 mM/kg, p.o.) and rats (LD_{50} > 20 mM/kg, i.p.); non-toxicity in normal human epithelial cell (TC_{50} = 2508-3102 μM)	174, 175
Betaine	No sub-acute and sub-chronic toxicity after intakes of 1, 2 and 5% of betaine for 90 consecutive days in rats	176
Caffeine	Minor acute toxicity in rats (LD_{50} = 367 mg/kg, p.o.); no observed adverse effect in healthy adults (400 mg/day)	177, 178
Capsaicin	High toxicity in mice (LD_{50} = 0.56-512 mg/kg, based on administration route); high toxicity in marine invertebrates (LC_{50} = 1252-5248 μg/L); acute toxicity as dietary supplement in man rarely occurs; cardiac functions and neuromuscular coordination do not change at therapeutic doses in mice	179-181
Chlorogenic Acid	Low cytotoxicity at 50 μg/μL	182
Cucurbitacin B	High acute toxicity in mice (death at 2 mg/kg); high cytotoxicity (IC_{50} = 0.04-0.13 μM)	183, 184
Curcumin	No Observed acute and sub-chronic toxicity at 2000 mg/kg or 720 mg/kg/day for 15 days or 90 days in rats (a solid lipid curcumin particle, p.o.); No observed adverse effect at 0.27 and 0.54 g/kg/day in mice and hamsters (curcumin-loaded nanocomplexes); minor toxicity in normal human epithelial cell (TC_{50} = 3.8-13.6 μM)	175, 185, 186
Ellagic Acid	No observed adverse effect at 5% (3011 mg/kg/day) for 90 days in male rats, and no observed adverse effect at 5% (3254 mg/kg/day) for 90 days in female rats	187
Epigallocatechin-3-Gallate	No acute toxicity at 2000 mg/kg, and no sub-acute toxicity at 10 mg/kg/day for 28 days in rats	188
Ergothioneine	No adverse effect at 1600 mg/kg/day for 90 days in rats; no cytotoxicity or mutagenicity at 5000 μg/plate	189, 190
Genistein	No adverse effect at 50 mg/kg/day for 4 weeks, 13 weeks and 52 weeks in rats	191
Hesperidin	No acute toxicity in rats (LD_{50} = 4837.5 mg/kg); low observed adverse effect at 1000 mg/kg for 13 weeks in rats; no cytotoxicity at 100 μM	192, 193
Hesperetin	No cytotoxicity at 100 μM	193
Lipoic Acid	No acute toxicity in rats (LD_{50} > 2000 mg/kg); no observed adverse effect at 61.9 mg/kg for 4 weeks in rats	194
Lycopene	No observed adverse effect at 500 mg/kg/day for 14 weeks or 1000 mg/kg/day for 4 weeks in rats	195
α-Mangostin	Minor acute toxicity in mice (LD_{50} = 150 mg/kg); minor toxicity to zebrafish embryos (LC_{50} = 5.75 μM); no cytotoxicity at 16 μg/mL	196-198
γ-Mangostin	No cytotoxicity at 12.5 μg/mL	199
Naringenin	No acute toxicity in rats (LD_{50} > 5000 mg/kg); no observed adverse effect at 150 to 900 mg in healthy adults	200, 201
Naringin	No acute toxicity in rats (LD_{50} > 16g /kg, p.o.); no observed adverse effect at 1250 mg/kg/day (p.o.) for 13 weeks or 6 months in rats; no observed adverse effect at 500 mg/kg/day (p.o.) for 3 and 6 consecutive months in Beagle dogs	202-204
Quercetin	No observed adverse effect at 2000 mg/day for 1 week in patients with chronic obstructive pulmonary disease	205
Resveratrol	No toxicity and mortality at 100 mg/day (p.o.) for 28 days in rats	206
Sinapic Acid	No toxicity at dietary levels, but amino acid digestibility is affected at higher levels in chickens	207
Syringic Acid	No major adverse effect at 1000 mg/kg/day (p.o.) for 14 days in rats; low cytotoxicity at 50 μg/μL	182, 208
Sulforaphane	No toxicity at 15 mg/kg/day (p.o.) for 14 days in rats	209
Ursolic Acid	No acute toxicity at 50-200 mg/kg (i.p.) in mice	210
Vanillic Acid	No adverse effect at 1000 mg/kg/day (p.o.) for 2 weeks in rats; low cytotoxicity at 50 μg/μL	182, 211
Vitamin C	No toxicity at 2000 mg in adults; safety at a single oral dose of 5-10 g in healthy adults	212, 213
Vitamin E	No toxicity at 1000 mg in adults	212
Yangonin	No mutagenic responses; no cytotoxicity at 10 μg/mL, but cytotoxicity can be observed at 20 μg/mL in mouse lymphoma cells	214

LD_{50}, median lethal dose; LC_{50}, median lethal concentration; TC_{50}, half-maximal toxic concentration