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Review Paper

Small Molecules in Liver Cell Growth and Regeneration: A Review

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ABSTRACT

Background: Liver diseases are a major global cause of mortality and are in urgent need of innovative therapeutic strategies. This review explores the role of small molecules as key modulators in liver tissue regeneration.

Methods: A comprehensive review of the literature was conducted to evaluate the regenerative potential of small molecules and their underlying mechanisms in liver tissue engineering and regenerative medicine. Particular attention was given to molecules involved in regulating key signaling pathways associated with hepatocyte proliferation, fibrosis inhibition, differentiation, and cell survival.

Results: The findings indicated that compounds such as CHIR99021 (activator of the Wnt/β-catenin signaling pathway), SB431542 (inhibitor of the TGF-β pathway), dexamethasone (inducer of hepatocytic differentiation), and Y-27632 (enhancer of cell survival) can effectively promote hepatocyte proliferation, reduce fibrotic progression, and enhance hepatic functionality through distinct molecular mechanisms. The targeted application of these molecules—especially within engineered microenvironments such as 3D-bioprinted scaffolds or hydrogels—can further improve regenerative outcomes by mimicking native extracellular matrix conditions and supporting cell–matrix interactions.

Conclusion: Despite existing challenges such as safety concerns, the need for targeted delivery systems, and limited clinical evidence, integrating these agents with advanced technologies, including 3D bioprinting and personalized medicine, offers a promising outlook for the treatment of liver diseases. Future efforts should focus on optimizing combinatorial small-molecule therapies, developing smarter delivery platforms, and validating these approaches in clinically relevant models to accelerate translation into regenerative hepatology.

Keywords: Liver regeneration, Regenerative medicine, Small molecules, Hepatocyte

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Highlights

- Small molecules promote liver regeneration via key signaling pathways.
- CHIR99021 and SB431542 enhance regeneration and suppress fibrosis.
- Dexamethasone and Y-27632 improve hepatocyte maturation and survival.
- Biomaterial-based delivery systems enhance therapeutic efficacy.
- Clinical translation requires improved safety and targeted delivery.

Plain Language Summary

Looking ahead, the future of liver regenerative medicine is expected to be driven by the rational design of next-generation small molecules with enhanced specificity, reduced toxicity, and multi-target capabilities. The integration of these agents with advanced technologies such as 3D bioprinting, organ-on-chip systems, and nanocarrier-based delivery platforms will likely enable more precise and effective therapeutic interventions. Additionally, the application of artificial intelligence for drug discovery and the adoption of personalized medicine approaches based on patient-specific molecular profiles are anticipated to significantly accelerate clinical translation. These innovations collectively offer a promising pathway toward safer, more efficient, and patient-tailored treatments for chronic liver diseases.

Introduction

The liver, as the largest gland and a vital metabolic organ in the human body (Figure 1), is responsible for numerous essential physiological functions, including detoxification, plasma protein synthesis, bile production, and glycogen storage [1]. These diverse functions render the liver an irreplaceable organ, such that any significant impairment in its function can rapidly threaten human life. Liver diseases—including viral hepatitis, non-alcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma (HCC)—are among the leading causes of global morbidity and mortality [2]. According to the latest estimates by the World Health Organization (WHO), liver diseases account for approximately two million deaths per year worldwide. The prevalence of these conditions, particularly NAFLD, continues to rise, largely due to the global epidemics of obesity and diabetes [3]. In the advanced stages of chronic liver disease, referred to as end-stage liver disease (ESLD), liver transplantation remains the only definitive therapeutic option. However, transplantation is associated with significant limitations, including a severe shortage of donor organs, substantial financial burden, the necessity for lifelong immunosuppression, and the inherent risk of graft rejection [4]. These challenges underscore the urgent need for alternative, innovative therapeutic strategies to promote liver tissue regeneration and functional recovery.

Although liver transplantation is regarded as the gold standard for treating ESLD, it faces significant inherent challenges and limitations. The most important issue is the profound mismatch between the number of patients in need of a transplant and the availability of donor organs. For instance, in the United States, thousands of individuals remain on the liver transplant waiting list, and a considerable proportion of them die before receiving a suitable graft [5]. In addition to donor scarcity, the transplantation process itself is associated with substantial complications and financial burdens. Recipients require lifelong immunosuppressive therapy to prevent graft rejection, which in turn predisposes them to an elevated risk of opportunistic infections and secondary malignancies [6]. Furthermore, the direct and indirect costs of surgical procedures, prolonged hospitalization, and ongoing pharmacotherapy impose a significant economic strain on healthcare systems and patients alike [7].

Alternative interventions, such as artificial liver support systems (e.g. molecular absorbents recirculating system), primarily serve as bridge therapies. While these systems may temporarily stabilize liver function, they do not possess the capacity to regenerate damaged tissue or restore long-term organ function [8]. These critical limitations highlight the urgent need to develop innovative therapeutic paradigms capable of stimulating the liver's intrinsic regenerative capacity and reversing fibrotic tissue remodeling. In response to the therapeutic challenges

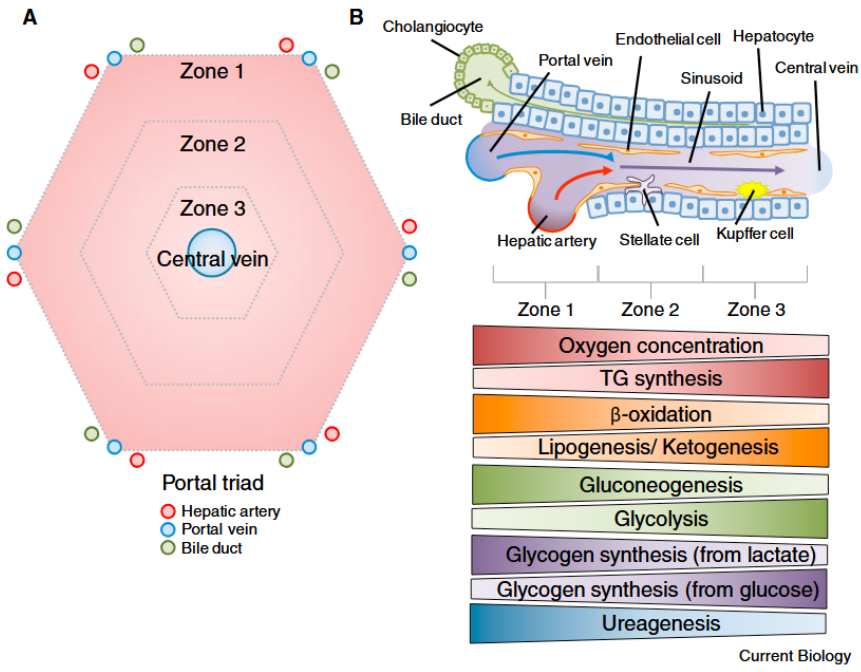

Figure 1. Organization of the liver

Note: A) Geometric representation of a hepatic lobule, B) schematic representation of a sinusoid within the liver and the corresponding zonation of several metabolic processes across the sinusoid [1]

posed by advanced liver diseases, regenerative medicine has emerged as a transformative and promising paradigm whose ultimate goal is to repair, replace, or regenerate damaged cells, tissues, and organs to restore their normal physiological function [9]. One of the core pillars of hepatic regenerative medicine is tissue engineering, which aims to construct functional three-dimensional structures by combining cells, biodegradable scaffolds, and bioactive growth factors [10]. In parallel, cell therapy—particularly involving the administration of various stem cells such as mesenchymal stem cells derived from bone marrow or adipose tissue—has gained attention as a powerful strategy for modulating immune responses, secreting trophic factors, and promoting endogenous tissue repair [11].

Revolutionary advancements in induced pluripotent stem cell (iPSC) technology have further opened new avenues in the field of hepatic regenerative medicine. These cells are generated by reprogramming adult somatic cells (e.g. skin fibroblasts) into a pluripotent state, enabling them to proliferate indefinitely and differentiate into virtually any cell type, including mature hepatocytes. This approach provides a potentially unlimited and patient-specific source of hepatic cells, significantly reducing the risk of immune rejection [12]. While cells and scaffolds constitute the fundamental components of regenerative medicine, precise control over cell fate—including differentiation, proliferation, and survival—is crucial for the success of tissue engineering strategies. Traditionally, this control has been predominantly achieved through protein-based growth factors, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF). However, the clinical and laboratory application of these proteins is limited by several drawbacks, including high production costs, instability under standard culture conditions, the need for ultra-low temperature storage, and the potential to trigger immunogenic responses [13]. In this regard, small molecules have emerged as powerful and attractive alternatives, which are low-molecular-weight organic compounds (typically <900 Daltons) capable of modulating intracellular signaling pathways by binding to specific receptors, enzymes, or ion channels [14]. Compared to protein-based growth factors, small molecules target different signaling pathways (Figure 2) and offer numerous advantages, including greater chemical and physical stability (they remain stable at room temperature and do not require complex cold-chain logistics), cost-effectiveness (their synthesis and large-scale production are generally more economical), improved cellular penetration (due to their small size, they can readily diffuse into cells and three-dimen-

sional tissues), reversibility and controllability (their effects can often be modulated or reversed by washing or adding antagonists), scalability and reproducibility (their defined and consistent chemical structures facilitate standardization and industrial-scale production) [15]. These properties make small molecules highly suitable for directing stem cell differentiation toward desired lineages, such as hepatocytes, enhancing cell proliferation, and establishing an optimal microenvironment for liver tissue regeneration [16-19].

Given the remarkable potential of small molecules to address challenges in hepatic regenerative medicine, this review systematically explores and categorizes the small molecules used to promote liver cell proliferation, differentiation, and functional enhancement. The primary focus is on compounds that have demonstrated efficacy in in vitro and in vivo studies for promoting hepatocyte regeneration, inhibiting liver fibrosis, and improving hepatic metabolic function. This review study seeks to provide a structured classification of small molecules based on their mechanisms of action—such as Wnt pathway activators, transforming growth factor (TGF)-β inhibitors, and hepatocyte differentiation inducers—as well as their clinical relevance, thereby offering a comprehensive resource for researchers in regenerative medicine, pharmacology, and cellular biology. Furthermore, this article addresses current challenges, including cytotoxicity, optimal dosing strategies, and the translation of experimental findings into clinical applications. It also discusses future directions in the design and development of next-generation small molecules with improved efficacy and safety profiles. Ultimately, by synthesizing current evidence, this review aspires to illuminate future research trajectories and contribute to the acceleration of small molecule–based therapeutic approaches for liver diseases.

Results

Signaling small molecules

Given the benefits of small molecules, numerous studies have investigated their use to induce hepatocyte regeneration, suppress liver fibrosis, and restore metabolic activity. This section provides an overview of the categories, mechanisms of action, and clinical relevance of small molecules used in liver tissue engineering, setting the stage for a more detailed examination of specific compounds and their therapeutic potential, summarized in Table 1.

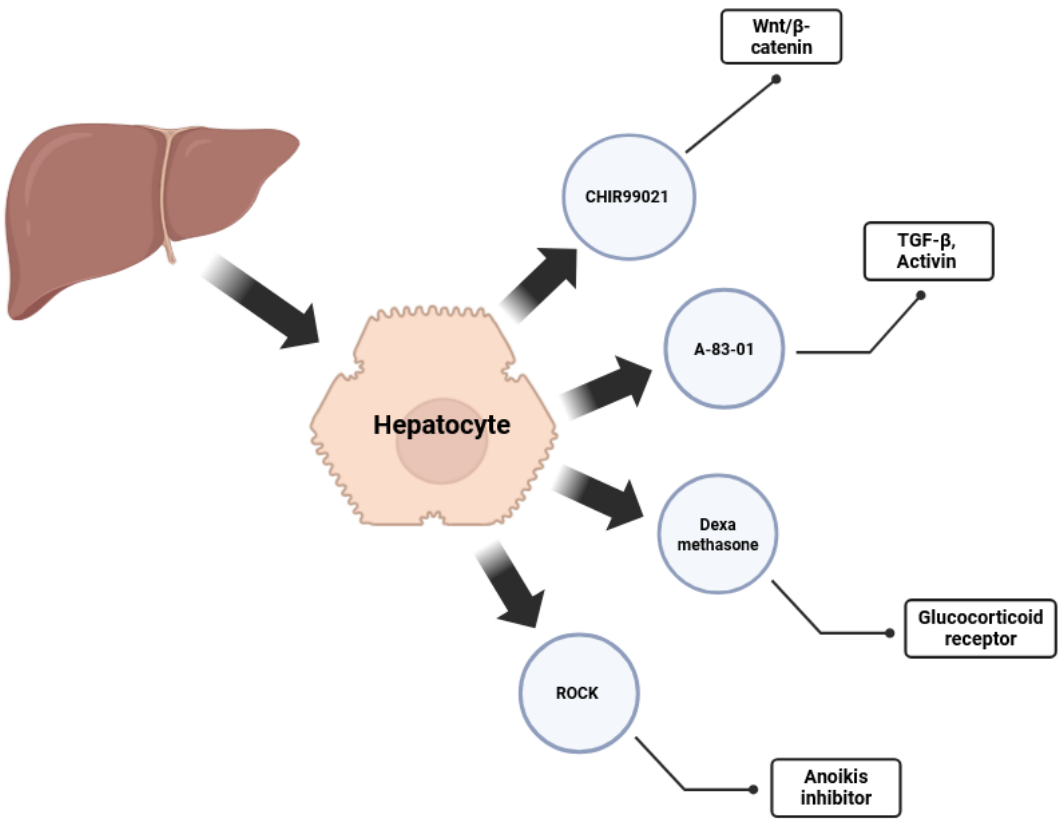

Figure 2. Schematic view of key signaling pathways targeted by small molecules in liver regeneration and therapy

Table 1. Key small molecules for liver cell growth and their mechanisms of action

Small Molecule	Primary Target/Pathway	Biological Effect on Liver Cells	Potential Clinical Application	Ref.
CHIR99021	GSK-3β / Wnt/β-catenin	Potently promotes the expansion and proliferation of human hepatocytes in vitro.	Liver regeneration, cell therapy	[16]
SB431542	TGF-β receptor (ALK5)	Inhibits TGF-β-induced Smad2/3 phosphorylation, effectively reducing activation of hepatic stellate cells and liver fibrosis.	Treatment of liver fibrosis	[43]
Sulforaphane	Keap1/Nrf2	Activates the Nrf2-mediated antioxidant response, enhancing expression of detoxification enzymes and protecting hepatocytes from oxidative stress and apoptosis.	Drug-induced liver injury, NAFLD	[39]
Phenobarbital	CAR	A classic agonist that induces the expression of cytochrome P450 enzymes (e.g. CYP2B6, CYP3A4), a hallmark of mature metabolic function in hepatocytes.	Maturation of hepatocytes, detoxification	[44]
Y-27632	ROCK (Rho-associated kinase)	Enhances survival, plating efficiency, and proliferation of primary hepatocytes and stem cell-derived hepatocyte-like cells by inhibiting apoptosis.	Hepatocyte culture, cell transplantation	[45]
Dexamethasone	Glucocorticoid receptor	Promotes hepatocyte maturation, enhances albumin secretion, and stabilizes hepatic metabolic functions in vitro.	In vitro model maturation	[46]

CAR: Constitutive androstane receptor.

Proliferation inducers and hepatic regeneration

Stimulating the proliferation of hepatocytes and hepatic progenitor cells is a central strategy for regenerating damaged liver tissue. Several small molecules have been identified that effectively activate key signaling pathways involved in cell division and tissue repair.

Wnt/β-catenin pathway activators: The Wnt/β-catenin pathway is essential for liver regeneration (Figure 3). Its activation potently stimulates hepatocyte proliferation. The small molecule CHIR99021 inhibits glycogen synthase kinase-3 beta (GSK-3β), stabilizing β-catenin and promoting its nuclear translocation. This activates the transcription of pro-proliferative genes like c-Myc and Cyclin D1, significantly enhancing liver cell growth in both in vitro and in vivo partial hepatectomy models [20]. Another notable compound, IQ-1, promotes hepatic proliferation indirectly by inhibiting the c-Jun N-terminal kinase (JNK), thereby enhancing β-catenin activity and supporting liver cell expansion [21].

Multi-targeting small molecules: Certain compounds exhibit multi-pathway activity, further enhancing their regenerative potential. For example, the small molecule CHIR99021 (a GSK-3β inhibitor) activates Wnt/β-catenin signaling and has been shown to promote significant expansion of human hepatocytes in vitro, highlighting its utility in liver regenerative applications [16]. Likewise, YKL-06 activates both Erk and Akt pathways, inducing robust proliferative responses in both murine and human hepatocytes [22].

Growth factor mimetics: Beyond Wnt signaling, some small molecules function as mimetics of HGF. While HGF is a large polypeptide, the discovery of small molecules that activate its receptor, c-Met, has opened promising avenues. These compounds mimic the mitogenic and morphogenic signaling of HGF, stimulating hepatocyte proliferation and migration [23].

Differentiation inhibitors for progenitor maintenance: In specific regenerative contexts, the goal may extend beyond promoting proliferation to include the prevention of premature differentiation, thereby maintaining cells in a progenitor-like state. A-83-01, primarily known as a TGF-β pathway inhibitor, also serves this purpose by sustaining the expansion of hepatic progenitor populations through inhibition of differentiation signals [24].

These classes of small molecules are particularly valuable in scenarios demanding rapid expansion of hepatic cell populations, such as in bioreactor systems or cell transplantation therapies. Their ability to fine-tune proliferative signaling while maintaining cellular plasticity underscores their significance in regenerative liver medicine.

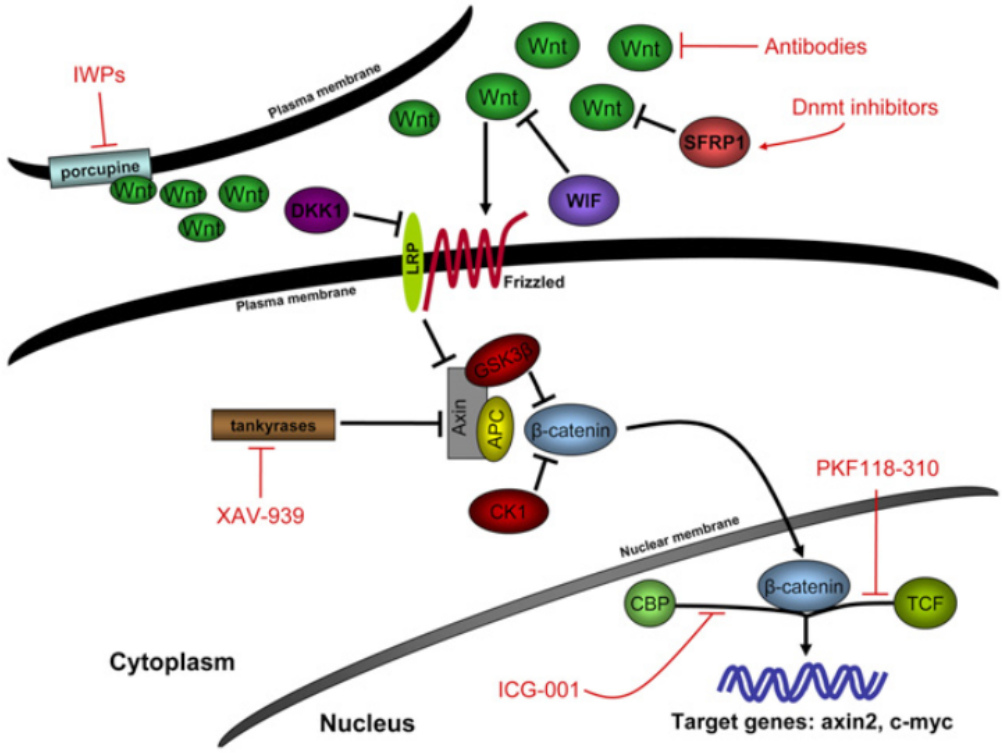

Figure 3. Canonical Wnt signaling and potential therapeutic interventions in fibrosis [25]

Fibrosis and scarring inhibitors

Liver fibrosis, characterized by the excessive accumulation of extracellular matrix (ECM) proteins—particularly collagen—represents the common ESLDs. This process not only disrupts the normal lobular architecture of the liver but also actively impedes parenchymal cell regeneration by creating a physically and biochemically hostile microenvironment [26]. Consequently, inhibiting fibrogenesis is a strategic therapeutic objective to establish favorable conditions for regeneration. Numerous small molecules have been developed to target key pathways involved in fibrogenesis.

TGF-β pathway inhibitors

The TGF-β signaling is the principal cytokine driver of fibrogenesis, stimulating the activation and differentiation of fibroblasts into collagen-producing myofibroblasts [27]. Inhibiting this pathway is therefore a rational therapeutic strategy. SB431542 is a selective inhibitor of TGF-β type I receptors (ALK4, ALK5, ALK7). By blocking the phosphorylation of Smad2/3, it inhibits downstream TGF-β signaling, effectively reducing collagen production and myofibroblast differentiation in both in vitro and in vivo models of liver fibrosis [25]. Galunisertib (LY2157299) is a selective oral inhibitor of the TGF-β receptor I (ALK5). It inhibit fibrosis progression in various animal models and has advanced to phase II clinical trials for the treatment of HCC [28]. A-83-01 is also a potent inhibitor of TGF-β and Activin receptors. This dual functionality makes it a valuable multi-targeted agent for simultaneously inhibiting fibrosis and promoting regeneration [24].

Inhibitors of other signaling pathways

Nintedanib is a broad-spectrum tyrosine kinase inhibitor that targets platelet-derived growth factor receptors, FGF receptors, and vascular endothelial growth factor receptors. These receptors play key roles in the proliferation, migration, and survival of myofibroblasts. Nintedanib has demonstrated efficacy in models of liver and lung fibrosis and is FDA-approved for the treatment of idiopathic pulmonary fibrosis. [29]. OCU-030 is a small molecule that inhibits the NF-κB pathway, a critical inflammatory and pro-fibrotic signaling cascade. By reducing the underlying inflammatory drive, OCU-030 indirectly suppresses the activation and persistence of myofibroblasts [30]. The application of these anti-fibrotic agents can create a permissive microenvironment, allowing the proliferation inducers mentioned in the previous section to effectively facilitate the regeneration of functional liver tissue.

Hepatocyte differentiation inducers

A primary objective of liver regenerative medicine is the generation of mature, fully functional hepatocyte populations for applications in cell transplantation, organoid bioengineering, and drug screening. The differentiation of hepatocytes from pluripotent stem cells (PSCs) requires the precise recapitulation of sequential developmental stages. Small molecules play an indispensable role in directing this complex, multi-step process [16]:

Phase I: Differentiation to mesendoderm. CHIR99021, as a GSK-3 inhibitor, provides a critical initial signal by strongly activating the Wnt/β-catenin pathway, which is necessary for the commitment of PSCs to the mesendodermal lineage. It is consequently a standard first molecule in many established hepatic differentiation protocols [31].

Phase II: Differentiation to definitive endoderm and hepatic progenitors. Signaling through the FGF pathways is essential for patterning the definitive endoderm and specifying it toward a hepatic progenitor cell fate. While often achieved with recombinant proteins, small-molecule FGF mimetics are an area of active research [32].

Phase III: Hepatocyte maturation and functionalization. This final phase is crucial for endowing progenitor cells with the sophisticated metabolic and synthetic functions of primary hepatocytes. A-83-01, By inhibiting TGF-β signaling, which can promote an epithelial-to-mesenchymal transition and impede terminal differentiation, A-83-01 significantly enhances the final maturation and functionality of iPSC-derived hepatocyte-like cells [32].

Dexamethasone, a synthetic glucocorticoid, activates the glucocorticoid receptor and acts as a powerful inducer of genes involved in hepatic maturation, including those regulating gluconeogenesis and ammonia metabolism. It promotes a more mature and stable epithelial phenotype [33]. Phenobarbital, a well-characterized agonist of the constitutive androstane receptor, is a classical inducer of cytochrome P450 enzyme expression (e.g. CYP2B6, CYP3A4). This induction is a defining functional characteristic of mature, metabolically competent hepatocytes and is a cornerstone phenomenon in xenobiotic metabolism research [34]. Dimethyl sulfoxide, a polar solvent, can enhance terminal differentiation by upregulating the expression of mature hepatocyte markers, such as albumin and transferrin, and is often used in the final stages of differentiation protocols to promote functional maturation [35].

Metabolic modulators and cytoprotective agents

Achieving successful liver regeneration requires more than the proliferation and differentiation of cells. It also depends on maintaining the survival and optimal function of hepatocytes in the face of environmental stressors—whether arising from tissue injury or in vitro culture conditions. Small molecules that modulate cellular metabolism or provide cytoprotection play an essential and often complementary role alongside proliferative and differentiation-inducing agents [36].

Apoptosis inhibitors

Caspase inhibitors (e.g. Z-VAD-FMK) are broadly recognized as general cytoprotective agents. By inhibiting caspases—the central executioners of programmed cell death—they significantly improve cell survival, particularly during early culture stages or after transplantation, when hepatocytes encounter oxidative and mechanical stress [37]. Among ROCK inhibitors, Y-27632 is primarily used to prevent anoikis, a form of apoptosis triggered by loss of ECM attachment. It is particularly valuable for enhancing the survival of dissociated hepatocytes or progenitor cells during culture or transplantation [38].

Activators of cell survival pathways

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a master transcriptional regulator of the cellular antioxidant response. Its activation promotes the expression of a wide array of cytoprotective genes, including those encoding detoxifying phase II enzymes and endogenous antioxidants, which is crucial for mitigating oxidative damage in hepatocytes [39]. Sulforaphane, a prominent naturally occurring isothiocyanate derived from cruciferous vegetables, is a potent activator of the Nrf2 pathway. It functions by modifying key cysteine residues on the Keap1 repressor protein, thereby disrupting the Keap1-Nrf2 interaction and preventing Nrf2 degradation. This leads to Nrf2 nuclear translocation and the subsequent upregulation of antioxidant gene expression, significantly enhancing cellular resistance to oxidative stress and promoting hepatocyte survival in models of liver injury [39]. Dimethyl fumarate (DMF), an FDA-approved drug for multiple sclerosis, also activates Nrf2 signaling. It has demonstrated protective effects in liver injury models, particularly in ischemia-reperfusion and oxidative stress contexts [40].

Energy metabolism modulators

AMP-activated protein kinase (AMPK) serves as a key intracellular energy sensor. Under metabolic stress (e.g. hypoxia, nutrient deprivation), AMPK activation promotes adaptive changes that support cellular survival [41]. AICAR, an AMP analog and pharmacological activator of AMPK, has been shown to protect hepatocytes from metabolic stress and reduce steatosis in experimental models [41]. The mammalian target of rapamycin (mTOR) is a central nutrient and growth sensor. Inhibition of mTOR signaling can induce autophagy—a protective process that removes damaged organelles and proteins. Rapamycin (Sirolimus), while primarily used as an immunosuppressant, also induces protective autophagy in hepatocytes and has shown therapeutic benefits in certain models of liver injury [42]. The judicious application of the mentioned cytoprotective and metabolic-modulating small molecules can significantly improve hepatocyte survival both in culture and after transplantation—ultimately enhancing the effectiveness of regenerative strategies.

Clinical applications, challenges, and future perspectives

Translational and clinical applications

Small molecules are emerging as ideal candidates for translational applications in liver regenerative medicine, due to their relatively low production costs, chemical stability, high tissue permeability, and scalability for large-scale manufacturing [47]. Small molecules are widely employed to support the growth, maturation, and functional enhancement of liver organoids derived from iPSCs or adult stem cells. Current differentiation protocols often utilize a combination of growth factors (e.g. FGF, HGF) and small molecules (such as A-83-01, CHIR99021, and DAPT) to maximize yield and functional fidelity [48]. One of the major barriers to effective cell therapy is the extensive early post-transplantation cell death. Pre-conditioning cells with cytoprotective agents (e.g. Y-27632 or Z-VAD-FMK) or administering these compounds systemically to the host has been shown to significantly improve graft survival and engraftment efficiency [38]. Small molecules can be incorporated into polymeric scaffolds or hydrogels to allow for controlled, localized release at the injury site. These "smart scaffolds" can mimic the native hepatic microenvironment, simultaneously supporting cell adhesion and migration while delivering biochemical signals that promote hepatocyte proliferation and differentiation [49].

Current challenges and limitations

Despite their promise, the clinical translation of small molecules in liver regenerative therapies faces several critical challenges summarized in Table 2.

A paramount challenge in the clinical translation of pro-regenerative small molecules is their potential oncogenic risk. Key pathways targeted for regeneration, such as Wnt/β-catenin and TGF-β, are frequently dysregulated in cancer. Consequently, the potent agonism of Wnt signaling or inhibition of TGF-β signaling—while beneficial for

Table 2. Major challenges in the clinical translation of pro-regenerative small molecules and proposed future directions

Challenge	Description	Potential Solution / Future Direction	Ref.
Oncogenic risk	Prolonged or off-target activation of proliferative pathways (e.g. Wnt/β-catenin) can promote tumorigenesis.	Dose optimization: Identify narrow therapeutic windows that maximize efficacy while minimizing risk. Temporary exposure: Develop transient delivery systems (e.g. degradable hydrogels) for short-term, localized treatment.	[50]
Off-target effects & toxicity	Small molecules can interact with unintended targets in non-liver tissues, leading to systemic toxicity.	Targeted delivery systems: Utilize nanoparticle carriers or ligand conjugation (e.g. targeting ligands for hepatocytes) to improve specificity and reduce systemic exposure.	[57]
Short half-life & stability	Many compounds have rapid clearance in vivo, requiring frequent dosing to maintain effective concentrations.	Advanced formulations: Develop sustained-release systems (e.g. microspheres, implantable devices) to provide long-term, controlled release at the target site.	[58]
Limited efficacy in complex disease	Monotherapy may be insufficient for multifactorial diseases like advanced fibrosis or cirrhosis.	Combination therapy: Strategically combine molecules targeting different pathways (e.g. a proliferative agent + an anti-fibrotic) for synergistic effects. Personalized medicine: Use patient-derived cells to test drug combinations before in vivo use.	[59]
Scalability & cost	Scaling up the production of high-purity small molecules and advanced delivery systems for clinical use is complex and expensive.	High-throughput screening: Use automated platforms and organoid models to efficiently identify lead compounds and optimal doses, reducing development time and cost.	[59]

driving proliferation and mitigating fibrosis—could inadvertently promote tumor initiation or progression if not meticulously controlled. Defining the critical threshold between regenerative and carcinogenic doses is therefore essential for the safe development of these therapies [50].

Most small molecules are systemically distributed and may affect non-hepatic tissues. The development of targeted delivery systems that can direct these agents specifically to hepatocytes or injured hepatic regions is essential to minimize systemic side effects [51]. Liver regeneration is governed by a highly interconnected network of signaling pathways. Modulation of one pathway can result in unintended crosstalk or compensatory activation in others. A deeper understanding of these signaling networks is crucial for designing small-molecule combinations that can synergistically modulate multiple targets [52]. Promising preclinical results in rodent models often fail to replicate in human trials due to fundamental differences in metabolism, physiology, and immune responses between species. Bridging this translational gap remains a significant hurdle in clinical development [53].

Future perspectives

The future of liver regenerative medicine is likely to revolve around personalized and integrative therapeutic strategies:

High-throughput screening and rational drug design: The use of high-throughput screening platforms to identify novel small molecules with high efficacy and minimal toxicity is an active area of research. Moreover, rationally designed multi-target compounds that can modulate several complementary pathways simultaneously may enhance therapeutic outcomes while minimizing adverse effects [54].

Integration with advanced technologies: Combining small molecules with cutting-edge technologies—such as 3D bioprinting of liver tissue, microfluidic organ-on-a-chip platforms, and gene editing—holds transformative potential. These integrations may lead to more accurate disease models and ultimately, the generation of fully functional transplantable hepatic tissues [55].

Combination therapies: It is increasingly evident that future protocols will rely on a strategic combination of small molecules (to promote proliferation, differentiation, and cytoprotection), cell therapies, and bioengineered scaffolds to create a fully supportive regenerative microenvironment [56].

Overall, small molecules have emerged as powerful tools in the regenerative medicine arsenal for liver diseases. While several challenges remain on the path to clinical implementation, ongoing research into optimizing dosage, timing, delivery mechanisms, and molecular combinations offers strong promise for realizing the full potential of these agents in future liver therapies.

Conclusion

Liver regenerative medicine has witnessed significant advancements through the application of small molecules, which have demonstrated substantial potential for modulating key cellular processes, including proliferation, differentiation, fibrosis inhibition, and cytoprotection. This review highlights the multifaceted roles of small molecules in hepatic tissue repair, emphasizing their ability to influence crucial signaling pathways. Compounds like CHIR99021 have been shown to enhance hepatocyte proliferation by activating the Wnt/β-catenin pathway, while agents such as SB431542 effectively inhibit fibrogenesis by targeting TGF-β signaling. Furthermore, small molecules including dexamethasone and A-83-01 have facilitated the efficient differentiation of stem cells into mature, functional hepatocytes. In addition, cytoprotective agents like Y-27632 have improved cell survival under stress conditions, which is critical for transplantation and in vitro culture.

Despite these promising outcomes, limitations persist—most notably the reliance on preclinical models, limited clinical data in humans, concerns regarding tumorigenicity, and the high cost of certain compounds. Looking ahead, future research must prioritize the development of next-generation small molecules with higher specificity, lower toxicity, and improved pharmacological profiles. Integrating smart delivery systems, such as nano-carriers and stimuli-responsive platforms, will be essential for targeted hepatic therapy. Moreover, translational research in human-relevant models and well-designed clinical trials are crucial to bridging the gap between bench and bedside. The convergence of small-molecule therapies with cutting-edge technologies (such as tissue engineering, personalized medicine, and artificial intelligence) holds immense promise for transforming the therapeutic landscape for liver diseases. Overall, while challenges remain, small molecules represent a powerful and versatile class of therapeutics that could revolutionize the treatment of chronic and end-stage liver conditions through their strategic integration into regenerative protocols.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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