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Review Article

Astragaloside IV in Liver Fibrosis: Mechanistic Insights, Preclinical Evidence, and Translational Challenges

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Abstract

Liver fibrosis is a dynamic and partially reversible pathological process driven by chronic liver injury, yet effective antifibrotic therapies remain limited. Astragaloside IV (AS-IV), a major bioactive constituent isolated from *Astragalus mongholicus* Bunge, exerts a broad range of pharmacological effects, including anti-inflammatory, antioxidant, and antifibrotic effects. This review synthesizes current evidence on the pharmacological characteristics, mechanistic basis, preclinical efficacy, and translational challenges of AS-IV in liver fibrosis. Available evidence indicates that AS-IV exerts its antifibrotic effects primarily by suppressing hepatic stellate cell activation, with modulation of transforming growth factor-β/Smad signaling representing the most consistently supported mechanism. Beyond this principal pathway, AS-IV may attenuate profibrotic amplification loops by enhancing antioxidant responses and suppressing inflammatory signaling, while also reducing upstream profibrotic stimuli through hepatoprotective effects. However, its clinical translation remains limited by poor oral bioavailability, inadequately defined pharmacokinetic-pharmacodynamic relationships, and a lack of high-quality clinical evidence. Overall, AS-IV represents a promising preclinical antifibrotic candidate, although clinical efficacy and pharmacological optimization remain to be established.

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Introduction

Liver fibrosis is a common pathological response to chronic liver injury resulting from viral hepatitis, alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune liver disease and cholestatic disorders.[1] Fibrosis stage is the strongest histological predictor of liver-related morbidity and mortality, as progression to advanced fibrosis and cirrhosis substantially increases the risks of portal hypertension, hepatic decompensation, and hepatocellular carcinoma.[2,3]

Importantly, fibrosis is no longer regarded as an irreversible endpoint of chronic liver disease; rather, it is recognized as a dynamic and partially reversible process when the underlying injury is controlled and profibrotic signaling is attenuated.[1,4]

Fibrogenesis is driven by coordinated interactions among multiple hepatic cell populations, including hepatocytes, Kupffer cells, infiltrating macrophages, liver sinusoidal endothelial cells, and cholangiocytes.[5–8] Among these components, activation of hepatic stellate cells (HSCs) is the central cellular event driving pathological extracellular matrix (ECM) deposition.[5] Transforming growth factor-β (TGF-β)/Smad signaling remains the dominant profibrotic pathway, directly regulating HSC transdifferentiation and ECM production.[9] In parallel, oxidative stress and chronic inflammation amplify fibrogenic responses through interconnected networks. In particular, nuclear factor kappa B (NF-κB)-mediated inflammatory signaling promotes the production of proinflammatory and profibrotic mediators, thereby linking immune activation and hepatocellular injury to HSC activation within the fibrogenic microenvironment.[10–12] These interconnected processes may partly explain why single-target antifibrotic approaches have achieved limited clinical success.

Fibrosis-directed treatment has recently advanced in metabolic dysfunction-associated steatohepatitis (MASH). Resmetirom (Rezdiffra) in 2024 and semaglutide (Wegovy) in 2025 received accelerated approval from the U.S. Food and Drug Administration (FDA) for adults with noncirrhotic MASH and moderate-to-advanced fibrosis (F2–F3).[13,14] Semaglutide approval was supported by the phase 3 ESSENCE trial, which demonstrated improvements in both MASH resolution and fibrosis histology.[15] Although its MASH indication is not restricted by body mass index (BMI), patients with BMI <25 kg/m^2 represented only 6.6% of the ESSENCE cohort, leaving efficacy and safety specifically in lean MASH insufficiently defined.[15] These approvals are specific to MASH with F2–F3 fibrosis and do not represent broadly approved antifibrotic

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therapies across liver disease etiologies; management otherwise remains focused on the underlying cause and prevention of fibrosis-related complications.[16,17]

Natural products have attracted increasing attention as potential antifibrotic candidates because of their capacity to modulate multiple pathological processes, including oxidative stress, inflammation, fibrogenic signaling, and metabolic dysregulation.[18–20] Such multitarget activity may be advantageous in liver fibrosis, which is driven by interconnected and compensatory pathogenic circuits. Nevertheless, the translation of natural compounds remains challenging because of variability in model quality, limited mechanistic resolution, insufficient pharmacological characterization, and pharmacokinetic constraints.[18,19]

Astragaloside IV (AS-IV), a major cycloartane-type triterpenoid saponin isolated from *Astragalus mongholicus* Bunge (Fabaceae; syn. *Astragalus membranaceus* Fisch. ex Bunge), has emerged as a representative natural compound with reported anti-inflammatory, antioxidant, and antifibrotic activities.[21,22] In experimental models of liver fibrosis, AS-IV has been associated with inhibition of HSC activation, modulation of oxidative stress responses, and regulation of inflammatory pathways.[23–26] However, the relative contributions of these mechanisms, their hierarchical relationships, and their translational relevance remain incompletely defined. This review therefore synthesizes current knowledge of the pharmacological properties, molecular mechanisms, preclinical efficacy, and translational challenges of AS-IV in liver fibrosis while identifying evidence gaps that currently limit rational clinical development.

Pharmacological and pharmacokinetic characteristics of AS-IV

Origin and chemical structure

AS-IV is a major bioactive constituent isolated from the dried root of *Astragalus mongholicus* Bunge, which is used medicinally as Astragali Radix (Huangqi).[27,28] AS-IV is classified as a cycloartane-type triterpenoid saponin and is considered a key constituent contributing to the anti-inflammatory, antioxidant, and antifibrotic properties of Astragali Radix.[21,27] Structurally, AS-IV consists of a cycloartane-type triterpenoid aglycone linked to sugar moieties via glycosidic bonds, forming a relatively stable and highly polar glycosylated structure.[27,29] This property contributes to its limited membrane partitioning and provides an important physicochemical basis for its absorption and pharmacokinetic limitations.[21,30]

Biopharmaceutical characteristics

The biopharmaceutical behavior of AS-IV is largely governed by its glycosylated saponin structure. Caco-2 cell studies indicate that AS-IV is transported mainly by passive mechanisms, including a paracellular component, but overall transepithelial permeability remains extremely low because of the compound's physicochemical constraints.[30,31] Classical efflux inhibitors exert minimal effects on its transport, indicating that restricted epithelial permeation, rather than active efflux, is the dominant barrier to intestinal uptake.[30,31] Consistent with these *in vitro* findings, *in vivo* studies suggest that limited intestinal absorption is the primary factor restricting systemic exposure after oral administration.[30]

Administration within an Astragali Radix extract matrix may partially improve absorption, implying that coexisting constituents or formulation-related factors can modulate uptake behavior.[30,32] In addition, the intestinal microbiota and coadministered compounds may influence the conversion of AS-IV to cycloastragenol, thereby affecting the exposure profiles of both the parent compound and its metabolite.[32] Together, these findings indicate that poor intestinal permeability, matrix-dependent absorption, and microbiota-related biotransformation are key determinants of AS-IV oral exposure.

Pharmacokinetic characteristics

Pharmacokinetic studies consistently indicate that AS-IV has limited systemic exposure after oral administration. The reported absolute oral bioavailability is approximately 2.2%–3.7% in rats and 7.4% in beagle dogs, suggesting that poor oral exposure is a reproducible finding across preclinical species.[30,33,34] These values also highlight the need to interpret orally administered efficacy studies in the context of achievable systemic and hepatic exposure. Following intravenous administration, AS-IV shows relatively dose-proportional pharmacokinetics within the tested dose ranges in rats and dogs.[33,35] Available data indicate moderate systemic clearance, a high degree of plasma protein binding, and preferential tissue distribution to the liver and lung, with limited brain penetration.[34,35] Biliary excretion and metabolism contribute to systemic disposition, although these elimination processes do not by themselves explain the low oral exposure observed after oral dosing.[33]

Clinical pharmacokinetic evidence remains limited. In healthy volunteers, intravenous Astragali Radix-derived total saponin injections produced approximately dose-proportional AS-IV exposure, no significant accumulation after repeated dosing, and good tolerability.[36] However, these findings were obtained from a multicomponent preparation rather than isolated AS-IV and therefore should be interpreted cautiously. In addition, cross-species extrapolation remains uncertain because metabolic capacity, biliary excretion, tissue distribution, and microbiota-mediated conversion may differ between animals and humans. Representative pharmacokinetic parameters are summarized in Table 1.[30,32–37]

Druggability challenges and optimization approaches

Given that limited intestinal permeability constrains AS-IV oral exposure, optimization strategies should focus on enhancing absorption or modifying molecular properties. Experimental studies have shown that permeability enhancers, such as chitosan and bile salt derivatives, can improve intestinal transport, supporting formulation-based optimization approaches.[31] Administration within an Astragali Radix extract matrix has also been observed to enhance absorption, suggesting that coexisting constituents may modulate uptake behavior.[30] Structural modification studies provide more direct evidence as exemplified by Qing *et al*., who reported that the water-soluble derivative LS-102 exhibited markedly improved oral permeability and approximately twofold higher relative bioavailability than native AS-IV.[37] These findings indicate that the exposure limitations of AS-IV are not insurmountable and can be mitigated through rational molecular design, formulation optimization, or delivery-system development.

Pathophysiological basis of liver fibrosis

At the cellular and molecular level, liver fibrosis is characterized by excessive deposition of ECM resulting from persistent liver injury and dysregulated wound-healing responses.[17,38] The progression of fibrosis is driven by coordinated interactions among multiple hepatic cell populations and signaling networks rather than a single linear pathway.[6,25,39,40] The core event in fibrosis is HSC activation, with oxidative stress and inflammation serving as major amplifying systems, while hepatocyte injury acts as the upstream trigger.[5,41,42]

Table 1. Summary of available pharmacokinetic parameters of astragaloside IV in preclinical and clinical studies

Species	Route/ dose	C_{max}	T_{max}	AUC	$t_{1/2}$	F	Key ADME characteristics	Study
Rat	i.v. 2.5 mg/kg; p.o. 20 mg/kg	0.38 μg/mL	0.43 h	5.99/1.06 μg·h/mL	3.37/4.65 h	2.20%	Very low intestinal permeability; negligible P-gp involvement	Gu *et al*.[30]
Rat	i.v. 1–4 mg/kg; p.o. 20 mg/kg	1.04 μg/mL	0.75 h	8.89/3.25 μg·h/mL	3.01/3.8 h	3.66%	Dose-proportional exposure; substantial metabolism indicated by ~50% parent-drug recovery	Du *et al*.[33]
Rat and beagle dog	Rat: i.v. 0.75–3 mg/kg; dog: i.v. 0.25–1 mg/kg	Rat: 3.79–7.79 μg/mL (male), 4.80–7.24 μg/mL (female); dog: 1.11–7.92 μg/mL (male), 1.13–8.86 μg/mL (female)	–	Rat: 153–551 μg·min/mL; dog: 65.8–362 μg·min/mL	Rat: 34.0–131.6 min; dog: 50.2–68.8 min	–	High protein binding; liver/lung enrichment; limited brain penetration	Zhang *et al*.[35]
Beagle dog	i.v. 0.5–2 mg/kg; p.o. 10 mg/kg	1.624 μg/mL	1.0 h	126.24–724.51/204.05 μg·min/mL	177.18–241.59/ 229.71 min	7.40%	Dose-proportional exposure; high protein binding; low oral bioavailability	Zhang *et al*.[34]
Healthy Chinese volunteers	i.v. infusion, AI 200–500 mL, equivalent AS-IV 18–45 mg	2.12–5.17 μg/mL	1.08–2.58 h	4.38–18.22 μg·h/mL	2.14–2.69 h	–	Dose-proportional exposure; no significant accumulation; low urinary excretion	Xu *et al*.[36]
Rat	p.o. 20 mg/kg	92.4 ± 14.2 ng/mL	1.0 ± 0.5 h	420.41 ± 129.01 μg·h/L	$t_{1/2\beta}$: 22.02 ± 8.26 h	LS-102 relative F ≈ 2-fold vs. AS-IV	LS-102 markedly improved intestinal permeability and oral exposure versus AS-IV	Qing *et al*.[37]
Normal/ T2DM rats	p.o. 64 mg/kg	176.51 ± 59.13/156.17 ± 62.36 ng/mL	3.68 ± 3.13/ 3.60 ± 1.67 h	AS-IV: 3,028.27 ± 1,628.81/3,517.81 ± 867.43 h·ng/mL; CAG: 5,943.53 ± 2,425.53/5,194.69 ± 1,534.69 h·ng/mL	11.75 ± 9.89/ 14.33 ± 6.11 h	–	T2DM altered AS-IV/CAG disposition	Lei *et al*.[32]

AI, astragaloside injection; ADME, absorption, distribution, metabolism, and excretion; C_{max}, maximum plasma concentration; AS-IV, astragaloside IV; AUC, area under the plasma concentration–time curve; CAG, cycloastragenol; CL, systemic clearance; F, absolute oral bioavailability; i.v., intravenous; LS-102, astragalosidic acid; Papp, apparent permeability coefficient; P-gp, P-glycoprotein; p.o., oral administration; T2DM, type 2 diabetes mellitus; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration. "–" indicates not applicable or not reported. For Lei *et al*., values before and after the slash represent normal and T2DM rats, respectively.

HSC activation

Activation of HSCs is the central cellular event in liver fibrogenesis.[5,6] In the healthy liver, quiescent HSCs reside in the space of Disse and primarily function as vitamin A-storing cells.[5,43] In response to chronic injury, they transdifferentiate into proliferative, contractile, and fibrogenic myofibroblast-like cells, characterized by increased expression of α-smooth muscle actin (α-SMA), collagen types I and III, and tissue inhibitor of metalloproteinase-1 (TIMP-1).[5,6,17] This phenotypic switch accounts for the majority of pathological ECM accumulation.[5,38,44] Among the signaling pathways driving HSC activation, the TGF-β/Smad axis remains the dominant profibrotic mechanism.[9,45] TGF-β1 induces phosphorylation of Smad2/3, which subsequently form complexes with Smad4 and promote transcription of ECM-related genes such as *COL1A1* and *COL3A1*.[9,46] Because this pathway integrates multiple upstream injury signals into a final fibrogenic response, it represents a direct pharmacological target for antifibrotic intervention and provides a key mechanistic reference point for evaluating AS-IV.

Oxidative stress and inflammation

Oxidative stress and inflammation act as interconnected amplification systems that sustain and exacerbate fibrogenesis.[38,41] Reactive oxygen species (ROS), generated from mitochondrial dysfunction, cytochrome P450 activity, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and inflammatory cells, not only induce hepatocellular injury but also function as signaling mediators that enhance HSC activation, particularly through crosstalk with TGF-β and mitogen-activated protein kinase (MAPK) pathways.[41] The

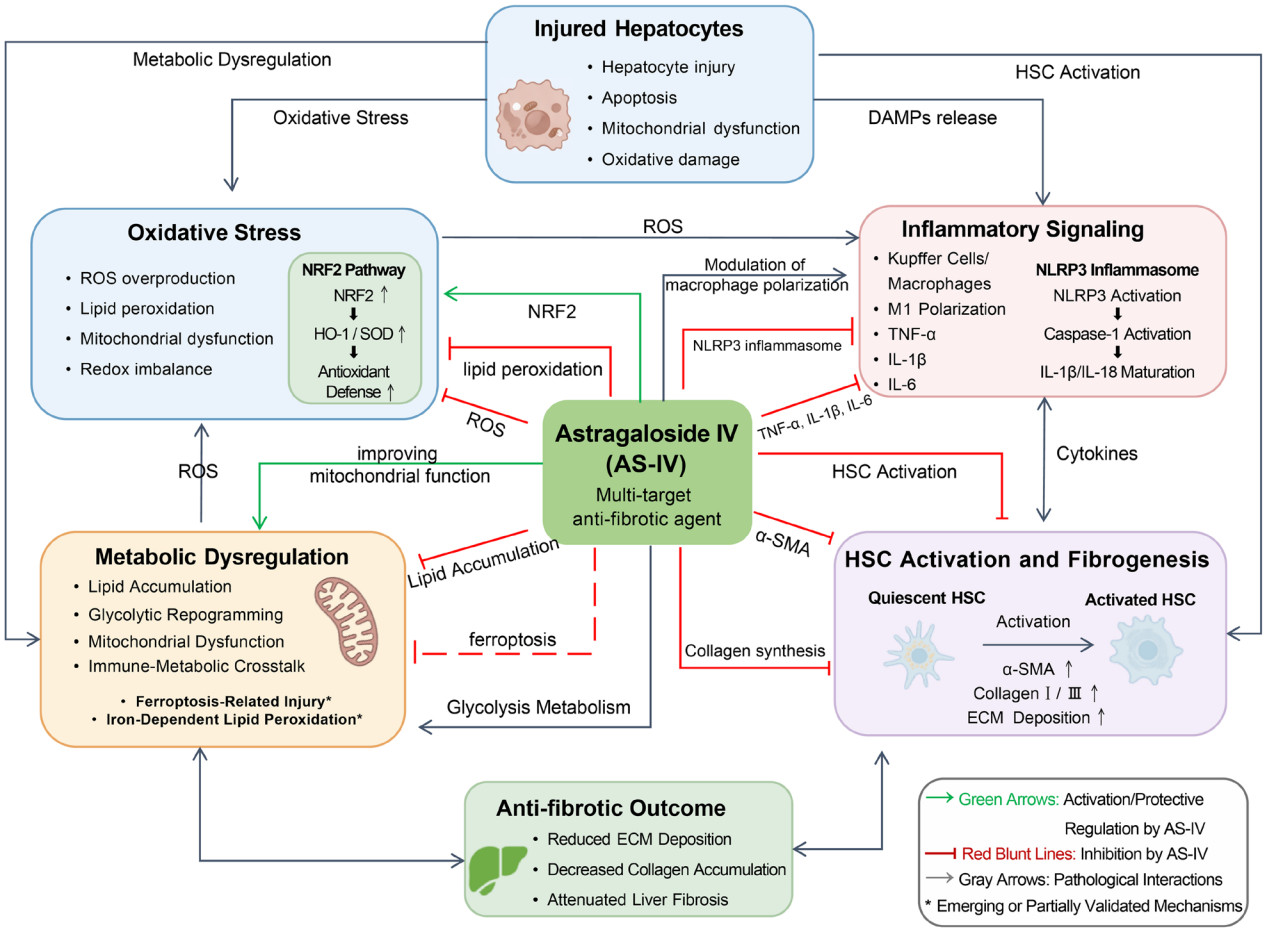


Fig. 1. Integrated mechanisms underlying the antifibrotic actions of AS-IV. Hepatocyte injury, oxidative stress, inflammatory signaling, and metabolic dysregulation converge on HSC activation and ECM deposition. AS-IV may suppress the HSC-ECM effector axis while limiting NRF2-NF-κB/NLRP3-associated redox-inflammatory amplification, macrophage activation, and hepatocyte-derived profibrotic signals. Green arrows indicate activation or protective regulation by AS-IV; red blunt-ended lines indicate inhibition by AS-IV; gray arrows indicate pathological interactions; dashed lines and asterisks indicate emerging or partially validated mechanisms. AS-IV, astragaloside IV; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; HO-1, heme oxygenase-1; HSC, hepatic stellate cell; IL, interleukin; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha; α-SMA, alpha-smooth muscle actin; ↑, increased expression or activity.

principal endogenous counter-regulatory mechanism is the Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-related factor 2 (NRF2) pathway, which induces the expression of antioxidant and cytoprotective enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1).[47,48] When this response is insufficient, persistent redox imbalance contributes to chronic injury and fibrosis progression.[41,47]

Inflammatory signaling further reinforces this process. Activated Kupffer cells and infiltrating macrophages release cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as profibrotic mediators, including TGF-β.[6,38] Among inflammatory pathways, NF-κB plays a central transcriptional role, while the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome links cellular stress to IL-1β maturation and fibrogenic signaling.[11,41]

Hepatocyte injury

Hepatocyte injury represents a key upstream event that initiates and sustains fibrogenesis.[38,42] Damaged hepatocytes release ROS, apoptotic bodies, and damage-associated molecular patterns (DAMPs), which activate resident macrophages and promote recruitment of inflammatory cells.[41,42] This establishes a microenvironment that facilitates HSC activation. Apoptotic hepatocytes can further amplify fibrogenesis through macrophage-mediated production of profibrotic cytokines such as TGF-β and TNF-α.[6,42] In addition, sublethal stress, including mitochondrial dysfunction, lipotoxicity, and endoplasmic reticulum stress, can maintain a proinflammatory and profibrotic milieu even in the absence of overt cell death.[42,49] Interventions targeting hepatocyte injury are generally considered indirect antifibrotic strategies because they act upstream of HSC activation.[5,42]

Mechanistic basis of the antifibrotic effects of AS-IV

Liver fibrosis is sustained by interconnected processes involving hepatocyte injury, oxidative stress, inflammation, and HSC activation. AS-IV appears to act across these interconnected layers, with direct effects on the HSC-ECM axis and additional regulation of the surrounding fibrogenic microenvironment.[24,38,50] An overview of these interconnected pathways is provided in Figure 1.

Table 2. Effects of AS-IV on hepatic stellate cell activation *in vitro* models and critical appraisal of the evidence

Model	Dosages	Quantitative findings	Mechanisms	Strengths	Limitations	Reference
PDGF-BB/TGF-β1-stimulated primary rat HSCs	1.5–24.0 mg/L, 24 h	↓ [^{3}H]-thymidine and [^{3}H]-proline incorporation (P<0.05, P<0.01)	Suppression of growth factor-driven HSC proliferation and collagen synthesis	Primary HSCs with direct functional endpoints	No target validation; no primary human HSCs	Liu *et al*.[50]
Culture-activated primary rat HSCs	1–100 μM, 24 h	↓ LPO by 17%–43%; ↑ GSH by 105%–245%; ↓ secreted collagen I by 28%–50%; ↓ α-SMA, collagen I, and fibronectin (P<0.05)	NRF2/GSH-dependent attenuation of oxidative stress and p38 MAPK signaling	Loss-of-function supports causal inference	Oxidative-stress model; no human HSC validation	Li *et al*.[24]
H_2O_2-injured HSC-T6 cells	100–200 μM, 24 h	↑ cell viability from 30.0% to 54.0%/68.0% (P<0.01); ↓ apoptosis from 68.0% to 51.7%/50.7% (P<0.05); ↓ caspase-3 from 143.8 to 114.4/100.3 U/mL; ↓ caspase-9 from 132.1 to 110.2/108.0 U/mL (P<0.05)	Attenuation of H_2O_2-induced ROS–caspase-9/3-dependent apoptosis	Multiple quantitative functional endpoints	Cytoprotection, not direct antifibrotic activity	Wang *et al*.[53]
PDGF-BB-stimulated HSC-T6 cells	20–40 μg/mL, 48 h	↓ COL1A1, α-SMA, and FN (P<0.01); ↑ SA-β-gal (P<0.001); ↑ apoptosis 2- to 3-fold (early and late, P<0.001 and P<0.05)	NF-κB activation-associated HSC senescence and apoptosis	Multidimensional functional endpoints	Immortalized cells; no human or *in vivo* validation	Chen *et al*.[52]
TGF-β1-stimulated HSC-T6 cells	5–20 μM, 24 h	↑ pSmad3C (P<0.01); ↓ pSmad3L, pSmad2C, pSmad2L, PAI-1, and α-SMA (P<0.01); ↑ pNRF2, NRF2, HO-1, and NQO1 (P<0.01)	Site-specific TGF-β/Smad3 phosphorylation and NRF2/HO-1 signaling	Site-specific Smad signaling analysis	No genetic validation; immortalized cells	Zhang *et al*.[51]

Quantitative values are presented as reported in the original publications. When exact group means were unavailable, only the reported direction of effect and statistical significance are shown. AS-IV, astragaloside IV; COL1A1, collagen type I alpha 1 chain; FN, fibronectin; GSH, glutathione; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase 1; HSC, hepatic stellate cell; LPO, lipid peroxidation; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NQO1, NAD(P)H:quinone oxidoreductase 1; NRF2, nuclear factor erythroid 2-related factor 2; PAI-1, plasminogen activator inhibitor-1; PDGF-BB, platelet-derived growth factor-BB; pSmad2C, C-terminally phosphorylated Smad2; pSmad2L, linker-phosphorylated Smad2; pSmad3C, C-terminally phosphorylated Smad3; pSmad3L, linker-phosphorylated Smad3; ROS, reactive oxygen species; SA-β-gal, senescence-associated beta-galactosidase; TGF-β1, transforming growth factor-beta 1; α-SMA, alpha-smooth muscle actin; [^{3}H], tritium-labeled; ↓, decrease; ↑, increase.

Inhibition of HSC activation

Inhibition of HSC activation is the most direct and consistently supported antifibrotic action of AS-IV. Across cellular and animal models, AS-IV reduces HSC proliferation, α-SMA expression, collagen synthesis, and ECM accumulation, indicating suppression of the activated myofibroblast-like phenotype.[24,50] Representative *in vitro* evidence is summarized in Table 2.[24,50,51,52,53]

The TGF-β/Smad pathway is the best-supported downstream signaling axis associated with AS-IV activity.[26,51] In rats with established carbon tetrachloride (CCl_4)-induced fibrosis, AS-IV treatment (14 $mg \cdot kg^{-1} \cdot d^{-1}$ for 4 weeks) reduced the collagen-positive area from 27.9% to 8.8% (P<0.01), accompanied by decreased α-SMA and TGF-β1 expression (P<0.01), suggesting that AS-IV may attenuate not only fibrogenic signaling activation but also measurable ECM deposition.[54] Regulation of the tissue inhibitor of metalloproteinase-matrix metalloproteinase balance may also contribute to matrix remodeling, although the evidence is less consistent than that for TGF-β1-Smad2/3 inhibition.

HSC-based studies provide further evidence of a direct cellular effect. AS-IV inhibited collagen synthesis and proliferation in activated HSCs, reduced ROS-p38 MAPK-dependent collagen production, and attenuated platelet-derived growth factor-BB-induced activation while modulating NF-κB-associated senescence and apoptosis.[24,50,52] In TGF-β1-stimulated HSC-T6 cells, AS-IV also reduced Smad2/3 activation.[51] Together, these findings identify HSC activation as the most robust cellular endpoint of AS-IV activity.

However, the molecular target that initiates these effects remains unresolved. Most studies measure downstream pathway markers rather than direct target engagement, and there is insufficient evidence that AS-IV binds TGF-β receptors, Smad proteins, or upstream regulatory complexes. Although Smad7 is an established inhibitor of canonical TGF-β signaling, its modulation by AS-IV has not been directly validated in liver fibrosis.[12,46] Thus, the available evidence supports inhibition of TGF-β1-Smad2/3 signaling but does not establish this pathway as a direct molecular target. The proposed inhibitory effects of AS-IV on canonical TGF-β/Smad signaling and downstream fibrogenic transcription are summarized in Figure 2.

Regulation of oxidative stress

Oxidative stress amplifies liver fibrogenesis by damaging hepatocytes and promoting redox-sensitive HSC activation. In activated HSCs, AS-IV reduced lipid peroxidation by up to 43% and increased glutathione by up to 245% across the tested concentration range; ROS accumulation and fibrogenic markers were also reduced (all P<0.05).[24] Loss-of-function experiments support involvement of the NRF2/glutathione-ROS-p38 MAPK pathway, but the study did not establish that this mechanism is sufficient to reverse established fibrosis *in vivo*.[24]

AS-IV also activates NRF2-associated antioxidant respons-

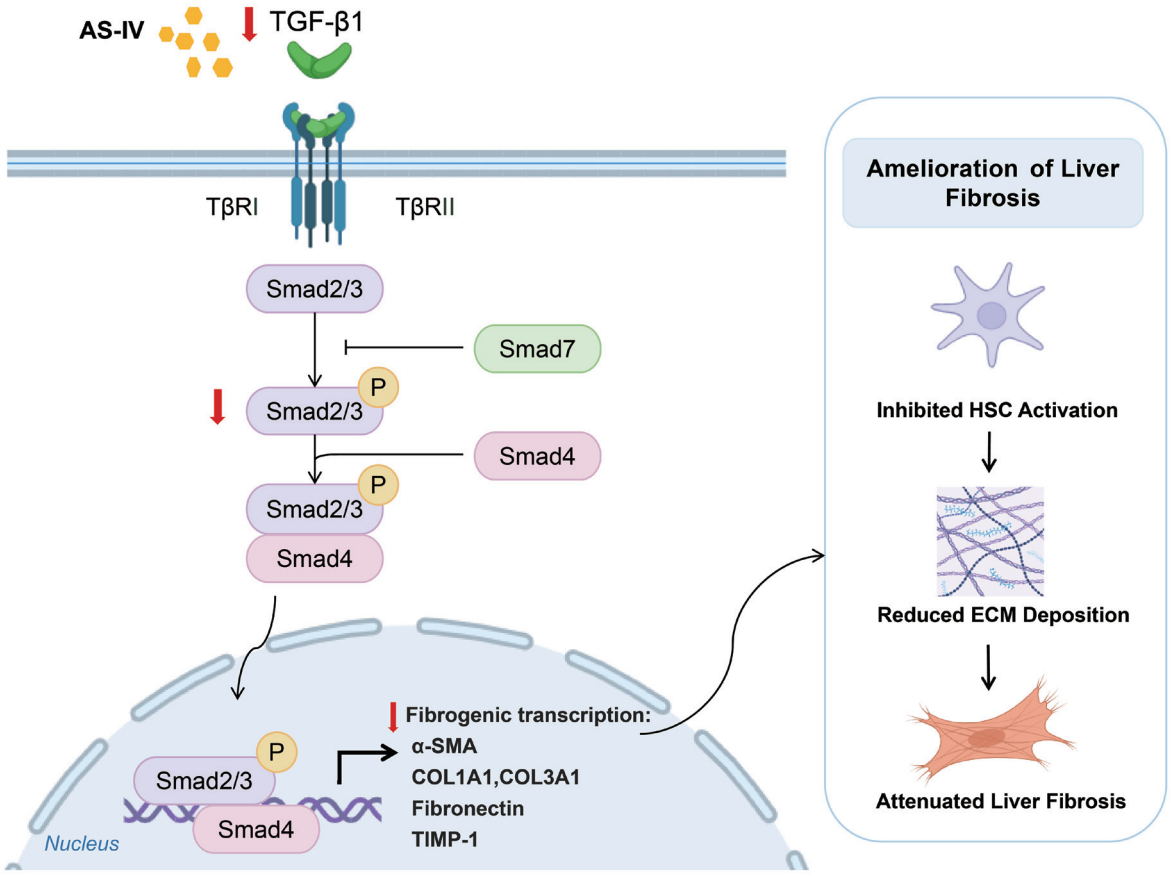


Fig. 2. AS-IV suppresses liver fibrogenesis by targeting the TGF-β/Smad pathway. Binding of TGF-β to TβRII and TβRI promotes Smad2/3 phosphorylation, formation of the Smad2/3/4 complex, and nuclear transcription of profibrotic genes, including α-SMA, COL1A1, COL3A1, fibronectin, and TIMP-1. Available evidence suggests that AS-IV attenuates this pathway by reducing TGF-β1 expression, inhibiting Smad2/3 phosphorylation, and suppressing downstream fibrogenic transcription; enhancement of inhibitory feedback through Smad7 may also contribute. Red downward arrows indicate inhibition or downregulation induced by AS-IV, and blunt-ended lines indicate inhibitory regulation. P indicates phosphorylation. AS-IV, astragaloside IV; COL1A1, collagen type I alpha 1 chain; COL3A1, collagen type III alpha 1 chain; ECM, extracellular matrix; HSC, hepatic stellate cell; TGF-β1, transforming growth factor-beta 1; TIMP-1, tissue inhibitor of metalloproteinase-1; TβRI, transforming growth factor-beta receptor type I; TβRII, transforming growth factor-beta receptor type II; α-SMA, alpha-smooth muscle actin.

es in liver injury models. For example, in acetaminophen-induced hepatic injury, AS-IV increased NRF2, HO-1, and NQO1 expression while restoring antioxidant capacity, although these findings mainly reflect hepatoprotective rather than fibrosis-regression effects.[22] Similar antioxidant and cytoprotective effects have been observed in metabolic liver disease and fibrosis-associated hepatocarcinogenesis models.[51,55]

These findings support a fibrosis-relevant antioxidant role for AS-IV, but their interpretation requires caution. Most evidence for NRF2 activation derives from acute hepatotoxicity, metabolic liver disease, or mixed injury models rather than established fibrosis-regression systems.[22,55,56] NRF2 activation therefore primarily contributes to the reduction of oxidative injury and preservation of hepatocellular homeostasis. Causal studies using NRF2 loss-of-function approaches are needed to determine whether this pathway is required for reductions in HSC activation and collagen deposition.

Regulation of inflammation and macrophage immunometabolism

AS-IV attenuates inflammatory signaling through pathways involving NF-κB, the NLRP3 inflammasome, and proinflammatory cytokines, including TNF-α, IL-1β, and IL-6.[22,57–60] These effects may reduce inflammatory reinforcement of HSC activation but should not be equated with direct suppression of ECM synthesis.

In CCl_4 plus ethanol-induced fibrosis, AS-IV administration (40 $mg \cdot kg^{-1} \cdot d^{-1}$ for 6 weeks) significantly decreased ALT, AST, hyaluronic acid, α-SMA mRNA, and collagen I mRNA levels (all $P<0.05$), together with suppression of C-X-C motif chemokine ligand 12 and NLRP3 expression ($P<0.01$), indicating coordinated regulation of inflammatory and fibrogenic responses.[59] In lipopolysaccharide-induced liver injury, AS-IV attenuated NRF2-associated oxidative stress and NLRP3-mediated inflammation.[57] Reduced expression of thioredoxin-interacting protein, NLRP3, apoptosis-associated speck-like protein containing a CARD, and IL-1β further supports an inhibitory effect on inflammasome signaling, although a causal relationship between NLRP3 suppression and fibrosis regression has not been established.[57]

Macrophage immunometabolism may provide an additional mechanism. Hu *et al*. further demonstrated that AS-IV (80 $mg \cdot kg^{-1} \cdot d^{-1}$) decreased alanine aminotransferase (ALT), aspartate aminotransferase (AST), hydroxyproline, IL-1β, IL-6, and TNF-α expression in mice with CCl_4-induced fibrosis (all $P<0.01$), while decreasing CD86/iNOS and increasing CD206/ARG-1 expression in macrophages (all $P<0.01$).[22]

This mechanism links metabolic reprogramming of macrophages to changes in the fibrogenic microenvironment. However, it is currently supported by limited preclinical evidence and should be considered emerging rather than a core antifibrotic axis. Validation in macrophage-specific models, therapeutic regression settings, and macrophage-HSC coculture systems is required.

Hepatocyte protection

Hepatocyte injury generates ROS, apoptotic bodies, and DAMPs that promote macrophage activation and HSC stimulation. AS-IV has shown hepatoprotective effects in experimental liver injury and metabolic disease models by attenuating apoptosis, oxidative stress, mitochondrial dysfunction, and ferroptosis-related processes.[22,55,56,61] In iron overload-induced injury, AS-IV reversed Bax upregulation and Bcl-2 downregulation, whereas in metabolic dysfunction-associated fatty liver disease, it modulated the solute carrier family 7 member 11 (SLC7A11)/glutathione peroxidase 4 (GPX4) axis and reduced ferroptosis-related lipid peroxidation.[56,61] These findings suggest that hepatocyte protection may reduce upstream profibrotic stimuli. However, most evidence derives from injury or metabolic models rather than fibrosis-regression systems, and current data do not establish hepatocyte ferroptosis inhibition as a direct antifibrotic mechanism of AS-IV.

Mechanistic hierarchy and pathway crosstalk

The mechanistic significance of AS-IV may lie not only in modulation of individual pathways but also in their crosstalk within the fibrogenic microenvironment.[24,26,50,51] A key interaction occurs between NRF2 and NF-κB/NLRP3 signaling. NRF2 activation restores redox balance and reduces ROS accumulation[22,47,48]; because excessive ROS promotes NF-κB activation and facilitates thioredoxin-interacting protein-dependent NLRP3 signaling, NRF2 activation may indirectly suppress inflammatory priming and cytokine production.[11,38,41,60] AS-IV may therefore interrupt a redox-inflammatory feed-forward loop that sustains HSC activation.[57,60] However, direct causal evidence demonstrating that AS-IV-induced NRF2 activation is required for NF-κB/NLRP3 suppression remains limited. Macrophage immunometabolism and hepatocyte protection may further reduce upstream inflammatory and injury-derived inputs to HSCs, although their causal contribution to fibrosis regression remains to be established.[23,55,56]

Translational relevance of preclinical models

AS-IV has been investigated in multiple preclinical models, including toxin-induced, cholestatic, and metabolic liver fibrosis models.[61–64] These studies provide complementary *in vivo* evidence supporting the biological relevance of the mechanisms described above. However, the translational value of current evidence remains heterogeneous because most studies rely on small-animal models, short treatment periods, and preventive or early-intervention designs rather than established fibrosis-regression models.[40,49] The quantitative efficacy and clinical relevance of available studies are summarized in Table 3.[23,50,54,59,61,63–65]

Chemically induced fibrosis models

Chemical injury models, particularly CCl_4- and dimethylnitrosamine (DMN)-induced fibrosis models, are the most extensively studied systems for evaluating AS-IV and provide consistent evidence supporting its antifibrotic effects.

In rats with DMN-induced fibrosis, Bai *et al*. treated animals with AS-IV (10 $mg \cdot kg^{-1} \cdot d^{-1}$) for 2 weeks after fibrosis induction. AS-IV reduced ALT ($P<0.01$), AST ($P<0.05$), and hepatic hydroxyproline from 427.9 to 281.8 μg/g wet liver ($P<0.01$), with lower α-SMA expression.[65] The quantified matrix-associated endpoint and concordant injury markers support an antifibrotic signal, but the short treatment period and limited mechanistic validation reduce confidence in durability and causal pathway assignment. Similarly, Dai *et al*. reported that AS-IV (14 $mg \cdot kg^{-1} \cdot d^{-1}$ for 4 weeks) in rats with CCl_4-induced fibrosis decreased ALT from 61.5 to 11.8 U/L and AST from 90.0 to 33.0 U/L, reduced collagen deposition from 27.9% to 8.8% (all $P<0.01$), and downregulated α-SMA and TGF-β1 expression.[54] This therapeutic timing and histological quantification make it one of the more clinically relevant studies, although small endpoint-specific sample sizes limit precision and direct extrapolation.

Additional toxin-based studies broaden the mechanistic picture but do not provide equivalent evidence of fibrosis regression. In CCl_4 plus ethanol-induced fibrosis, AS-IV (40 $mg \cdot kg^{-1} \cdot d^{-1}$) improved biochemical and molecular endpoints (all $P<0.05$), whereas the lower dose did not improve the fibrosis score, suggesting that enzyme or pathway changes may not track histological benefit.[59] In mice with CCl_4-induced fibrosis, AS-IV reduced hydroxyproline and inflammatory markers and altered macrophage polarization markers (all $P<0.01$), supporting an emerging forkhead box O1 (FoxO1)-related immunometabolic mechanism.[23] Both studies used preventive or concurrent-treatment designs; consequently, they are more informative for mechanism and dose selection than for predicting reversal of advanced human fibrosis.

The major advantage of toxin-induced models is their reproducibility and suitability for investigating HSC activation, inflammatory amplification, and ECM remodeling. However, these models poorly mimic the long-term and multifactorial progression of human fibrosis. Moreover, many studies initiate AS-IV treatment during early injury stages, which may overestimate therapeutic efficacy compared with that in patients with established fibrosis. Therefore, toxin models provide strong mechanistic evidence but limited direct prediction of clinical efficacy.

Cholestatic fibrosis models

Cholestatic models provide complementary evidence because biliary obstruction and bile acid accumulation are important drivers of human cholestatic liver diseases. In rats with bile duct ligation (BDL), Zhao *et al*. evaluated AS-IV monotherapy (10.8 mg/kg), ferulic acid (FA) monotherapy (4.8 mg/kg), and their combination for 28 days.[63] AS-IV monotherapy significantly improved histological fibrosis grading compared with untreated BDL rats ($P<0.05$), whereas the combination produced a greater antifibrotic effect ($P<0.05$) and was superior to either monotherapy ($P<0.05$).[63] The therapeutic timing and disease-specific model are strengths. However, the BDL model represents a specific obstructive cholestatic etiology and does not fully reproduce the heterogeneity of chronic human cholestatic liver diseases.

From a clinical perspective, the bile duct ligation model captures biliary obstruction but not the full heterogeneity of chronic cholestatic disorders or their standard-of-care treatment context.[66] The available study therefore provides preliminary evidence for an independent antifibrotic effect of AS-IV monotherapy while also demonstrating greater efficacy of the AS-IV/FA combination. Nevertheless, this evidence is derived from a single BDL model, and treatment was initiated after bile duct ligation rather than after independently confirmed chronic fibrosis had been established. Replication in

Table 3. Effects of AS-IV in liver fibrosis and fibrosis-relevant animal models and critical appraisal of the evidence

Model	Dosages	Quantitative findings	Mechanisms	Translational appraisal	Reference
Porcine serum-induced fibrosis in rats	2.0–4.0 $mg \cdot kg^{-1} \cdot d^{-1}$, 12 weeks	↓ Hyp: 2.88 → 1.62 mg/g; HA: 230.2 → 131.1 ng/mL; PCIII: 222.2 → 149.9 ng/mL (all $P<0.01$); ↓ HSC collagen synthesis and proliferation ($P<0.05$)	TGF-β1 reduction; inhibition of HSC activation	Dose-response validated; preventive design limits translation	Liu *et al*.[50]
DMN-induced fibrosis in rats	10 $mg \cdot kg^{-1} \cdot d^{-1}$, 2 weeks	↓ Hyp: 427.9 → 281.8 μg/g ($P<0.01$); ↓ α-SMA ($P<0.05$); ↓ fibrosis grade ($P<0.05$)	HSC activation inhibition	Quantitative efficacy shown; mechanistic evidence remains limited	Bai *et al*.[65]
CCl_4-induced fibrosis in rats	14 $mg \cdot kg^{-1} \cdot d^{-1}$, 4 weeks	↓ collagen area from 27.9% to 8.8% ($P<0.01$); ↓ α-SMA from 0.267 to 0.193 ($P<0.01$); ↓ TGF-β1 from 0.460 to 0.317 ($P<0.01$)	Regulation of EMT-associated markers and TGF-β1	Therapeutic design strengthens relevance; causality remains unproven	Dai *et al*.[54]
CCl_4 plus ethanol-induced fibrosis in rats	20–40 $mg \cdot kg^{-1} \cdot d^{-1}$, 6 weeks	↓ fibrosis score and HA ($P<0.05$); ↓ α-SMA and collagen I ($P<0.01$)	Inhibition of HSC activation via CXCL12/CXCR4 and TXNIP/NLRP3 pathways	Mixed-etiology model; histological fibrosis improved only at higher dose	Su *et al*.[59]
CCl_4-induced fibrosis in mice; LPS-stimulated macrophages	20–80 $mg \cdot kg^{-1} \cdot d^{-1}$, 6 weeks; 20–80 μM, 24 h	↓ Hyp, collagen deposition, α-SMA, and collagen I ($P<0.05$)	Possible DNMT3A/FoxO1-associated regulation of glycolysis-driven M1 macrophage polarization	Novel immunometabolic mechanism; causality requires confirmation	Hu *et al*.[23]
BDL-induced cholestatic fibrosis/cirrhosis in rats	AS-IV 10.8 mg/kg, FA 4.8 mg/kg, 28 days	Fibrosis stage shifted from F0–F4 0/1/2/5/0 to 1/4/4/0/0 with AS-IV ($P<0.05$); ↓ α-SMA, fibronectin, and collagen I/III ($P<0.05$); the combination produced greater histological improvement	AS-IV: NRF2/GSK-3β antioxidant activity; FA: TGF-β/Smad inhibition	Blinded histology assessment; etiology-specific model limits generalizability	Zhao *et al*.[63]
HFD-fed *Ldlr*$^{-/-}$ mice	10 $mg \cdot kg^{-1} \cdot d^{-1}$, 12 weeks	↓ hepatic TC and TG ($P<0.01$); ↓ serum ALT and AST ($P<0.01$); ↓ hepatic IL-1β, IL-6, and TNF-α mRNA ($P<0.01$)	Inhibition of MAPK/NF-κB signaling and inflammatory responses	Metabolically relevant model; no fibrosis-specific efficacy assessment.	Zhang *et al*.[64]
HFD-induced MAFLD in mice; FFA-induced steatosis in HepG2 cells	12.5–50 $mg \cdot kg^{-1} \cdot d^{-1}$, 8 weeks; 20–60 μM, 24 h	↓ hepatic TC/TG, ALT/AST, and lipid accumulation; ↓ MDA/4-HNE and iron accumulation; ↑ GSH-Px/SOD (all $P<0.05$)	Inhibition of ferroptosis through ↑ SLC7A11/GPX4 and ↓ ACSL4, with improved redox homeostasis	Dose-ranging validation; no fibrosis-specific assessment.	Chen *et al*.[61]

Quantitative values are presented as reported in the original publications. When exact group means were unavailable, only the reported direction of effect and statistical significance are shown. AS-IV, astragaloside IV; BDL, bile duct ligation; CCl_4, carbon tetrachloride; Col I/III, collagen types I/III; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor 4; DMN, dimethylnitrosamine; DNMT3A, DNA methyltransferase 3A; EMT, epithelial–mesenchymal transition; FA, ferulic acid; FFA, free fatty acid; FoxO1, forkhead box O1; GSK-3β, glycogen synthase kinase-3 beta; HA, hyaluronic acid; HFD, high-fat diet; HSC, hepatic stellate cell; Hyp, hydroxyproline; LPS, lipopolysaccharide; MAFLD, metabolic dysfunction-associated fatty liver disease; NLRP3, NOD-like receptor family pyrin domain containing 3; NRF2, nuclear factor erythroid 2-related factor 2; PCIII, procollagen type III; TC, total cholesterol; TG, triglyceride; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; TXNIP, thioredoxin-interacting protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; GPX4, glutathione peroxidase 4; GSH-Px, glutathione peroxidase; ACSL4, acyl-CoA synthetase long-chain family member 4; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; SOD, superoxide dismutase; SLC7A11, solute carrier family 7 member 11; ↓, decrease; ↑, increase.

therapeutic, exposure-characterized cholestatic models with appropriate active comparators is required before prioritizing a cholestatic indication.[67]

Metabolic models

Metabolic models are clinically important because MASLD/MASH is a major contemporary cause of liver fibrosis.[68] Current evidence suggests that AS-IV improves metabolic abnormalities, hepatic injury, oxidative stress, and inflammatory responses, although direct evidence of fibrosis regression remains limited.[61,64] In high-fat diet-fed low-density lipoprotein receptor knockout (*Ldlr*$^{-/-}$) mice, AS-IV (10 $mg \cdot kg^{-1} \cdot d^{-1}$ for 12 weeks) reduced serum lipids and transaminases, hepatic lipids, inflammatory cytokine transcripts, and MAPK/NF-κB activation (all $P<0.05$).[64] Chen *et al*. further reported that AS-IV (50 $mg \cdot kg^{-1} \cdot d^{-1}$) improved high-fat diet-induced metabolic dysfunction-associated fatty liver disease by modulating ferroptosis-related pathways, including increased

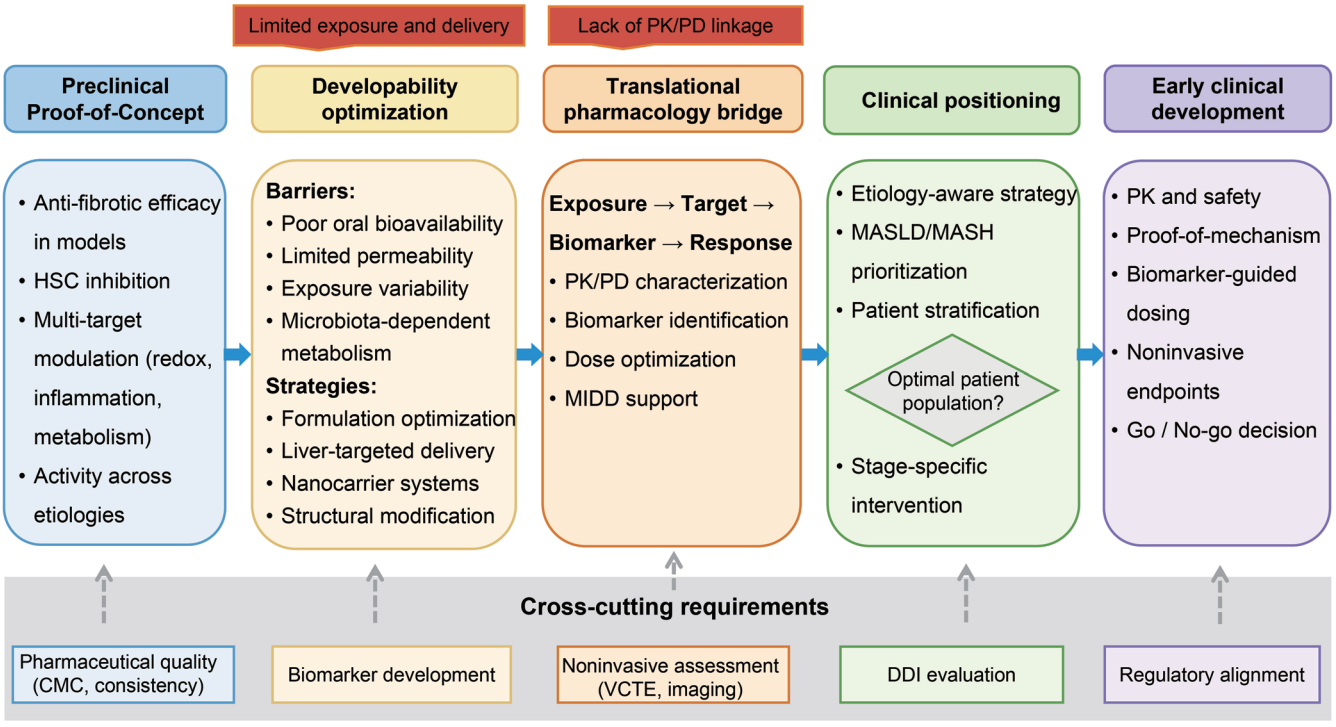


Fig. 3. Translational priorities for the development of AS-IV in liver fibrosis. Key steps include preclinical proof-of-concept, developability optimization, establishment of an exposure-target-response relationship, biomarker-guided clinical assessment, clinically relevant indication and patient selection, and early clinical development. Blue arrows indicate progression through the translational pathway, and gray dashed arrows indicate cross-cutting requirements supporting individual development stages. AS-IV, astragaloside IV; CMC, chemistry, manufacturing, and controls; DDI, drug-drug interaction; HSC, hepatic stellate cell; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MIDD, model-informed drug development; PK, pharmacokinetics; PK/PD, pharmacokinetic/pharmacodynamic; VCTE, vibration-controlled transient elastography.

SLC7A11 and GPX4 expression and decreased acyl-CoA synthetase long-chain family member 4 (ACSL4) expression (all $P<0.01$).[61]

The major advantage of metabolic models is their closer relationship with current clinical disease patterns, particularly MASLD/MASH-associated fibrosis. However, most studies focus on improvements in steatosis, oxidative stress, or inflammation rather than histologically confirmed regression of advanced fibrosis. Whether AS-IV can reverse established metabolic fibrosis remains unclear. Future studies should use fibrosis-enriched dietary models, establish disease before treatment, quantify collagen by validated histological and biochemical methods, and relate these outcomes to systemic and hepatic exposure.

Translational challenges and development priorities

Despite encouraging preclinical findings, AS-IV remains at an early stage of antifibrotic development.[1,69] Translation is primarily limited by the heterogeneity of preclinical evidence, poor oral exposure, undefined exposure-response relationships, and the absence of clinical efficacy data.[1,70,71] Future development should therefore focus on rigorous therapeutic validation, pharmacokinetic (PK)/pharmacodynamic (PD) integration, biomarker-guided assessment, and clinically realistic positioning.[71,72] The major translational bottlenecks and development priorities are summarized in Figure 3.

Indication selection and biomarker-guided clinical development

A major strength of the current evidence is the convergence of antifibrotic signals across different experimental systems, particularly reductions in HSC activation, collagen-associated endpoints, oxidative stress, and inflammatory signaling.[24,69] Several studies also provide quantitative evidence of biological activity. However, the magnitude and clinical relevance of these effects remain uncertain because studies differ substantially in species, fibrosis etiology, dose, treatment timing, endpoint selection, and statistical reporting. Importantly, many studies used small endpoint-specific sample sizes, preventive or concurrent-treatment designs, and incompletely reported randomization or blinding procedures. Several reports provide only threshold *P* values without confidence intervals or standardized effect estimates, limiting assessment of precision and between-study comparability.[3,40,62,69,70] These limitations do not negate the observed antifibrotic signals, but they reduce confidence in their reproducibility and make pooled quantitative interpretation inappropriate. Clinically, this means that the available evidence is insufficient to define an effective human dose, treatment duration, target population, or expected magnitude of fibrosis improvement.[3,71]

The current evidence also does not yet support selection of a specific clinical indication with confidence. MASLD/MASH with F2–F3 fibrosis may represent a pragmatic future target because of its disease burden, availability of noninvasive assessment tools, and regulatory precedent; however, current AS-IV metabolic studies have not demonstrated histological regression of established fibrosis.[13,70] Cholestatic fibrosis has preliminary supportive evidence from a BDL model, but this remains limited to a single etiology-specific study.[63] Therefore, indication selection should follow confirmation of

efficacy in therapeutic models with established fibrosis and clinically relevant drug exposure.

Early clinical development should prioritize proof-of-mechanism and exposure-biomarker relationships before attempting definitive histological efficacy trials. Noninvasive assessments such as vibration-controlled transient elastography (VCTE), the Enhanced Liver Fibrosis (ELF) score, procollagen III N-terminal propeptide (PRO-C3), and MRI-based assessments could be combined with selected fibrogenic and inflammatory biomarkers.[3,70] Concurrent measurement of AS-IV and relevant metabolites would further determine whether pharmacodynamic responses are exposure-dependent. Drug-drug interaction assessment will also be important, particularly in MASLD/MASH populations in whom polypharmacy is common.[71,72]

Exposure optimization and therapeutic positioning

Poor intestinal permeability and low oral bioavailability represent major pharmacological barriers to AS-IV development.[30,31,35,36] More importantly, most efficacy studies report administered doses without measuring plasma exposure, hepatic concentrations, or active metabolites, making it difficult to establish exposure-response relationships or determine whether observed effects are mediated by parent AS-IV, metabolites such as cycloastragenol, or indirect modulation of the hepatic microenvironment.[32] Future studies should therefore integrate plasma and hepatic pharmacokinetics, metabolite profiling, and fibrosis-relevant pharmacodynamic endpoints within the same experimental design. Measurements of phosphorylated Smad2/3, α-SMA, collagen content, hydroxyproline, and histological fibrosis burden could help define exposure-target-response relationships and support rational dose selection. Improved systemic exposure alone should not be considered sufficient evidence of improved efficacy without corresponding evidence of hepatic exposure, target engagement, and antifibrotic activity.

Structural modification, formulation optimization, and liver-targeted delivery are potential strategies to overcome these limitations. The water-soluble derivative LS-102 showed improved intestinal permeability and approximately twofold higher relative oral bioavailability than native AS-IV, providing proof of principle that AS-IV druggability can be improved.[37] Nevertheless, such approaches should ultimately be evaluated according to their effects on hepatic exposure and pharmacodynamic efficacy rather than plasma exposure alone. Given the absence of clinical antifibrotic efficacy data, AS-IV is currently more appropriately considered a potential disease-modifying adjunct than a first-line antifibrotic monotherapy.[1,70,71] Its multitarget effects on fibrogenic, inflammatory, oxidative, and metabolic pathways could complement more selective therapies, but combination strategies will require mechanistic justification, compatible pharmacokinetics, and adequate safety evaluation.[71]

Comparative positioning of AS-IV among antifibrotic candidates

Compared with representative natural products, including curcumin, silymarin, and notoginsenosides, AS-IV similarly provides multitarget modulation of oxidative, inflammatory, and fibrogenic pathways, while poor oral exposure and limited clinical validation remain common barriers.[18,73–75] Its relatively consistent effects on HSC activation and TGF-β/Smad signaling may provide closer mechanistic alignment with core fibrogenic processes, although direct head-to-head efficacy data are unavailable.[26,69] In contrast, resmetirom has a defined molecular target and phase III efficacy, whereas other targeted classes, such as farnesoid X receptor (FXR) agonists, have shown antifibrotic signals but raised safety or tolerability concerns.[13,76] Evidence for the safety of isolated AS-IV also remains limited because available human data are largely derived from multicomponent Astragali Radix-derived saponin preparations.[36] Accordingly, AS-IV is better positioned as a potential multitarget adjunct than as a direct competitor to approved or late-stage therapies. The main differences between AS-IV and representative antifibrotic candidates are summarized in Supplementary Table 1.

Strengths and limitations

A strength of this review is its integrated evaluation of AS-IV across pharmacological and pharmacokinetic characteristics, mechanistic evidence, preclinical fibrosis models, and translational considerations. Particular emphasis was placed on distinguishing direct antifibrotic evidence from indirect hepatoprotective, antioxidant, and anti-inflammatory effects and on evaluating the relative strength and translational relevance of different mechanistic findings. However, several limitations should be acknowledged. As a narrative review, the literature was not synthesized using a predefined systematic-review protocol or formal risk-of-bias assessment, and publication or selection bias cannot be excluded. In addition, substantial heterogeneity in experimental models, treatment regimens, outcome measures, and reporting methods precluded quantitative synthesis. Because the available evidence is predominantly preclinical and human data remain limited, some conclusions regarding clinical translation and therapeutic positioning necessarily remain provisional.

Conclusions

AS-IV has shown antifibrotic activity across preclinical models, with the strongest evidence supporting suppression of HSC activation and modulation of TGF-β-related fibrogenic signaling. Antioxidant, anti-inflammatory, immunometabolic, and hepatoprotective effects may further reduce upstream profibrotic stimuli. However, the evidence base remains heterogeneous, with limitations including small sample sizes, preventive or concurrent-treatment designs, limited human-cell validation, and frequent reliance on injury or metabolic endpoints rather than established fibrosis regression.

Future development should prioritize adequately powered therapeutic studies with prespecified fibrosis endpoints, transparent statistical reporting, human-cell validation, and integrated plasma/hepatic PK/PD assessment. AS-IV should therefore be viewed as a promising preclinical lead and potential adjunctive candidate, not as a clinically validated antifibrotic therapy.

Supporting information

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Conflict of interest

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Author contributions

Study concept and design (TL, YY); literature acquisition and evidence collection (TL, YY, XL); analysis and interpretation of data and evidence (TL, YY, XL); drafting of the original manuscript (TL); major scientific revision and restructuring of the manuscript (TL, YY); critical revision of the manuscript for important intellectual content (TL, YY, XL, XH); table revision and evidence integration (YY); study supervision (XH, XL). TL and YY contributed equally to this work and share first authorship. XL and XH serve as co-corresponding authors. All authors have made a significant contribution to this study and have approved the final manuscript.

References

[1] Nair DG, Weiskirchen R. Liver Fibrosis: Current Treatments, Bottlenecks, and Future Prospects for Translational Medicine. Sci 2026;8(1):9. doi:10.3390/sci8010009.

[2] Lindvig KP, Thorhauge KH, Hansen JK, Kjærgaard M, Hansen CD, Johansen S, *et al*. Development, validation, and prognostic evaluation of LiverPRO for the prediction of significant liver fibrosis in primary care: a prospective cohort study. Lancet Gastroenterol Hepatol 2025;10(1):55–67. doi:10.1016/S2468-1253(24)00274-7, PMID:39674225.

[3] Castera L, Rinella ME, Tsochatzis EA. Noninvasive Assessment of Liver Fibrosis. N Engl J Med 2025;393(17):1715–1729. doi:10.1056/NEJMra2403308, PMID:41160822.

[4] Ma X, Huang T, Chen X, Li Q, Liao M, Fu L, *et al*. Molecular mechanisms in liver repair and regeneration: from physiology to therapeutics. Signal Transduct Target Ther 2025;10(1):63. doi:10.1038/s41392-024-02104-8, PMID:39920130.

[5] Schwabe RF, Brenner DA. Hepatic stellate cells: balancing homeostasis, hepatoprotection and fibrogenesis in health and disease. Nat Rev Gastroenterol Hepatol 2025;22(7):481–499. doi:10.1038/s41575-025-01068-6, PMID:40404839.

[6] Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 2021;18(3):151–166. doi:10.1038/s41575-020-00372-7, PMID:33128017.

[7] Akkız H, Gieseler RK, Canbay A. Liver Fibrosis: From Basic Science towards Clinical Progress, Focusing on the Central Role of Hepatic Stellate Cells. Int J Mol Sci 2024;25(14):7873. doi:10.3390/ijms25147873, PMID:39063116.

[8] Pei Q, Yi Q, Tang L. Liver Fibrosis Resolution: From Molecular Mechanisms to Therapeutic Opportunities. Int J Mol Sci 2023;24(11):9671. doi:10.3390/ijms24119671, PMID:37298621.

[9] Zhu W, Cui Y, Qiu J, Zhang X, Gao Y, Shang Z, *et al*. Exploring the Therapeutic Potential of TGF-β Inhibitors for Liver Fibrosis: Targeting Multiple Signaling Pathways. J Clin Transl Hepatol 2025;13(7):588–598. doi:10.14218/JCTH.2025.00029, PMID:40937077.

[10] Shamsan E, Almezgagi M, Gamah M, Khan N, Qasem A, Chuanchuan L, *et al*. The role of PI3k/AKT signaling pathway in attenuating liver fibrosis: a comprehensive review. Front Med (Lausanne) 2024;11:1389329. doi:10.3389/fmed.2024.1389329, PMID:38590313.

[11] Sayaf K, Battistella S, Russo FP. NLRP3 Inflammasome in Acute and Chronic Liver Diseases. Int J Mol Sci 2024;25(8):4537. doi:10.3390/ijms25084537, PMID:38674122.

[12] Zhang Y, Ren L, Tian Y, Guo X, Wei F, Zhang Y. Signaling pathways that activate hepatic stellate cells during liver fibrosis. Front Med (Lausanne) 2024;11:1454980. doi:10.3389/fmed.2024.1454980, PMID:39359922.

[13] Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, *et al*. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med 2024;390(6):497–509. doi:10.1056/NEJMoa2309000, PMID:38324483.

[14] Sanyal Arun J, Newsome Philip N, Kliers I, Østergaard Laura H, Long Michelle T, Kjær Mette S, *et al*. Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis. N Engl J Med 2025;392(21):2089–2099. doi:10.1056/NEJMoa2413258.

[15] Bansal MB, Patton H, Morgan TR, Carr RM, Dranoff JA, Allen AM. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance. Hepatology (Baltimore, Md) 2026;83(5):1326–1340. doi:10.1097/hep.0000000000001608, PMID:41201884.

[16] Parola M, Pinzani M. Liver fibrosis in NAFLD/NASH: from pathophysiology towards diagnostic and therapeutic strategies. Mol Aspects Med 2024;95:101231. doi:10.1016/j.mam.2023.101231, PMID:38056058.

[17] Cerrito L, Galasso L, Iaccarino J, Pizzi A, Termite F, Esposto G, *et al*. Present and Future Perspectives in the Treatment of Liver Fibrosis. Pharmaceuticals (Basel) 2025;18(9):1321. doi:10.3390/ph18091321, PMID:41011192.

[18] Ma X, Jiang Y, Wen J, Zhao Y, Zeng J, Guo Y. A comprehensive review of natural products to fight liver fibrosis: Alkaloids, terpenoids, glycosides, coumarins and other compounds. Eur J Pharmacol 2020;888:173578. doi:10.1016/j.ejphar.2020.173578, PMID:32976828.

[19] Niu Q, Mou Y, Wang K, Dong H, Zeng Z, Li H. Natural medicines for treating liver fibrosis by modulating post-translational modifications. Front Pharmacol 2025;16:1660908. doi:10.3389/fphar.2025.1660908, PMID:41293253.

[20] Mungamuri SK, Chatterjee N, Ara D. Phytotherapy for liver fibrosis: Insights from the biology of hepatic stellate cells-A narrative review. Liver Int Commun 2025;6(1):e70015. doi:10.1002/lci2.70015.

[21] Liang Y, Chen B, Liang D, Quan X, Gu R, Meng Z, *et al*. Pharmacological Effects of Astragaloside IV: A Review. Molecules 2023;28(16):6118. doi:10.3390/molecules28166118, PMID:37630371.

[22] Li L, Huang W, Wang S, Sun K, Zhang W, Ding Y, *et al*. Astragaloside IV Attenuates Acetaminophen-Induced Liver Injuries in Mice by Activating the Nrf2 Signaling Pathway. Molecules 2018;23(8):2032. doi:10.3390/molecules23082032, PMID:30110942.

[23] Hu Y, Kuang M, Song H, Tan Y, Zhou F, Pei G, *et al*. Astragaloside IV prevents liver fibrosis by blocking glycolysis-mediated macrophage M1 polarization. Eur J Pharmacol 2025;995:177353. doi:10.1016/j.ejphar.2025.177353, PMID:39971227.

[24] Li X, Wang X, Han C, Wang X, Xing G, Zhou L, *et al*. Astragaloside IV suppresses collagen production of activated hepatic stellate cells via oxidative stress-mediated p38 MAPK pathway. Free Radic Biol Med 2013;60:168–176. doi:10.1016/j.freeradbiomed.2013.02.027, PMID:23459070.

[25] Wu M, Li K, Wu J, Zhang Q, Ma X, Dai W, *et al*. Astragaloside IV: A multipotent phytochemical for treating fibrotic diseases (Review). Int J Mol Med 2026;57(2):50. doi:10.3892/ijmm.2025.5721, PMID:41456499.

[26] Yuan X, Gong Z, Wang B, Guo X, Yang L, Li D, *et al*. Astragaloside Inhibits Hepatic Fibrosis by Modulation of TGF-β1/Smad Signaling Pathway. Evid Based Complement Alternat Med 2018;2018:3231647. doi:10.1155/2018/3231647, PMID:29853950.

[27] Zhang J, Wu C, Gao L, Du G, Qin X. Astragaloside IV derived from Astragalus membranaceus: A research review on the pharmacological effects. Adv Pharmacol 2020;87:89–112. doi:10.1016/bs.apha.2019.08.002, PMID:32089240.

[28] Takeuchi DM, Kishino S, Ozeki Y, Fukami H, Ogawa J. Analysis of astragaloside IV metabolism to cycloastragenol in human gut microorganism, bifidobacteria, and lactic acid bacteria. Biosci Biotechnol Biochem 2022;86(10):1467–1475. doi:10.1093/bbb/zbac130, PMID:35904311.

[29] Stępnik K, Jarząb A, Niedźwiadek R, Głowniak-Lipa A, Głowniak K, Kukula-Koch W. In Vivo Insights into the Role of Astragaloside IV in Preventing and Treating Civilization Diseases: A Comprehensive Review. Int J Mol Sci 2025;26(9):4250. doi:10.3390/ijms26094250, PMID:40362487.

[30] Gu Y, Wang G, Pan G, Fawcett JP, A J, Sun J. Transport and bioavailability studies of astragaloside IV, an active ingredient in Radix Astragali. Basic Clin Pharmacol Toxicol 2004;95(6):295–298. doi:10.1111/j.1742-7843.2004.t01-1-pto950508.x, PMID:15569275.

[31] Huang CR, Wang GJ, Wu XL, Li H, Xie HT, Lv H, *et al*. Absorption enhancement study of astragaloside IV based on its transport mechanism in caco-2 cells. Eur J Drug Metab Pharmacokinet 2006;31(1):5–10. doi:10.1007/BF03190635, PMID:16715776.

[32] Lei Y, Xie J, Xie Z, Zhao X, Huang J, Wang C. Comparative drug-drug interactions of berberine and astragaloside IV in normal and type 2 diabetes mellitus rats based on UPLC-QqQ-MS/MS. Acta Mater Med 2025;4:51–69. doi:10.15212/AMM-2024-0078.

[33] Du Y, Zhang Q, Chen GG, Wei P, Tu CY. Pharmacokinetics of Astragaloside IV in rats by liquid chromatography coupled with tandem mass spectrometry. Eur J Drug Metab Pharmacokinet 2005;30(4):269–273. doi:10.1007/BF03190631, PMID:16435572.

[34] Zhang Q, Zhu LL, Chen GG, Du Y. Pharmacokinetics of astragaloside iv in beagle dogs. Eur J Drug Metab Pharmacokinet 2007;32(2):75–79. doi:10.1007/BF03190995, PMID:17702194.

[35] Zhang WD, Zhang C, Liu RH, Li HL, Zhang JT, Mao C, *et al*. Preclinical pharmacokinetics and tissue distribution of a natural cardioprotective agent astragaloside IV in rats and dogs. Life Sci 2006;79(8):808–815. doi:10.1016/j.lfs.2006.02.032, PMID:16564551.

[36] Xu M, Yin J, Xie L, Zhang J, Zou C, Zou J, *et al*. Pharmacokinetics and tolerance of toal astragalosides after intravenous infusion of astragalosides injection in healthy Chinese volunteers. Phytomedicine 2013;20(12):1105–1111. doi:10.1016/j.phymed.2013.05.004, PMID:23838148.

[37] Qing LS, Chen TB, Sun WX, Chen L, Luo P, Zhang ZF, *et al*. Pharmacokinetics Comparison, Intestinal Absorption and Acute Toxicity Assessment of a Novel Water-Soluble Astragaloside IV Derivative (Astragalosidic Acid, LS-102). Eur J Drug Metab Pharmacokinet 2019;44(2):251–259. doi:10.1007/s13318-018-0515-5, PMID:30315409.

[38] Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Cells 2020;9(4):E875. doi:10.3390/cells9040875, PMID:32260126.

[39] Caligiuri A, Gentilini A, Pastore M, Gitto S, Marra F. Cellular and Molecular Mechanisms Underlying Liver Fibrosis Regression. Cells 2021;10(10):2759. doi:10.3390/cells10102759, PMID:34685739.

[40] Sultana M, Islam MA, Khairnar R, Kumar S. A guide to pathophysiology, signaling pathways, and preclinical models of liver fibrosis. Mol Cell Endocrinol 2025;598:112448. doi:10.1016/j.mce.2024.112448, PMID:39755140.

[41] Ramos-Tovar E, Muriel P. Molecular Mechanisms That Link Oxidative Stress, Inflammation, and Fibrosis in the Liver. Antioxidants (Basel) 2020;9(12):1279. doi:10.3390/antiox9121279, PMID:33333846.

[42] Lan R, Lin J, Chen S, Lu Z, Gong Y, Tan S, *et al*. Communication initiated by hepatocytes: The driver of HSC activation and liver fibrosis. Hepatol Commun 2025;9(8):e0753. doi:10.1097/HC9.0000000000000753, PMID:40658809.

[43] Kamm DR, McCommis KS. Hepatic stellate cells in physiology and pathology. J Physiol 2022;600(8):1825–1837. doi:10.1113/JP281061, PMID:35307840.

[44] Peng M, Fang F, Wang B. Nanoparticle technologies for liver targeting and their applications in liver diseases. Front Bioeng Biotechnol 2025;13:1661872. doi:10.3389/fbioe.2025.1661872, PMID:41209301.

[45] Wang W, Gao Y, Chen Y, Cheng M, Sang Y, Wei L, *et al*. TGF-β inhibitors: the future for prevention and treatment of liver fibrosis? Front Immunol 2025;16:1583616. doi:10.3389/fimmu.2025.1583616, PMID:40655154.
[46] Chen F, Lyu L, Xing C, Chen Y, Hu S, Wang M, *et al*. The pivotal role of TGF-β/Smad pathway in fibrosis pathogenesis and treatment. Front Oncol 2025;15:1649179. doi:10.3389/fonc.2025.1649179, PMID:40969268.
[47] Li N, Hao L, Li S, Deng J, Yu F, Zhang J, *et al*. The NRF-2/HO-1 Signaling Pathway: A Promising Therapeutic Target for Metabolic Dysfunction-Associated Steatotic Liver Disease. J Inflamm Res 2024;17:8061–8083. doi:10.2147/JIR.S490418, PMID:39512865.
[48] Zhou J, Zheng Q, Chen Z. The Nrf2 Pathway in Liver Diseases. Front Cell Dev Biol 2022;10:826204. doi:10.3389/fcell.2022.826204, PMID:35223849.
[49] Tilg H, Petta S, Stefan N, Targher G. Metabolic Dysfunction-Associated Steatotic Liver Disease in Adults: A Review. JAMA 2026;335(2):163–174. doi:10.1001/jama.2025.19615, PMID:41212550.
[50] Liu H, Wei W, Sun WY, Li X. Protective effects of astragaloside IV on porcine-serum-induced hepatic fibrosis in rats and in vitro effects on hepatic stellate cells. J Ethnopharmacol 2009;122(3):502–508. doi:10.1016/j.jep.2009.01.035, PMID:19429320.
[51] Zhang C, Li L, Hou S, Shi Z, Xu W, Wang Q, *et al*. Astragaloside IV inhibits hepatocellular carcinoma by continually suppressing the development of fibrosis and regulating pSmad3C/3L and Nrf2/HO-1 pathways. J Ethnopharmacol 2021;279:114350. doi:10.1016/j.jep.2021.114350, PMID:34157326.
[52] Chen Z, Yao L, Liu Y, Pan Z, Peng S, Wan G, *et al*. Astragaloside IV regulates NF-κB-mediated cellular senescence and apoptosis of hepatic stellate cells to suppress PDGF-BB-induced activation. Exp Ther Med 2019;18(5):3741–3750. doi:10.3892/etm.2019.8047, PMID:31641375.
[53] Wang J, Song RP, Sun D. Effect of Astragalus Saponin on Oxidative Damage in Rats with Hepatic Stellate Cells. Med Pharm J Chin PLA 2018;30(09):1–4.
[54] Dai HZ, An ZX, Huang D, Tang DX, He YL. Study on Mechanism of Improvement Effects of Astragaloside IV on Hepatic Fibrosis Model Rats. Chin J Mod Appl Pharm 2022;39(10):1268–1274.
[55] Liang XY, Hong FF, Yang SL. Astragaloside IV Alleviates Liver Inflammation, Oxidative Stress and Apoptosis to Protect Against Experimental Non-Alcoholic Fatty Liver Disease. Diabetes Metab Syndr Obes 2021;14:1871–1883. doi:10.2147/DMSO.S304817, PMID:33953586.
[56] Xie D, Zhou P, Liu L, Jiang W, Xie H, Zhang L, *et al*. Protective Effect of Astragaloside IV on Hepatic Injury Induced by Iron Overload. Biomed Res Int 2019;2019:3103946. doi:10.1155/2019/3103946, PMID:31428632.
[57] Sun Y, Ma Y, Sun F, Feng W, Ye H, Tian T, *et al*. Astragaloside IV attenuates lipopolysaccharide induced liver injury by modulating Nrf2-mediated oxidative stress and NLRP3-mediated inflammation. Heliyon 2023;9(4):e15436. doi:10.1016/j.heliyon.2023.e15436, PMID:37113780.
[58] Zhu Y, Chai Y, Xiao G, Liu Y, Xie X, Xiao W, *et al*. Astragalus and its formulas as a therapeutic option for fibrotic diseases: Pharmacology and mechanisms. Front Pharmacol 2022;13:1040350. doi:10.3389/fphar.2022.1040350, PMID:36408254.
[59] Su Y, Song HF, Wang X, Liu J, Xiao P, Xu XY, *et al*. Astragaloside IV inhibits liver fibrosis by acting on CXCL12/CXCR4 signal axis and TXNIP/NLRP3 inflammasome pathway. Chin Tradit Herb Drugs 2023;54(08):2453–2461.
[60] Sun M, Zhang Y, Guo A, Xia Z, Peng L. Progress in the Correlation Between Inflammasome NLRP3 and Liver Fibrosis. J Clin Transl Hepatol 2024;12(2):191–200. doi:10.14218/JCTH.2023.00231, PMID:38343611.
[61] Chen S, Xu H, Zhang Z, Li X, Tang X, Ying D. Astragaloside IV alleviates metabolic associated fatty liver disease by regulating ferroptosis via the SLC7A11/GPX4 pathway. Chin J Anal Chem 2026;54(2):100625. doi:10.1016/j.cjac.2025.100625.
[62] Schönke M, Rensen PCN. Mouse Models for the Study of Liver Fibrosis Regression In Vivo and Ex Vivo. J Clin Transl Hepatol 2024;12(11):930–938. doi:10.14218/JCTH.2024.00212, PMID:39544245.
[63] Zhao XM, Zhang J, Liang YN, Niu YC. Astragaloside IV Synergizes with Ferulic Acid to Alleviate Hepatic Fibrosis in Bile Duct-Ligated Cirrhotic Rats. Dig Dis Sci 2020;65(10):2925–2936. doi:10.1007/s10620-019-06017-3, PMID:31900718.
[64] Zhang Y, Du M, Wang J, Liu P. Astragaloside IV Relieves Atherosclerosis and Hepatic Steatosis via MAPK/NF-κB Signaling Pathway in LDLR(-/-) Mice. Front Pharmacol 2022;13:828161. doi:10.3389/fphar.2022.828161, PMID:35264962.
[65] Bai X, Lu L, Liu Z, Bian Y. Effects of astragaloside IV on dimethylnitrosamine-induced hepatic fibrosis in rats. J Hunan Univ Chin Med 2020;40(01):22–27.
[66] Feng S, Xie X, Li J, Xu X, Chen C, Zou G, *et al*. Bile acids induce liver fibrosis through the NLRP3 inflammasome pathway and the mechanism of FXR inhibition of NLRP3 activation. Hepatol Int 2024;18(3):1040–1052. doi:10.1007/s12072-023-10610-0, PMID:38172440.
[67] Tang G, Nierath WF, Leitner E, Xie W, Revskij D, Seume N, *et al*. Comparing animal well-being between bile duct ligation models. PLoS One 2024;19(7):e0303786. doi:10.1371/journal.pone.0303786, PMID:38950046.
[68] Fu Y, Hua Y, Alam N, Liu E. Progress in the Study of Animal Models of Metabolic Dysfunction-Associated Steatotic Liver Disease. Nutrients 2024;16(18):3120. doi:10.3390/nu16183120, PMID:39339720.
[69] Chen C, Bu X, Deng L, Xia J, Wang X, Chen L, *et al*. Astragaloside IV as a promising therapeutic agent for liver diseases: current landscape and future perspectives. Front Pharmacol 2025;16:1574154. doi:10.3389/fphar.2025.1574154, PMID:40337517.
[70] Jahagirdar V, Rama K, Cabrera D, Idalsoaga F, Díaz LA, Arrese M, *et al*. Implications of liver fibrosis in clinical trials. Ann Hepatol 2025;30(2):102112. doi:10.1016/j.aohep.2025.102112, PMID:40930219.
[71] Zeng X, Huang D, Zhu Z, Cai Q, Yang Y, Lu H, *et al*. Mechanism-guided drug development and treatment for liver fibrosis: a clinical perspective. Front Pharmacol 2025;16:1574385. doi:10.3389/fphar.2025.1574385, PMID:40492139.
[72] Tacke F, Weiskirchen R. Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)-related liver fibrosis: mechanisms, treatment and prevention. Ann Transl Med 2021;9(8):729. doi:10.21037/atm-20-4354, PMID:33987427.
[73] Farzaei MH, Zobeiri M, Parvizi F, El-Senduny FF, Marmouzi I, Coy-Barrera E, *et al*. Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. Nutrients 2018;10(7):855. doi:10.3390/nu10070855, PMID:29966389.
[74] Chen SR, Chen XP, Lu JJ, Wang Y, Wang YT. Potent natural products and herbal medicines for treating liver fibrosis. Chin Med 2015;10:7. doi:10.1186/s13020-015-0036-y, PMID:25897319.
[75] Abolfazli S, Butler AE, Jamialahmadi T, Sahebkar A. A Golden Shield: The Protective Role of Curcumin against Liver Fibrosis. Curr Med Chem 2025;32(10):1987–2004. doi:10.2174/0929867331666230821095329, PMID:37605399.
[76] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, *et al*. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385(9972):956–965. doi:10.1016/S0140-6736(14)61933-4, PMID:25468160.