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Microbiome-derived bile acids as endogenous regenerative mediators in liver repair

Surya Nath Pandey [a], Kavita Goyal [b], Mohit Rana [c], Soumya V. Menon [d], Subhashree Ray [e], Haider Ali [f], Popat S. Kumbhar [g], John Disouza [h], Sachin Kumar Singh [i], Gaurav Gupta [j,k], Ling Shing Wong [l], Vinoth Kumarasamy [m,*], Vetriselvan Subramaniyan [n]

[a] Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, 244001, Uttar Pradesh, India
[b] Department of Biotechnology, Graphic Era (Deemed to be University), Clement Town, Dehradun, 248002, India
[c] Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India
[d] Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India
[e] Department of Biochemistry, IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, 751003, India
[f] Centre for Global Health Research, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[g] Department of Pharmaceutics, Tatyasaheb Kore College of Pharmacy, Warana University, Warananagar 416113, Maharashtra, India
[h] Bombay Institute of Pharmacy and Research, Dombivli, Mumbai, Maharashtra, 421 203, India
[i] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, 144411, India
[j] Centre for Research Impact & Outcome, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, 140401, India
[k] Centre of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates
[l] Faculty of Health and Life Sciences, INTI International University, Nilai, 71800, Malaysia
[m] Department of Parasitology and Medical Entomology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Cheras, 56000, Kuala Lumpur, Malaysia
[n] Division of Pharmacology, Department of Biomedical Sciences, Sir Jeffrey Cheah Sunway Medical School, Faculty of Medical and Life Sciences, Sunway University, Malaysia

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ABSTRACT

The liver's extraordinary capacity for self-repair is often compromised by chronic injury, fibrosis, or extensive resection, creating an urgent need for innovative regenerative therapies to restore liver function. Emerging evidence suggests that microbiome-derived bile acid metabolites are potent endogenous mediators of hepatic regeneration. Beyond their canonical role in lipid emulsification, these chemically diverse molecules engage nuclear and membrane receptors, most notably the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), to stimulate hepatocyte proliferation, modulate inflammatory responses, and reactivate quiescent progenitor cells. In this review, we integrate mechanistic insights from partial hepatectomy, germ-free, and antibiotic-treated animal models with early clinical observations to illuminate how primary and secondary bile acids orchestrate cell cycle progression, cytokine balance, and extracellular matrix remodeling. We then examined the therapeutic landscape, from synthetic FXR/TGR5 agonists to live-biotherapeutic approaches, genetically modified probiotic strains, and fecal microbiota transplantation. We highlight the preliminary indicators of efficacy and challenges in manufacturing consistency, safety profiling, and regulatory classification. We address the interindividual variability in microbiome composition, potential biomarkers such as serum FGF19, imaging-based measures of functional liver mass, and considerations for optimal trial design. This is the first comprehensive review to frame microbiome-driven bile acids as direct modulators of liver regeneration and chart a coherent translational development pathway. By integrating stem cell biology, hepatology, microbiology, and bioengineering perspectives, we demonstrate the underexplored therapeutic potential of these approaches to transform the future of hepatic repair.

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* Corresponding author.
E-mail address: vinoth.ukm@hotmail.com (V. Kumarasamy).

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1. Introduction

The liver's capacity for self-renewal after injury or resection is unique among solid organs. However, chronic disease, fibrosis, or massive tissue loss can overwhelm the liver's intrinsic repair programs, leading to liver failure and transplantation [1]. Recent studies have identified microbiome-derived bile acid metabolites as novel modulators of hepatic regeneration [2]. In addition to their classical roles in lipid digestion, these structurally diverse molecules function as signaling ligands that drive hepatocyte proliferation, modulate immune responses, and reactivate dormant progenitor niches [3,4]. We hypothesize that the gut–liver–microbiome axis, through its diverse secondary bile acid species, represents an endogenous reservoir of regenerative signaling molecules whose therapeutic potential is only beginning to be explored. At the molecular level, specific bile acid species engage both nuclear receptors, principally the farnesoid X receptor (FXR), and membrane-bound sensors such as Takeda G-protein-coupled receptor 5 (TGR5) to orchestrate cell cycle entry, cytokine balance, and extracellular matrix remodeling [5,6]. For instance, FXR activation in hepatocytes upregulates cyclin D1 and other key cell cycle regulators, whereas TGR5 signaling in Kupffer cells fosters an anti-inflammatory milieu that supports tissue repair [7,8]. Beyond these canonical axes, emerging evidence implicates additional receptors and epigenetic modulators that respond to distinct bile acid conjugates, suggesting a finely tunable regenerative network [9,10].

Translating these mechanistic insights into effective therapies presents both opportunities and challenges [11,12]. Liver-biotherapeutic products, engineered microbes programmed to deliver targeted bile acids, and rationally designed small-molecule agonists offer precision tools to stimulate regeneration [13,14]. Preclinical models of partial hepatectomy and toxin-induced injury have shown that the administration of selected secondary bile acids accelerates recovery, and early clinical observations have indicated improvements in liver function markers among patients with cholestatic disorders [15,16]. However, scaling up microbial therapeutics requires stringent control of strain stability, metabolite consistency, and safety profiling, whereas synthetic agonists must negotiate complex pharmacokinetic behaviors and off-target risks [17,18].

The regulatory pathways for these novel agents are still evolving. Liver biotherapeutic products straddle the definitions of biologics and probiotics, requiring the alignment of quality control standards across global agencies. Small-molecule bile acid modulators must demonstrate regenerative efficacy and maintain metabolic homeostasis [19,20]. Moreover, reliable biomarkers, ranging from imaging-based assessments of functional liver mass to standardized metabolomic signatures or circulating progenitor cell counts, are urgently needed to optimize dosing, monitor response, and expedite clinical trial design [21,22].

The novelty of this review lies in its regenerative-centric synthesis; to date, no review has integrated microbiome-driven bile acid chemistry, molecular signaling pathways, and translational challenges into a unified framework for hepatic repair. We aim to illuminate how microbiome-derived bile acids can be harnessed as next-generation, regenerative mediators. We guide basic researchers and translational teams toward therapies that move beyond supportive care to restorative intervention. By articulating these mechanistic insights alongside practical considerations for development and regulation, we chart a clear path from bench to bedside in the emerging field of bile acid-mediated liver regeneration.

2. Liver regeneration: cellular and molecular foundations

Hepatic regeneration is a tightly regulated cascade of cellular and molecular events that restores the liver parenchyma and function after injury or resection. Extensive in vivo, in vitro, and clinical studies have elucidated these mechanisms of action. In 2003, Ren et al. demonstrated that IL-6–deficient mice fail to mount an adequate proliferative response after 70 % partial hepatectomy; hepatocyte DNA synthesis was virtually absent until exogenous stem cell factor (SCF) was administered, which restored cyclin D1 expression and BrdU incorporation to wild-type levels by 72 h post-resection. This finding cemented IL-6's role in the "priming" phase of regeneration and uncovered SCF as an alternative mitogenic backstop in its absence [23]. In 2008, Sudo et al. used bone marrow transplantation to show that TNF-α-knockout donor cells transferred into irradiated wild-type recipients resulted in a 40 % reduction in hepatocyte S-phase entry after hepatectomy, confirming TNF-α as a non-redundant initiator of the pro-regenerative cytokine cascade. Together, these genetic models defined the earliest molecular triggers of the IL-6/STAT3 and TNF-α/NF-κB axes that license hepatocytes to re-enter the cell cycle [24].

Building on these priming paradigms, researchers in the mid-2000s began to dissect downstream transcriptional and morphogenetic programs. In 2006, Tan et al. delivered adenoviral vectors encoding Hepatocyte Nuclear Factor 6 (HNF6) to partially hepatectomized mice, finding that forced HNF6 expression accelerated the $G_1 \rightarrow S$ transition by upregulating cyclin E and PCNA at 24 h, identifying HNF6 as a key transcriptional driver of early proliferation [25]. In parallel, Kwon et al. (2013) investigated Vitamin D_3–upregulated protein 1 (VDUP1) and showed that VDUP1 knockout mice exhibited amplified JNK and STAT3 activation within 4 h of resection, a 30 % increase in BrdU-positive hepatocytes at 24 h, and faster restoration of liver mass, highlighting how intracellular stress-sensing pathways modulate regenerative kinetics [26]. By 2015, Yang et al. turned to in vitro systems: primary mouse hepatocytes cultured with graded doses of Wnt5a demonstrated dose-dependent suppression of β-catenin nuclear translocation and a 40 % decrease in cyclin D1 mRNA levels, an effect recapitulated in vivo where Wnt5a overexpression delayed peak DNA synthesis by 36 h after two-thirds hepatectomy. These studies collectively mapped a continuum from cytokine priming (IL-6, TNF-α) through transcriptional effectors (HNF6, VDUP1) to morphogen gradients (Wnt5a) that coordinate hepatocyte cell cycle entry [27].

The past decade has deepened our understanding of spatial heterogeneity, nonparenchymal interactions, and translational interventions. In 2007, in vivo perfused liver models infused with deoxycholic acid showed a 2.5-fold increase in hepatocyte Cyclin D1 levels and 35 % faster mass recovery than controls, implicating secondary bile acids as systemic accelerants of regeneration [28]. In 2011, Kurinna and Barton applied single-cell RNA sequencing to regenerating murine livers, revealing three transcriptional "waves": immediate-early NF-κB/AP-1 targets (0–4 h), mid-phase cell cycle genes (Cyclin D1, Aurkb; 12–36 h), and late extracellular matrix remodelers (MMP9, TIMP1; 48–72 h) [29]. In 2017, Tacke used clodronate liposomes to deplete Kupffer cells in CCl_4-injured mice, observing a 60 % drop in STAT3 phosphorylation and a corresponding 55 % decrease in Ki-67^+ hepatocytes at day 2, solidifying the dual role of resident macrophages in priming and inflammation resolution [30]. Building on intercellular crosstalk, McConnell et al. (2023) used VE-cadherin–Cre to delete FGFR1 in sinusoidal endothelial cells, which reduced HGF secretion by 40 % and delayed DNA synthesis by over 30 %, demonstrating that endothelial angiocrine support is indispensable for synchronizing vascular and parenchymal regrowth [31]. Recently, in vivo studies and clinical translations have gained attention. In 2023, Du et al. delivered mRNA-lipid nanoparticles encoding the Yamanaka factors (Oct4, Sox2, Klf4, c-Myc) to partially hepatectomized mice, achieving a 45 % increase in $BrdU^+$ hepatocytes and markedly improved survival in a toxin-induced acute liver failure model, demonstrating that controlled dedifferentiation enhances regenerative capacity [32]. Clinically, a Phase I trial of a recombinant human HGF mimetic (HGFlow) in 15 patients undergoing extended hepatectomy showed a 20 % faster volumetric recovery at 30 days versus historical controls, with excellent safety and tolerability, paving the way for growth-factor–based therapies in humans [33].

These investigations, from targeted gene deletions and modulation of key transcription factors to single-cell transcriptomic profiling, bile acid

signaling studies, endothelial–parenchymal interactions, and in vivo cellular reprogramming, establish a progressive timeline of mechanistic insights. They delineated a unified framework in which pro-inflammatory cytokines initiate hepatocyte cell-cycle entry through defined transcriptional networks, non-parenchymal cell populations, and circulating metabolites fine-tune the spatial and temporal dimensions of proliferation, and advanced bioengineering approaches are positioned to bridge experimental findings with clinical application. Future efforts incorporating organoid-based modeling, precise genome-editing technologies, and targeted gut–liver axis manipulation are essential for realizing customized, durable regenerative therapies for acute hepatic failure and chronic liver disease (Fig. 1). These cellular and molecular paradigms of hepatocyte priming, cytokine signaling, and extracellular matrix remodeling frame the liver's intrinsic capacity to regenerate. Section 3 examines how this intrinsic program is modulated by enterohepatic feedback, as the gut–liver axis provides a dynamic conduit for bile acids and microbial metabolites to influence hepatic homeostasis and repair processes.

3. Gut–liver axis: a bidirectional communication network

The gut–liver axis constitutes a complex bidirectional communication network in which bile acids (BAs), microbial metabolites, and enterohepatic signaling pathways coordinate hepatic homeostasis, injury response, and regeneration. Emerging evidence from animal models, cell lines, and preclinical transplantation studies demonstrates that microbiome-derived BAs act not only as amphipathic agents but also as endogenous ligands that trigger nuclear and membrane receptor pathways to promote hepatocyte proliferation and tissue repair.

In 2020, intestinal-specific FXR knockout mice revealed that loss of ileal Fgf15 (the murine ortholog of human FGF19) leads to intrahepatic BA accumulation, massive necrosis, and failed hepatocellular proliferation after resection, and adenoviral Fgf15 replacement restored BA homeostasis, rescued survival, and reinstated BrdU incorporation in remnant liver tissue [34]. Caballeria-Casals et al. (2021) confirmed in rats that pharmacologic BA depletion via cholestyramine delays regenerative kinetics and dampens early cytokine signaling (TNF-α, IL-6), whereas cholic acid supplementation reverses these effects only in the presence of intact FGFR4 signaling, underscoring the centrality of the BA–FGF15/19–FGFR4 axis in vivo [35]. Naugler (2014) further demonstrated, in a two-thirds hepatectomy model, that acute BA sequestration impairs early STAT3 and cyclin D1 activation, effects fully rescued by cholic acid repletion, which normalizes immediate-early gene induction [36]. Studies using both hepatotoxic injury and transplantation models have reinforced these findings. Meng et al. (2010) utilized CCl_4-induced hepatotoxicity to demonstrate that pharmacologic FXR activation with GW4064 enhances hepatocyte proliferation, attenuates centrilobular necrosis, and upregulates cyclin D1, whereas FXR deficiency exacerbates injury and impairs regenerative repair [37]. Van Golen et al.(2018) administered the FXR agonist obeticholic acid to cholestatic rats before partial hepatectomy and, despite enlarged pre-resection liver mass, observed paradoxically slower regrowth attributable to down-regulation of FGFR4 transcripts and compensatory STAT3 activation, suggesting that preloaded BA signaling can desensitize key mitogenic receptors [38]. Gulfo et al. (2020) treated brain-dead donor rats undergoing cold ischemia with FGF15 and documented

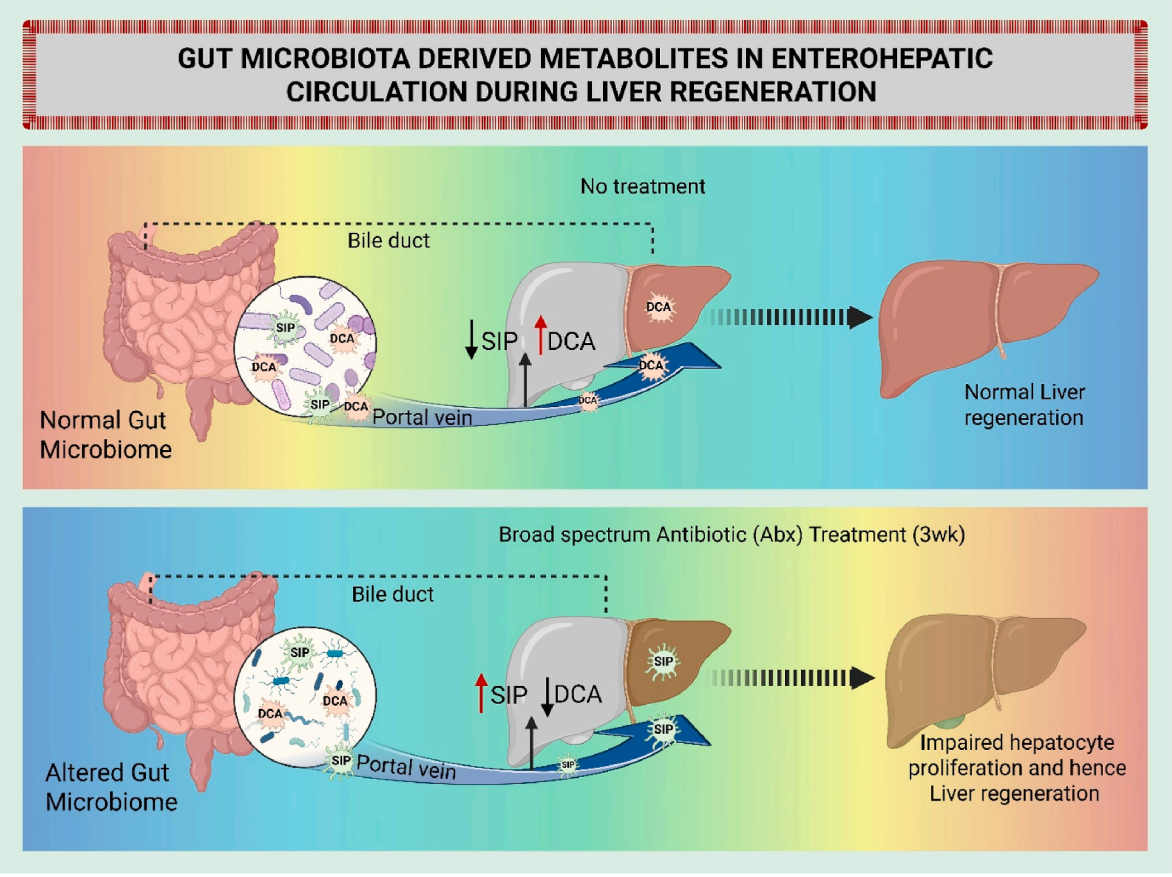


Fig. 1. Antibiotic-Induced Loss of Microbial DCA and S1P in Enterohepatic Circulation. The enterohepatic circulatory pathway enables gut microbiome compounds to participate in liver regeneration, as depicted in the figure. The natural gut bacteria produce Sphingosine-1-phosphate (S1P) and deoxycholic acid (DCA) only when antibiotics are not administrated because these compounds promote liver regeneration. Three weeks of broad-spectrum antibiotic treatment reduce the levels of DCA and S1P in the microbiome because these compounds are vital for hepatocyte proliferation and liver regeneration.

reduced graft BA overload, activation of YAP signaling, and improved post-transplant hepatocyte survival and proliferation, illustrating the translational potential in transplantation settings [34]. Roos et al. (2021) established human cholangiocyte (biliary) organoids from bile that retain a local cholangiocyte phenotype and can repopulate bile ducts in vitro, providing a biliary epithelial model relevant to ductular repair within the gut–liver axis [39]. Finally, Murphy et al. (2022) used gnotobiotic mice colonized with defined BA-transforming bacteria to demonstrate that the restoration of secondary BA pools fully rescues regeneration after partial hepatectomy in antibiotic-depleted animals, confirming the indispensable role of the microbiome in supplying regenerative BA signals [40]. Together, these studies delineate how microbiome-derived BAs, via FXR/TGR5 receptors and FGF15/19 effectors, orchestrate canonical and non-canonical pathways converging on hepatocyte priming, proliferation, and repair, offering multiple avenues for regenerative therapies in liver failure and post-resection recovery. Having established the gut–liver axis as a two-way signaling network, it is crucial to dissect the specific molecular species that traverse this route. Section 4 details the metabolic origins of bile acids, their microbial transformations, and the receptor-mediated pathways through which they exert systemic physiological effects.

4. Bile acids: metabolic origin and physiological roles

Bile acid (BAs) biosynthesis is initiated in hepatocytes via the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1), which converts cholesterol into primary BAs. Wang et al. (2014) showed in primary rat hepatocytes that insulin and fibroblast growth factors tightly repress CYP7A1 transcription, establishing endocrine feedback control over BA synthesis [41]. In 2005, Horvath and Gao demonstrated that ileal FXR activation by BAs induces the expression of the enterokine FGF15 (the murine ortholog of human FGF19), which returns to the liver to inhibit CYP7A1, thus completing a gut–liver negative-feedback loop [42]. At the same time, Parhofer and Barrett (2006) identified the 7α-dehydroxylase activity of Clostridium scindens as the principal microbial enzyme converting cholic acid into the secondary BA deoxycholic acid (DCA) [43], while Ohno et al. (2008) characterized bile salt hydrolase (BSH) enzymes in Lactobacillus species that deconjugate taurine- and glycine-conjugated BAs, modifying BA hydrophobicity and enterohepatic circulation [44]. Helguera et al. (2013) used germ-free versus conventional mice to reveal that the microbiome profoundly shifts the BA pool composition, increasing secondary BA levels and suppressing hepatic CYP7A1 expression via FGF15 feedback, thereby linking microbial metabolism to host BA homeostasis [45]. Vermulst et al. (2009) further showed that microbial-modified BAs engage the membrane receptor TGR5 on enteroendocrine cells to stimulate GLP-1 secretion and enhance energy expenditure, underscoring the integrative metabolic roles of microbiome-derived BA species [46].

Beyond synthesis and enterohepatic recirculation, BAs exert diverse physiological effects via nuclear (FXR) and membrane (TGR5/GPBAR1) receptors in the liver, intestine, and extrahepatic tissues. Watanabe et al. (2006) first cloned TGR5 in murine macrophage and hepatocyte cell lines, demonstrating that BA binding raises intracellular cAMP and activates downstream kinases [47]. Jonker et al. (2012) used primary human hepatocyte cultures to show that chenodeoxycholic acid (CDCA) selectively induces FXR target genes involved in lipid and glucose metabolism. In contrast, FXR antagonism disrupts these transcriptional programs [48]. Reich et al. (2016) revealed that tauroursodeoxycholic acid (TUDCA) activation of TGR5 promotes cholangiocyte proliferation via EGFR transactivation in cholangiocyte cell lines [49]. In a translational advancement, Golen et al. (2018) administered the semi-synthetic FXR agonist obeticholic acid to cholestatic rats before partial hepatectomy, and found that preloading BA signaling paradoxically downregulated hepatic FGFR4, yet enhanced STAT3 activation to accelerate remnant liver growth [38]. He et al. (2025) engineered probiotic strains expressing BSH to modulate host BA profiles in vitro, restoring FXR signaling in hepatocyte cultures that were compromised by antibiotic depletion [50]. Finally, Wu et al. (2024) utilized gnotobiotic mice colonized with defined BA-transforming bacteria to show that secondary BA reconstitution fully rescues liver regeneration after partial hepatectomy in antibiotic-treated animals, confirming the indispensability of microbiome-derived BAs for efficient hepatic repair [51]. Together, these studies delineate the metabolic origins of BAs, their microbial transformations, and their receptor-mediated physiological roles, establishing a basis for the therapeutic modulation of bile acid signaling. With the biosynthesis, enterohepatic circulation, and receptor engagement of bile acids defined, we can now focus on their direct impact on regenerative contexts. In Section 5, original studies are reviewed to trace how microbiome-modified bile acids serve as endogenous mediators driving hepatocyte proliferation and tissue repair.

5. Microbiome-derived bile acids in liver regeneration

The gut microbiota generates a diverse pool of secondary bile acids that extend beyond classical detergent functions and serve as potent signaling molecules in hepatic physiology. These microbiome-derived bile acids orchestrate signaling cascades that prime hepatocytes for regeneration by engaging nuclear receptors (e.g., FXR) and G protein-coupled receptors (e.g., TGR5). In 2012, Zhang et al. (2012) demonstrated that $FXR^{-/-}$ mice subjected to a 70 % partial hepatectomy exhibited delayed liver regrowth and reduced induction of the cell cycle regulator FoxM1b. In contrast, cholic acid supplementation accelerated regeneration in control animals, establishing BA–FXR signaling as essential for hepatocyte priming [52]. Lian et al. (2025) showed in murine hepatocyte cell lines that lithocholic acid activation of TGR5 potentiates STAT3 phosphorylation and cyclin D1 expression, thereby expediting S-phase entry after injury [53]. In parallel, Shackel et al. (2014) reported that $Fgf15^{-/-}$ mice display deficient JNK, ERK, and MAPK activation following two-thirds hepatectomy, leading to reduced hepatocyte proliferation, that and adenoviral Fgf15 reconstitution restored these pathways and normalized regenerative kinetics [54]. Meng et al. (2010) then applied a CCl_4-induced toxic injury model to demonstrate that pharmacologic FXR agonism with GW4064 attenuates centrilobular necrosis, up-regulates cyclin D1, and accelerates liver repair. In contrast, FXR deficiency prolongs tissue damage and impairs repair [55].

Translational studies have extended these findings to clinically relevant settings. Avalos-de Knight et al. (2019) treated brain-dead donor rat livers with recombinant FGF15 during cold ischemia. They observed reduced BA accumulation, YAP signaling activation, and enhanced post-transplant hepatocyte survival and proliferation [56–58]. Most recently, Liu et al. (2016) colonized gnotobiotic mice with defined bile acid–transforming bacteria and showed that restoration of secondary BA pools fully rescues liver regeneration after partial hepatectomy in antibiotic-depleted animals, confirming the indispensable role of microbiome-derived bile acids in endogenous hepatic repair [59,60]. These studies articulate a sequential framework in which microbiome-derived bile acids, via FXR, TGR5, and FGF15/19 effectors, orchestrate convergent signaling networks that drive hepatocyte proliferation and tissue regeneration (Fig. 2). After delineating the pro-regenerative actions of bile acids on mature hepatocytes, attention is turned to their influence on the liver's progenitor populations. Section 6 explores how bile acid signaling via FXR, TGR5, YAP, and Wnt pathways governs the activation, expansion, and differentiation of hepatic stem and progenitor cells.

6. Bile acid signaling in liver regeneration

The bile acid receptors FXR and TGR5 orchestrate hepatocyte survival, differentiation, and proliferation during liver regeneration [60–62]. The relationship between liver healing and hepatocyte replication is important in chronic damage situations because it enhances

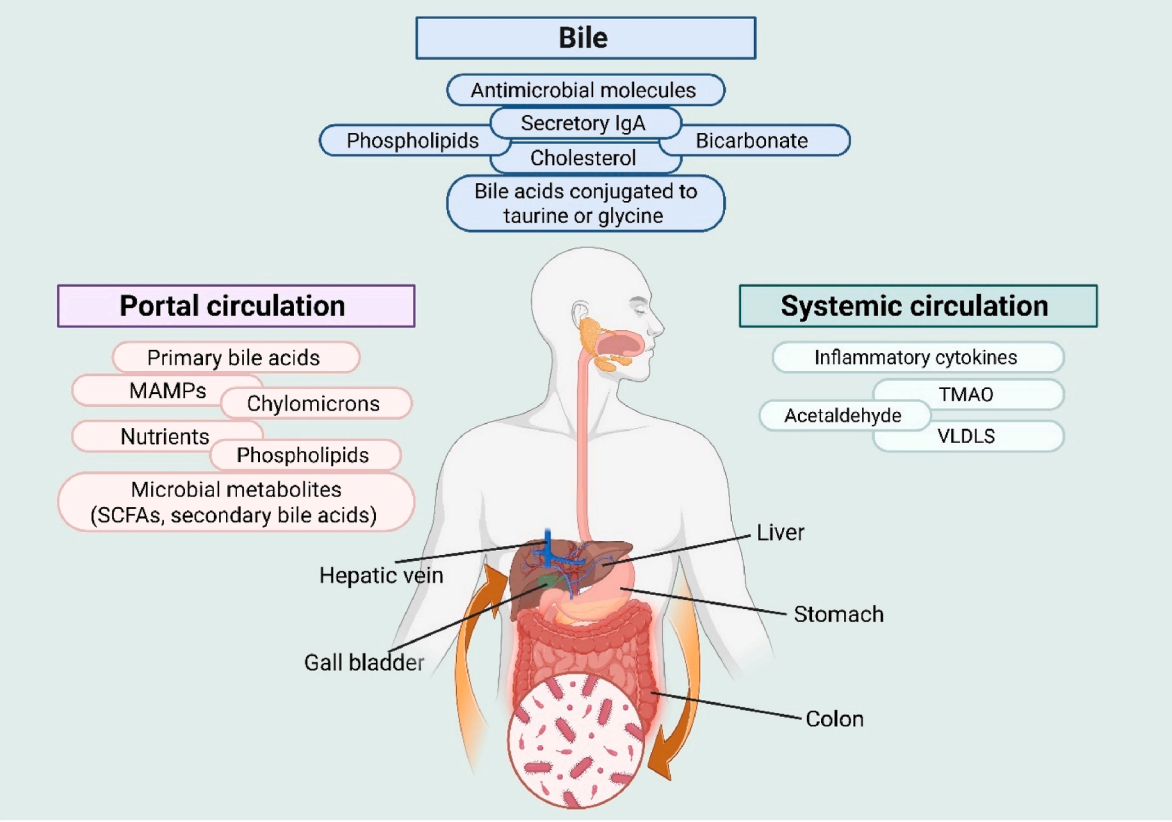


Fig. 2. Gut–Liver Axis: Bile and Microbial Metabolite Trafficking shows the circulation pattern along with the elements found in bile and gut chemicals throughout the human body. Bile contains taurine or glycine-conjugated bile acids, cholesterol and phospholipids, secretory IgA and antimicrobial substances, and bicarbonate, among other components. Compounds enter the digestive system and modify bacterial functions in the colon. Through portal circulation, the liver receives primary bile acids and nutrients, microbial metabolites, chylomicrons, and microbe- or pathogen-associated molecular patterns (MAMPs). Bloodstream entry occurs when VLDLs (very low-density lipoproteins), acetaldehyde TMAO (trimethylamine N-oxide), and inflammatory cytokines join blood circulation. Bile and metabolic activities display the interconnection between the gut microbiome and liver-body health systems.

liver recovery even when hepatocyte replication rates are limited. Bile acid-mediated pathways represent a potential therapeutic strategy for liver conditions, as they demonstrate the potential to boost the results of stem cell-based regenerative therapies [63,64]. FXR is a nuclear receptor primarily found in liver cells and intestinal tissue, where it acts as a bile acid activator. FXR regulates inflammation, lipid metabolism, and bile acid balance. During liver regeneration, FXR helps preserve tissue functionality by stimulating hepatocyte multiplication, lowering the formation of fibrous tissue, and fine-tuning immune function [65,66]. Fan et al.'s research revealed that FXR and TGR5 receptors trigger activation by bile acids during liver regeneration processes. FXR mitigates age-associated regenerative decline and promotes liver regeneration after surgical removal of the liver tissue. BA signaling is a critical metabolic pathway in liver regeneration because BA hydrophobicity and excretion are controlled by the membrane-bound receptor TGR5 [67, 68].

TGR5 is a G protein-coupled bile acid receptor expressed in immune and hepatic cells. The receptor is officially known as GPBAR1, but it is also known as TGR5. The receptor controls inflammation, cell growth, and bile acid interaction pathways to sustain essential liver regeneration. Activation of the TGR5 receptor supports tissue restoration and maintains proper liver balance during the healing process [69–71]. Experimental findings by Sorrentino et al. showed that stem cell population expansion with epithelial restoration occurs through the activities of BAs and TGR5 agonists. ISCs activated by TGR5 signaling trigger the YAP1 and SRC signaling pathways, enabling the body to regenerate after colitis and maintain homeostasis. The healing process of the intestinal epithelium requires TGR5, as damage to this receptor in ISCs produces intensified colitis symptoms [72,73]. In chronic injury, when hepatocyte replication is limited, liver progenitor (oval) cells ($EpCAM^{+}/CK19^{+}$) are activated. FXR signaling supports liver regeneration in vivo and is implicated in modulating progenitor responses, based on hepatectomy and toxic-injury models [52,55,64,74].

7. Preclinical liver regeneration insights

7.1. *In vitro models of hepatocyte proliferation*

Several in vitro platforms have been developed to model hepatocyte proliferation and screen for regenerative signals. March et al. (2015) described micropatterned co-cultures of primary human hepatocytes with stromal cells, which supported hepatocyte proliferation and maintained metabolic activity for over four weeks [75]. In 2020, Schneeberger and colleagues developed $Lgr5^{+}$ biliary organoids, also known as cholangiocyte organoids, which exhibit strong self-renewal capabilities. Although these cells can be guided to develop some characteristics similar to hepatocytes, they do not function as fully mature hepatocytes [76]. Takebe and Taniguchi (2013) generated vascularized liver buds by combining iPSC-derived hepatic endoderm with mesenchymal and endothelial cells; after transplantation into mice, these constructs expanded in situ [77]. Rennert et al. (2015) used three-dimensional liver tissues in microfluidic "liver-on-a-chip" devices, where continuous perfusion increased hepatocyte proliferation and cytochrome P450 activity compared with static cultures. [78]. Ijima et al. (2009) seeded primary rat hepatocytes onto decellularized liver extracellular-matrix scaffolds and observed a two-fold increase in DNA

synthesis relative to collagen gels [79]. Tran et al. (2024) applied a CRISPR activation screen in HepaRG cells to identify transcription factors such as E2F1 and FoxM1 that drive entry into S phase [80]. These platforms have identified key growth factors (HGF, EGF, FGF19) and matrix components (laminin-511, fibronectin) that regulate hepatocyte cell cycle re-entry and support high-throughput testing of small-molecule agonists.

7.2. Rodent injury models and cellular mechanisms

The two-thirds partial hepatectomy (PH) model, first described by Higgins and Anderson (1931) and refined by Mitchell and Willenbring (2008), induces synchronized hepatocyte proliferation, peaking 24–48 h after surgery [81]. Carbon tetrachloride (CCl_4)–induced centrilobular necrosis models have been used to study inflammatory and stellate cell contributions, and interleukin-6 and TNFα signaling are required for hepatocyte priming [82]. Bile duct ligation (BDL) models trigger cholangiocyte proliferation and ductular reactions, mediated in part by TGR5 activation [83]. FXR-deficient mice subjected to PH exhibit delayed regeneration and reduced FoxM1b induction, highlighting the role of nuclear receptors in cell cycle regulation [74]. In the retrorsine-PH paradigm, mature hepatocyte division is blocked, revealing the activation of $EpCAM^{+}$ oval cells that drive liver repair [84]. These models have detailed cytokine release patterns (IL-6, HGF), growth factor receptor activation (c-Met, EGFR), and downstream networks (STAT3, β-catenin) that coordinate hepatocyte entry into the cell cycle and serve as platforms for testing targeted interventions in vivo.

7.3. Biomarkers and signaling pathways with translational potential

Translating preclinical findings into clinical applications requires reliable biomarkers and druggable pathways. Wnt/β-catenin signaling, as implicated by Monga et al. (2001), promotes hepatocyte proliferation after PH, and serum Dkk1 has been proposed as a regenerative biomarker in patients with cirrhosis [85]. The Hippo–YAP pathway regulates organ size: YAP activation accelerates liver regrowth in mice [86], and elevated plasma YAP levels correlate with recovery in human acute liver failure [87]. FXR agonists, such as obeticholic acid, enhance FoxM1 expression and hepatocyte proliferation in rodent cholestatic injury [38] and are under investigation for postoperative liver insufficiency. FGF19 analogs (e.g., aldafermin) have shown safety and upregulation of proliferative gene clusters in patients with MASH (metabolic dysfunction–associated steatohepatitis), indicating potential metabolic and regenerative benefits [88]. Circulating microRNA-122 levels increase after resection and predict regenerative capacity [89]. Finally, serum HGF and EGF kinetics measured by ELISA in rodent PH models parallel postoperative human profiles, suggesting their value as companion diagnostics for growth-factor–based therapies [90].

8. Clinical translation and therapeutic development

The use of probiotics, altered bacteria, and fecal microbiota transplantation belong to the category of microbiota-targeted therapeutics that medical researchers have utilized during liver regeneration therapeutic development to enhance gut-liver interaction outcomes [91,92]. It is possible to evaluate whether pharmacological agents, such as bile acid derivatives and FXR agonists, improve hepatic recovery by activating regeneration signaling pathways. Clinical trials have assessed these methods; however, preclinical translation remains a challenge because of variability in microbiomes, regulatory difficulties, and safety constraints that prompt the requirement for specific treatment protocols [93,94]. Fecal microbiota transplantation (FMT) involves the delivery of donor feces via the gastrointestinal tract to restore the gut microbial balance. FMT aids in gut-liver axis communication, inflammation reduction, and dysbiosis correction during liver regeneration. This treatment promotes better liver restorative processes, benefiting overall liver health, especially in cirrhosis and hepatic encephalopathy [95]. According to Bajaj et al., modifying the gut microbiota is an innovative treatment approach for liver disease. Research models have demonstrated the role of the microbiome in the pathophysiological processes of liver disease. This review outlines precision-restoring methods that utilize engineered bacteria, postbiotics, and phages, in addition to the untargeted therapy of probiotics and fecal microbiota transplantation, to recover liver function [96].

9. Industrial perspectives and regulatory challenges

Bile acid- and microbiome-based therapeutics are valuable for liver regeneration and novel liver disorder treatments through commercial development. The safety and effectiveness requirements for these treatments are difficult to satisfy because both bile acid modulators and live biotherapeutics are subject to multifaceted regulatory frameworks [97,98]. Regulatory bodies should address the challenges of live microbial product certification and maintain a consistent product quality. The practice of regenerative medicine calls for rigorous examination of both long-term impacts and unexpected secondary effects, as it involves ethical challenges when modifying the human microbiome [99,100]. Therapy application requires a properly calculated equilibrium between innovative approaches, secure operations, and ethical compliance [101]. The therapeutic value of substances of human origin (SoHO), including stem cells, blood, and tissues, lies in their capacity to promote tissue repair, modulate immune responses, and stimulate hepatocyte proliferation. Their therapeutic use presents encouraging opportunities for treating chronic liver disorders and liver failure in regenerative medicine [102]. Rodriguez et al. indicated that Europe is adopting new regulatory changes to accommodate the rising demand for microbiota-based treatments. Emerging pharmaceuticals' therapeutic benefits require further advances in microbiome regulatory science, and the Regulation on Substances of Human Origin (SoHO) enables substantial changes, according to Rodriguez et al. [103]. The Microbiome Therapeutics Innovation Group (MTIG) represents businesses that create microbiome-based products and FDA-approved therapeutic methods. The Microbiome Therapeutics Innovation Group (MTIG) addresses liver-related diseases. It focuses on establishing a sustainable economic framework with financial backing and a regulatory environment to accelerate the development of microbiome drugs. The initiative executes concrete policy and regulatory solutions for the rapidly evolving microbiome field through collaboration between patients, healthcare providers, and policymakers [104]. Barberio et al. studied the vital manufacturing challenges of live biotherapeutic products (LBPs) along with regulatory gaps and proposed upcoming regulations. The authors emphasized the need for regulatory partnerships among academic institutions, business entities, and regulators through MTIG while identifying the strengths and limitations of current practices to advance microbiota-based drugs toward clinical use [105] (Fig. 3; Table 1).

10. Future directions and emerging opportunities

10.1. Integrative multi-omics for bile acid regeneration

Advancing our understanding of bile acid-mediated liver regeneration requires the integration of metagenomics, transcriptomics, metabolomics, and proteomics [115,116]. These technological tools enable scientists to evaluate host-microbiome interactions in depth, showing how microbial bile acid metabolites modify hepatic organ immunological regulation, receptor signaling, and gene expression patterns. The capability to identify essential regulatory mechanisms in regeneration exists by combining systems biology with computer modeling [117,118]. The discovery of new therapeutic targets and biomarkers has become feasible because of all-encompassing screening procedures. Multi-omics strategies can effectively understand the complexities of the gut-liver axis while creating practical strategies for regenerative

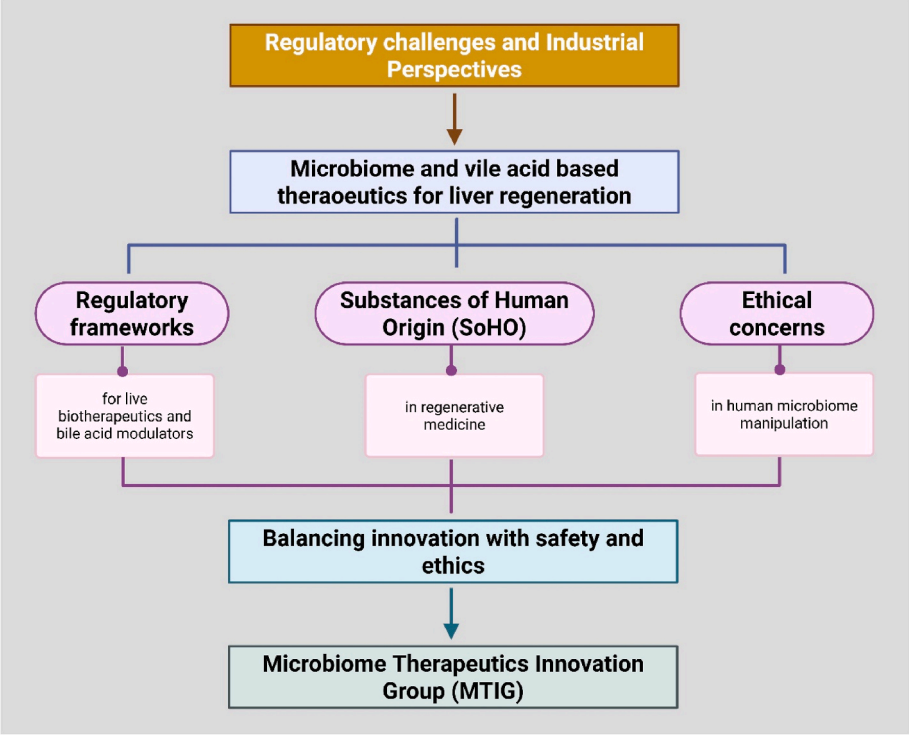


Fig. 3. Ethical and Regulatory Landscape of Microbiome-Bile Acid Therapeutics This figure details both moral and regulatory barriers during treatment development utilizing bile acids and the microbiota for liver regeneration purposes. According to the figure, the field demands better regulatory oversight of live biotherapeutics while also needing classifications for human-origin substances in regenerative medicine and moral considerations about microbiota manipulation. The Microbiome Therapeutics Innovation Group (MTIG) emerged to handle intricate multidisciplinary problems after recognizing the need for ethical and safety-focused innovations in addition to creativity.

Table 1
The table provides extensive information about liver regeneration processes by explaining cellular participants and signaling protocols and reporting immune-microbial processes and regeneration detection methods.

Cellular Player	Signaling Pathway	Immune-Microbial Interaction	Bile Acid Signaling	Regeneration Markers and Tools	Reference
Hepatocytes	Wnt/β-catenin, Hippo/YAP, IL-6/STAT3	Modulated by macrophage cytokines	FXR, TGR5 activation by BAs	PCNA expression, lineage tracing	[106] [107]
Liver progenitor cells	Notch, Wnt	Stimulated during hepatocyte loss; immune regulation required	FXR/TGR5 promotes progenitor activation	SOUP profiling, organoids	[108]
Biliary epithelial cells	Notch, YAP	Interact with immune cells for ductal repair	FXR-TGR5 regulates cholangiocyte function	Single-cell RNA sequencing	[67,107]
LSECs	VEGF, Angiocrine signaling	Recruit immune cells for vascular remodeling	BA signaling affects LSEC angiocrine function	Angiocrine profiling, scRNA-seq	[108]
Kupffer cells	TLR4, NF-κB	Sense LPS secrete IL-6 and TNF-α to trigger regeneration	Indirectly modulated by BA-mediated FXR/TGR5	Cytokine profiling	[108,109]
MDSCs	STAT3, PPARD	Suppress inflammation, support regeneration	Butyrate from microbiota enhances MDSC via FXR/HDAC3 inhibition	Flow cytometry, immune assays	[12]
Gut microbiota	FXR, TGR5 via BAs; TLR4 via LPS	SCFAs and LPS modulate hepatic inflammation and repair	Microbially conjugated BAs activate FXR, TGR5	Metabolomics, germ-free models	[17,110, 111]
Microbiota-derived metabolites (e.g., SCFAs, BAs)	FXR, VDR, TGR5	Modulate immune cell recruitment and cytokine profiles	FXR/TGR5 affects immune regulation and hepatocyte proliferation	Nutrigenomics, bile acid profiling	[67,112]
HGF from mesenchymal cells	c-Met pathway	Enhanced by microbiota and immune stimuli	HGF-induced proliferation influenced by BA signaling	HGF assays, partial hepatectomy models	[110]
FXR, TGR5 receptors	FXR: nuclear; TGR5: GPCR	Modulate immune cell function and reduce fibrosis	Regulate BA homeostasis, enhance hepatocyte regeneration	BA agonists, receptor knockout models	[67,113]
Cyp2c70 enzyme	BA synthesis regulation	Affects BA composition and immune response	Produces muricholic acids; influences FXR/TGR5 pathways	Knockout mouse models	[112]
Enterohepatic cycle	BA recycling pathways	Maintains BA pool, modulates immunity via microbiota	BA reabsorption activates FXR/TGR5, supporting regeneration	Dietary and surgical models	[114]
Lipopolysaccharide (LPS)	TLR4/NF-κB	Triggers hepatic inflammation, primes regeneration	Indirectly influences FXR/TGR5 pathways	Endotoxin assays	[109]

medicine based on molecular discoveries [119,120].

10.2. Probiotic design for bile acid synthesis

Synthetic biology enables the creation of advanced probiotics that produce restorative bile acid metabolites with enhanced biosynthetic capabilities [121,122]. Scientists can enhance bile acid receptor activation by adjusting microbial strains to produce bile salt hydrolases and hydroxysteroid dehydrogenases, which can then be deployed in situ. Altered probiotics are biotherapeutic agents that produce beneficial gut metabolites through targeted and persistent operations [123,124]. Assured administration charts enable the thorough modulation of pharmaceutical medicines through a controlled method that generates safer substitutes. Synthetic probiotics will emerge as specific instruments for liver regeneration control through microbiome treatment designs because of advances in technologies such as CRISPR-based genome editing and chassis optimization [125,126].

10.3. Host–microbe personalized regeneration

The need for individualized microbiome-based regenerative medicine exists because people show different responses to bile acid metabolism receptor activity and microbiome composition. The combination of machine learning techniques and host genetic investigation with microbiome profiling allows healthcare providers to produce personalized therapy programs based on specific patient and microbial characteristics [126,127]. Three examples of personalized therapies are customized probiotic formulations, selective bile acid receptor modulators, and specific prebiotic chemicals. By using patient-specific treatment strategies, healthcare professionals can enhance therapeutic outcomes and minimize adverse effects, especially among patients from diverse backgrounds who present with different liver conditions. Adaptive medicines can be personalized according to each patient's disease and microbiome changes.

11. Conclusion

Hepatic regeneration requires modulation by microbial bile acid metabolites because of the complex interactions between host metabolism, gut microbiota, and liver repair mechanisms. Secondary bile acids undergo microbial enzyme conversion after activating liver receptors through FXR and TGR5 mechanisms to affect multiple liver functions. Studies have shown that receptor activation has three main effects on hepatic cells: it promotes proliferation while decreasing inflammation and controlling the activity of essential liver stem and progenitor cells. Research on germ-free animal studies and bacterial therapies alongside receptor agonists has shown that bacterial bile acid breakdown functions in liver regeneration pathways and as an output of gastrointestinal and hepatic system interactions. These findings validate bile acid signaling as a therapeutic target for enhancing liver restoration after damage. Bile acid signaling provides a system-wide therapeutic opportunity for the treatment of liver diseases because it controls metabolic functions and interacts with immune response mechanisms and regenerative networks. Bile acid metabolites generated by the microbiome represent a new therapeutic opportunity as regenerative medicine continues to advance toward individualized treatment methods. Three potential transformative liver regeneration therapies include the development of probiotic microorganisms to generate specific bile acid compounds, administration of patient-specific treatments, and modification of gut microbial communities. The incorporation of basic science with therapeutic approaches depends on additional research using patient-microbiome profiling, omics technologies, and synthetic biology techniques to create useable therapeutic methods for hepatic regeneration.

Consent to participate

Not applicable.

Author contributions

SNP, KG, MR, and SVM: Conceptualization, Methodology, Software. SR, HA, and PSK: Writing – Original Draft Preparation. JD, SKS, and GG: Data curation, writing, Review & Editing. LSW: Data Curation and Methodology. VK: Methodology and Software. VS: Conceptualization, Methodology, Software.

Availability of data and material

Not Applicable.

Code availability

Not applicable.

Ethics approval

Not applicable.

Consent for publication

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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