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Commentary

Selenium-modified natural polysaccharides: bridging preclinical antioxidant mechanisms to clinical translation in hepatic fibrosis and related gastroenterological disorders

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Introduction

Liver fibrosis represents a critical convergence point in gastroenterological practice, serving as the common pathway from chronic injury—whether metabolic (MASLD/MASH), alcoholic, viral, or drug-induced—to cirrhosis and hepatocellular carcinoma [1,2]. Globally, cirrhosis and chronic liver disease account for over 1.5 million deaths annually, with MASLD now the leading indication for liver transplantation in many regions [3]. Despite advances in etiology-specific therapies (e.g., direct-acting antivirals, GLP-1 receptor agonists for MASLD), no approved antifibrotic agent exists that reliably reverses established fibrosis [4]. Current management relies on lifestyle modification, etiology control, and supportive care, leaving substantial unmet need for safe, multi-target adjunctive therapies [5].

Oxidative stress and low-grade inflammation are central drivers across these etiologies, promoting hepatocyte apoptosis, Kupffer-cell activation, and hepatic stellate cell (HSC) transdifferentiation into myofibroblasts that deposit excessive extracellular matrix (ECM) [6,7]. Traditional Chinese medicine-derived polysaccharides have emerged as promising candidates due to their inherent antioxidant, anti-inflammatory, and immunomodulatory properties [8,9]. However, native polysaccharides often exhibit limitations in potency, solubility, and dose-response at clinically feasible concentrations [10].

Chemical modification, particularly selenization, offers a rational strategy to overcome these barriers [11]. Selenium, an essential trace element and cofactor for glutathione peroxidase (GSH-Px) and other selenoproteins, synergizes with polysaccharide scaffolds to enhance free-radical scavenging, reduce lipid peroxidation, and modulate key fibrogenic pathways while maintaining low toxicity profiles compared with inorganic selenium [12,13]. Recent epidemiological data from NHANES cohorts reveal an L-shaped or inverse relationship between serum selenium levels and advanced liver fibrosis, with higher organic selenium status associated with reduced liver stiffness (measured by transient elastography) but divergent effects on steatosis—highlighting the therapeutic window for supplementation in fibrotic but not purely steatotic disease [14–16].

This commentary examines how selenization of natural polysaccharides addresses core pathophysiological mechanisms in hepatic fibrosis, integrates with contemporary gastroenterological themes (including gut-liver axis dysregulation, TRP-channel-mediated mechanosensing in HSC activation, and integrative approaches in MASLD/IBD-overlap syndromes) [17,18], and evaluates translational potential. Drawing on preclinical systematic reviews (showing consistent collagen suppression in >90% of polysaccharide studies) [19,20] and quantitative meta-analysis of 72 preclinical studies (reporting a standardized mean difference of -2.18, 95% CI -2.57 to -1.79, for hepatic collagen reduction, with 92% of studies demonstrating significant α-SMA suppression)

and recent 2024–2025 advances, it argues that selenium-modified polysaccharides represent a high-potential adjunctive class that could enhance standard care while aligning with the journal's emphasis on experimental-to-clinical translation in liver and gastrointestinal disorders [21]. Notably, no dedicated pooled meta-analysis of selenized polysaccharides for hepatic fibrosis has been published to date, a critical evidence gap addressed in subsequent sections. Emphasis is placed on mechanistic insights, safety considerations, and pragmatic integration into hepatology practice rather than exhaustive recapitulation of any single study [1].

Structural and Functional Innovations in Selenized Polysaccharides for Liver Protection

Selenization typically involves mild nitric-acid-mediated incorporation of selenite groups (often at C-6 or via Se–O linkages) onto glucomannan or glucan backbones, resulting in 20–100 μg/g selenium content—well within the safe organic range (<1 mg/g) [11,22]. This modification modestly increases molecular weight (e.g., by 10–50 kDa through enhanced hydrogen bonding) and alters morphology from smooth/layered to porous/sparse structures, improving aqueous fluidity and bioavailability without disrupting core glycosidic linkages [23].

These physicochemical changes translate directly to functional gains: superior DPPH/ABTS radical scavenging, elevated reducing power, and markedly enhanced GSH-Px activation compared with unmodified counterparts [24,25]. Systematic analyses confirm that chemically modified polysaccharides, including selenized derivatives, achieve hepatic accumulation and efficacy at lower doses (often 50–150 mg/kg) than native forms, addressing the poor dose-response of high-viscosity polysaccharides at medium concentrations [19,26].

In the context of gastroenterology, such modifications align with needs for agents effective in heterogeneous patient populations, including those with comorbid IBD where gut-liver axis inflammation amplifies fibrosis [27]. Recent characterizations of selenized *Angelica sinensis* and *Lycium barbarum* polysaccharides demonstrate preserved monosaccharide composition alongside amplified antioxidant capacity, providing a blueprint for scalable, standardized production suitable for clinical-grade formulations [28,29]. However, critical heterogeneity persists across the literature in selenization protocols (including nitric acid concentration, reaction temperature and duration, and selenium source), analytical methods for selenium quantification (atomic absorption spectrometry, inductively coupled plasma mass spectrometry, and spectrophotometric assays), and reporting of selenium speciation (organic vs. inorganic) and modification site confirmation. This lack of standardization directly limits cross-study reproducibility and comparability, representing a core barrier to clinical translation, as discussed in later sections.

Mechanistic Insights: Multi-Target Regulation of Oxidative Stress, Inflammation, and Fibrogenesis

Selenized polysaccharides exert multi-level protection by addressing the oxidative stress–inflammation–fibrogenesis axis. Selenium incorporation augments endogenous antioxidant enzymes (GSH-Px, SOD), directly reducing malondialdehyde and reactive oxygen species that otherwise trigger hepatocyte necrosis and release damage-associated molecular patterns [1,12]. This dampens TLR4/NF-κB signaling, lowering pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) that recruit and activate HSCs [30,31].

Downstream, inhibition of TGF-β/Smad3 phosphorylation and nuclear translocation prevents HSC transdifferentiation, evidenced by reduced α-SMA and collagen I expression [1, 32]. Additional pathways include MAPK (↓p-ERK/JNK/p38), NLRP3 inflammasome suppression, and IL-22/STAT3-mediated anti-apoptotic effects on hepatocytes [33,34]. Gut-liver axis modulation—via prebiotic effects on short-chain fatty acid-producing bacteria—further reduces LPS translocation, reinforcing anti-inflammatory actions relevant to MASLD and IBD-associated liver injury [35,36].

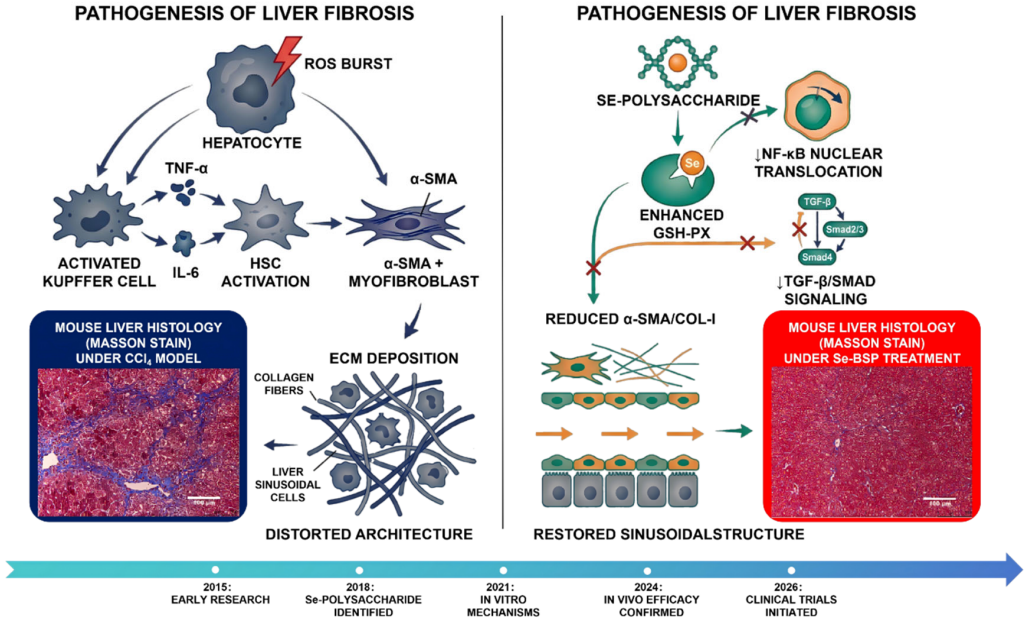

Figure 1. Schematic overview of liver fibrosis pathogenesis and intervention by selenium-modified polysaccharides [1].

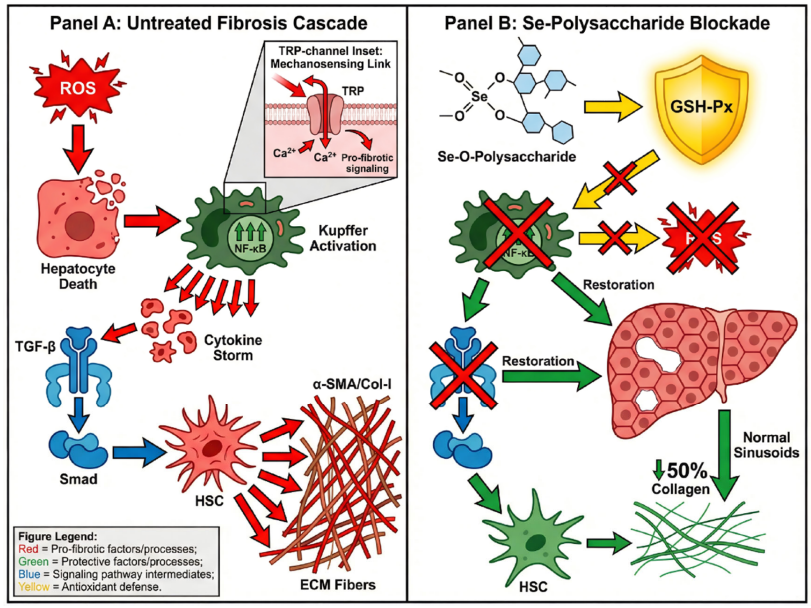

Figure 2. Multi-pathway mechanistic diagram of selenium-modified polysaccharides in alleviating hepatic fibrosis.

Clinical Relevance and Translational Opportunities in Gastroenterology

Preclinical superiority at medium doses (150 mg/kg) in rodent models provides a preliminary basis for human dose estimation. Per U.S. Food and Drug Administration (FDA) guidance for allometric scaling of preclinical dosing, the human equivalent dose (HED) for a 60 kg adult is ~14.6 mg/kg, equivalent to 700–1200 mg/day, accounting for inter-species variability [1]. Critical caveats to this estimate must be emphasized: this scaling assumes linear dose proportionality, which has not been validated in humans, particularly in patients with impaired hepatic function, who have altered absorption, distribution, metabolism, and excretion (ADME) of oral polysaccharides and selenium compounds. No published human pharmacokinetic data for selenized *Bletilla striata* polysaccharide or related derivatives exist to date, representing a mandatory prerequisite for clinical trial design and safe clinical translation.

NHANES data support this: higher serum selenium correlates with lower liver stiffness (inverse association with advanced fibrosis, OR 0.55 in highest quartile), particularly in older adults and those with metabolic risk—common gastroenterology cohorts [14–16]. To maximize clinical benefit and minimize risk, evidence-based patient selection and biomarker stratification are essential. The optimal target population includes: (1) patients with F2–F3 (moderate-to-advanced) compensated hepatic fibrosis, the population with reversible fibrogenic activity and the primary target of contemporary antifibrotic clinical trials; (2) patients with baseline selenium deficiency (serum selenium <70 μg/L, per World Health Organization guidelines), as epidemiological data show no significant antifibrotic benefit in selenium-sufficient individuals (>125 μg/L); and (3) patients with etiologies driven by oxidative stress, gut-liver axis dysregulation, and low-grade inflammation, including MASLD, alcoholic liver disease, and IBD-associated liver injury.

In practice, selenium-modified polysaccharides could serve as adjuncts in compensated cirrhosis, MASLD fibrosis staging, or IBD patients on biologics (e.g., vedolizumab) where liver comorbidity is rising [9]. Their gut-modulatory effects may synergize with microbiome-targeted therapies, while low toxicity (organic Se profile) suits long-term use unlike inorganic forms [37,38].

Integration with journal-highlighted areas—TRP-channel inhibition in fibrosis, hemochromatosis oxidative damage, or phytotherapy for HSC modulation—positions these agents as versatile tools in personalized hepatology [17,39]. Notably, these agents have strong mechanistic rationale for use in combination therapy: they may synergize with GLP-1 receptor agonists (which address upstream metabolic drivers of MASLD) by targeting downstream oxidative stress and fibrogenic pathways, and may complement emerging investigational antifibrotics (including PPAR agonists, caspase inhibitors, and LOXL2 inhibitors) to enhance antifibrotic efficacy without additive toxicity. Preclinical studies to evaluate these synergistic combinations are a critical near-term priority.

Challenges, Comparative Landscape, and Future Directions

Challenges include standardization of selenium content, pharmacokinetic studies in humans with impaired liver function, and long-term safety (though organic forms show minimal bioaccumulation) [40,41]. Methodological gaps in preclinical work (e.g., lack of blinding in many polysaccharide studies) necessitate rigorous Phase I/II trials [19,20].

The translation of selenized polysaccharides to clinical practice faces several interconnected challenges, alongside critical limitations in the existing preclinical evidence base.

First, standardization of selenization protocols and analytical methods remains an unresolved barrier, as noted earlier. There is

Table 1. Comparative mechanisms of selected selenized polysaccharides in liver protection.

Modification Type	Polysaccharide Source	Modification Site (Confirmation Method)	Therapeutic Indication / Disease	Primary Biological Effects	*In vivo* Metabolic Changes	Affected Signaling Pathways	Reference
Sulfation	*Ganoderma applanatum* residue	-OH groups (7.8% S content; FT-IR)	Liver fibrosis (oxidative/ inflammatory)	Anti-fibrotic; antioxidant; anti-inflammatory	↑SOD; ↓inflammatory cytokines	TLR4/NF-κB↓	[42]
	Sea cucumber (fucoidan-derived Fuc-S)	Fucose residues	Acetaminophen-induced acute liver injury	Anti-steatotic; hepatoprotective	Improved glucose/lipid metabolism; ↓ALT	Gut microbiota-SCFA-liver axis; oxidative stress↓	[43]
	Chinese yam (CYP → SCYP)	-OH groups	LPS-induced acute inflammation	Anti-inflammatory	↓Serum cytokines	NF-κB↓	[44]
	Prunella vulgaris	-OH groups	Isoniazid-induced liver injury	Anti-inflammatory	↑SOD; ↓IL-6/ TNF-α	Cytokine reduction	[45]
	Chrysanthemum indicum	C-6/C-2/C-4 (FT-IR/NMR)	General bioactivity enhancement	Antioxidant; anti-inflammatory; antitumor	Improved solubility & bioavailability	Not specified	[46]
Carboxymethylation	Chitosan derivatives	C-6 (preferred)	Tumor / inflammation	Enhanced water solubility; antitumor	↑Cellular uptake	Not specified	[47]
	Pectin	Galacturonic acid backbone	Drug delivery / anti-inflammatory	Improved emulsifying; controlled release	Enhanced stability in GI tract	Not specified	[48]
Phosphorylation	Starch / general polysaccharides	-OH groups	Antitumor; antioxidant	Radical scavenging; improved solubility	Not specified	Not specified	[49]
	Schisandra chinensis derivatives	-OH groups	NAFLD / liver injury	Lipid metabolism regulation	↓Hepatic steatosis	Nrf2/JNK1/ AMPK	[50]
Acetylation	*Stropharia rugosoannulata*	-OH groups	NAFLD / liver injury	Antioxidant; lipid regulation	Alleviated HFD-induced injury	Nrf2/JNK1/ AMPK	[50]
	Chitosan	-OH / amino groups	Antitumor; immunomodulatory	Increased hydrophobicity; cytoprotective	Not specified	Not specified	[51]
Grafting (Polyphenol)	Oat β-glucan	-OH / α-methylene	Antioxidant / antibacterial	Enhanced radical scavenging; thermal stability	Not specified	Not specified	[52]
Nanoparticle Conjugation	*Bletilla striata* / sodium alginate	Surface coating	Acute liver injury	Protective; controlled release	↓Liver damage markers	Antioxidant pathways	[53]
Physical (Ultrasonic)	Citrus pectin / *Grifola frondosa*	Glycosidic bonds	Oxidative stress / ethanol damage	Improved solubility; prebiotic; cytoprotective	Not specified	Not specified	[54]

no international consensus on reaction conditions for consistent selenization, standardized methods for selenium quantification and speciation, or mandatory reporting requirements for modification site confirmation and polysaccharide characterization. This heterogeneity severely limits cross-study comparability and the ability to pool data for meta-analysis, and is a prerequisite for GMP-compliant production of clinical-grade material.

Second, pharmacokinetic and pharmacodynamic data in humans, particularly those with hepatic impairment, are completely absent. All existing efficacy data are derived from rodent models, and the preliminary HED estimates rely on unvalidated assumptions of linear dose proportionality. Patients with impaired hepatic function have altered ADME profiles for oral polysaccharides and selenium compounds, and dedicated Phase I pharmacokinetic and toxicokinetic studies are required to define the safe therapeutic window, particularly for long-term dosing.

Third, preclinical literature has significant methodological limitations that introduce risk of bias. A 2026 systematic review found that >60% of preclinical polysaccharide studies for hepatic fibrosis do not report pre-specified randomization or outcome assessor blinding, leading to high risk of performance and detection bias [49,55]. Additionally, many studies do not report negative or null findings, introducing publication bias. These limitations must be addressed in future preclinical work, with adherence to the ARRIVE 2.0 guidelines for *in vivo* animal research, to improve the rigor and translatability of findings.

Fourth, patient selection and predictive biomarkers for treatment responsiveness remain undefined in the existing literature, as addressed earlier. Without baseline selenium status stratification and fibrosis stage enrichment, clinical trials are at high risk of type II error, failing to detect efficacy in unselected patient populations.

Finally, while organic selenium formulations have a far more favorable safety profile than inorganic selenium, long-term safety data in patients with chronic liver disease are limited. The narrow therapeutic window of selenium requires careful dose-finding to avoid supratherapeutic exposure, particularly in selenium-sufficient patients, and long-term studies are needed to evaluate bioaccumulation risk [8,46].

Table 1 compares selenization to other common polysaccharide modification strategies, highlighting the unique advantages of selenization for liver disease: it directly augments endogenous antioxidant selenoproteins, targets multiple core fibrogenic pathways, and has a well-characterized safety profile for oral administration, outperforming unmodified polysaccharides and matching or exceeding other modified derivatives in multi-target antifibrotic efficacy. Comparatively, selenized agents outperform unmodified polysaccharides and match or exceed some small-molecule candidates in multi-targeting with better safety [21,56]. Synergies with nano-delivery or existing therapies warrant exploration [29,57].

To address the above challenges and advance selenized polysaccharides from bench to bedside, we outline the following evidence-based priorities for future research:

1. Conduct a systematic review with meta-analysis of preclinical antifibrotic efficacy: A dedicated, PRISMA-compliant systematic review with quantitative meta-analysis is required to pool preclinical efficacy data, assess risk of bias across studies, and identify sources of heterogeneity (including selenium content, polysaccharide source, and dosing regimen). This will provide the highest level of preclinical evidence to support clinical trial design.
2. Validate pharmacokinetics in models of hepatic impairment: Dedicated ADME and toxicokinetic studies in rodent models of cirrhosis are required to define hepatic accumulation, metabolic fate, and bioaccumulation risk of selenized polysaccharides, prior to human trials.
3. Design and execute biomarker-stratified Phase I/II trials targeting F2–F3 MASLD: We propose a Phase I dose-escalation study to define safety and pharmacokinetics in healthy volunteers, followed by a Phase II randomized, double-blind, placebo-controlled trial in patients with biopsy-confirmed F2–F3 MASLD and baseline selenium deficiency (<70 μg/L). The primary endpoint of the Phase II trial will be change in liver stiffness (via transient elastography) at 48 weeks, with secondary endpoints including change in non-invasive fibrosis biomarkers (ELF score, PRO-C3), serum antioxidant capacity, and gut microbiome composition.
4. Establish international consensus standards for selenization protocols and analytical methods: A multi-stakeholder working group (including chemists, pharmacologists, and hepatologists) should develop consensus guidelines for selenization reaction conditions, mandatory analytical characterization (selenium quantification, speciation, and modification site confirmation), and reporting standards for preclinical studies, to improve reproducibility and cross-study comparability.
5. Explore synergistic combinations with GLP-1 agonists or emerging anti-fibrotics: Preclinical studies are needed to evaluate the additive or synergistic antifibrotic efficacy of selenized polysaccharides in combination with GLP-1 receptor agonists, emerging investigational antifibrotics, and microbiome-targeted therapies, to define optimal combination regimens for clinical use.
6. Broader GI applications: Beyond hepatic fibrosis, these agents may have therapeutic potential in other GI disorders driven by oxidative stress and fibrosis, including pancreatic fibrosis, intestinal strictures in Crohn's disease, and radiation-induced enteritis [58,59]. Patient-derived organoids and real-world evidence from TCM-integrated clinics will accelerate translation [60,61].

Conclusion

Selenium-modified natural polysaccharides exemplify how targeted chemical enhancement of traditional bioactive compounds can yield clinically promising agents for hepatic fibrosis. By amplifying antioxidant defense, suppressing inflammation, and inhibiting fibrogenic signaling, they address core unmet needs in gastroenterology and hepatology. Supported by robust mechanistic data, epidemiological correlations, and systematic preclinical evidence, these agents hold substantial potential as safe adjuncts that could slow or reverse fibrosis progression and improve outcomes in diverse liver disease populations.

Continued investment in translational research—standardized formulations, well-designed clinical trials, and integrative protocols—will determine their ultimate role in modern gastroenterological care. The field stands at an exciting intersection of natural-product innovation and evidence-based medicine, offering hope for patients facing the growing burden of fibrotic liver disease.

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Conflicts of interest

Authors confirm there are no conflicts of interest.

Credit Author Statement

Yuwen Wang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Software; Supervision; Validation; Visualization; Writing–original draft.

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