Gut-liver-kidney axis: A systems biology framework for understanding and treating chronic kidney disease (Review)

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Abstract. Chronic kidney disease (CKD) is traditionally studied through an organ-centric paradigm, despite its frequent coexistence with intestinal dysbiosis and metabolic dysfunction-associated steatotic liver disease, which confers a 38% increased CKD risk. Multi-organ crosstalk along the gut-liver-kidney axis remains inadequately addressed in current guidelines. The present study aimed to establish the gut-liver-kidney axis as an integrated systems biology framework for understanding CKD progression and to translate this framework into diagnostic, therapeutic and clinical trial strategies. The present review aimed to combine mechanistic summaries with systems biology perspectives, including weighted gene co-expression network analysis, Bayesian causal inference and ordinary differential equation-based dynamic modeling, to map bidirectional signaling across microbial, metabolic, inflammatory and hemodynamic dimensions, with diabetic kidney disease (DKD) as the principal exemplar. The axis operates through anatomically and molecularly defined positive feedback loops in which gut dysbiosis drives barrier failure and endotoxemia, amplifying hepatic lipotoxicity and bile acid dysregulation, precipitating renal tubular injury and fibrosis. This self-perpetuating cycle, sustained by uremic toxin signaling, dysregulated peroxisome proliferator-activated receptor/farnesoid X receptor (FXR)/Takeda G protein-coupled receptor 5 (TGR5) pathways and trained immunity (a persistent hyperinflammatory state of innate immune cells driven by epigenetic and metabolic reprogramming), is most pronounced in DKD. Microbiome-targeted interventions and FXR/TGR5 modulators are as the most clinically advanced axis-directed strategies, though most remain at preclinical or early-phase stages. Reframing CKD as gut-liver-kidney axis dysfunction enables systems-level mechanistic integration, precision diagnostics through composite microbiome-metabolomic signatures, and adaptive trial designs targeting upstream pathology, providing a foundation for incorporating axis-based approaches into future CKD management.

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1. Introduction

The principal limitation of kidney disease (KD) research is the organ-centric view that renal pathology can be separated from the contributions of other organs. Early description of the renin-angiotensin-aldosterone system in hypertension-mediated nephropathy transformed understanding of intrarenal hemodynamics (1,2). By the late 1990s, the 'hyperfiltration theory' and its systematic account of diabetic glomerulosclerosis through renal hemodynamic alterations offered key insights into the pathophysiological mechanisms and therapeutic targets for KD (3,4). More recently, the development of sodium-glucose cotransporter-2 (SGLT2) inhibitors and

other renal-directed therapies has continued to augment the therapeutic spectrum (5,6). Nevertheless, clinical problems, particularly in individuals with diabetic KD (DKD), which commonly occurs concomitantly with other complications, remain unresolved. This suggests the intricate organ crosstalk between the liver and intestine, as an important metabolic and inflammatory driver in renal dysfunction, requires further investigation to understand multi-organ involvement in disease progression (7,8). This organ-centered approach prevents proper understanding of the multi-organ injury axis of visceral dysbiosis, gut barrier failure, hepatic insulin resistance and lipotoxicity in tubulocentric injury (9-11). However, this knowledge gap persists despite advancements in clinical practice as the current guidelines dedicate minimal attention to gut-liver-kidney crosstalk in the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) recommendations (12).

Against this historical basis and in the context of comorbidities now recognized as a key challenge in global health, multi-organ communication networks are essential for systemic homeostasis (8). Notably, a complex interplay exists between intestinal dysbiosis, metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic KD (CKD), all episodic or concurrent, owing to common risk factors (such as insulin resistance, obesity, type 2 diabetes and systemic inflammation) and pathophysiological mechanisms (including gut dysbiosis, chronic low-grade inflammation, oxidative stress and metabolic dysregulation). The gut microbiome serves as an initiator and mediator of this axis, generating metabolites and inflammatory cues that have effects on hepatic and renal function. In addition to their classic roles, recent research indicates that kidneys impact on pulmonary, intestinal, hepatic and muscular functions, as well as on neurological function in altered states, with multi-organ dysfunction responsible for increasing death and disability (13).

Therefore, composite endpoints combining gut permeability and microbiome testing should be integrated in clinical trials of patients with CKD. However, classic renal-metabolic studies incorporate gut-derived uremic toxins and liver metabolic factors, evaluated against kidney-relevant outcomes. Nevertheless, this nephrocentric but integrative model would more comprehensively represent the role of intestinal dysbiosis and hepatic damage in CKD progression, thus offering insight into new therapeutic targets that afford renoprotection by targeting these upstream causes of kidney injury from the gut-liver axis. This is particularly relevant as a recent meta-analysis reported a 38% increased CKD risk (95% CI: 1.28-1.50) in MASLD populations (14). Additionally, in June 2023, the global hepatology societies changed the terminology non-alcoholic fatty liver disease to MASLD based on the Delphi consensus of >200 experts (15). This modification was made due to concerns about stigmatizing language and a more accurate description of the metabolic pathogenesis involved in gut-liver-kidney axis dysfunction (16).

The present review aimed to provide a novel viewpoint and extend current single-organ research by examining the gut-liver-kidney axis from microbial, metabolic, inflammatory and hemodynamic perspectives, with DKD as an example of multimorbidity. Thus investigating the bidirectional signaling may provide insight into how altered gut microbiota and permeability precede and augment liver and kidney dysfunction. In addition, the present study aimed to suggest novel diagnostic strategies using microbiome signatures and gut-derived metabolites as early biomarkers of kidney injury and therapeutic strategies to manipulate the intestinal ecosystem for renoprotection. Existing reviews have largely treated the axis components in isolation, with gut-kidney literature focusing on microbial dysbiosis and uremic toxins, the gut-liver literature on hepatic metabolic dysfunction and the MASLD-CKD literature on epidemiological association, while typically treating the liver as a passive conduit rather than an active regulatory hub (17-19). The present review aimed to position the liver as a co-equal node uniting the gut-kidney and gut-liver axes into a single tripartite framework. The present study aimed to apply systems biology methodology that reframes these mechanisms as an analyzable, self-perpetuating network and describe subtype specificity (DKD vs. non-DKD CKD) and therapeutics strategies (20,21). The literature search strategy and selection criteria are provided in Supplementary material 1.

2. Physiological basis of gut-liver-kidney communication

The gut-liver-kidney axis is a complex physiological system that mediates systemic homeostasis through sophisticated anatomical connections, molecular signaling pathways and integrated physiological responses (Fig. 1). These organs have evolutionarily conserved regulators of bidirectional communication, which are key for nutrient assimilation, immune surveillance, detoxification and fluid-electrolyte balance (22). An appreciation of this three-organ association is critical to better understand how alterations in one organ can lead to pathogenic cascades that affect distal tissue in other organs but share a common link in terms of etiology and may impact the development and progression of KD.

Anatomical foundations of interorgan communication

Vascular networks: Portal circulation and systemic connections. Vascular crosstalk between the gut, liver and kidney establishes a complex circulatory network that is integral for interorgan crosstalk. This network relies on portal circulation to send ~75% of the hepatic blood flow from the capillaries in the intestine into the liver to allow for the first-pass metabolism of absorbed nutrients and toxins before they are delivered throughout the body by systemic circulation (23,24). Hepatic venous outflow, which constitutes ~25% of the cardiac output, influences renal flow through changes in central venous pressure (25). This linear arrangement is key for handling and eliminating xenobiotics.

Lymphatic pathways linking intestinal, hepatic and renal systems. The lymphatic system is a key communication system in the gut-liver-kidney axis as it absorbs most dietary long-chain fatty acids (FAs) in the intestine, especially via lacteals in the villi, thus avoiding first-pass hepatic metabolism (26-28). Moreover, intestinal lymphatics carry immune cells and cytokines of gut origin, reinforcing an alternative route for communication besides the portal circulation (29,30). The liver is the largest lymph-producing organ, contributing 25-50% of the lymph flow in the thoracic duct, and is affected by hemodynamic variation in intrahepatic

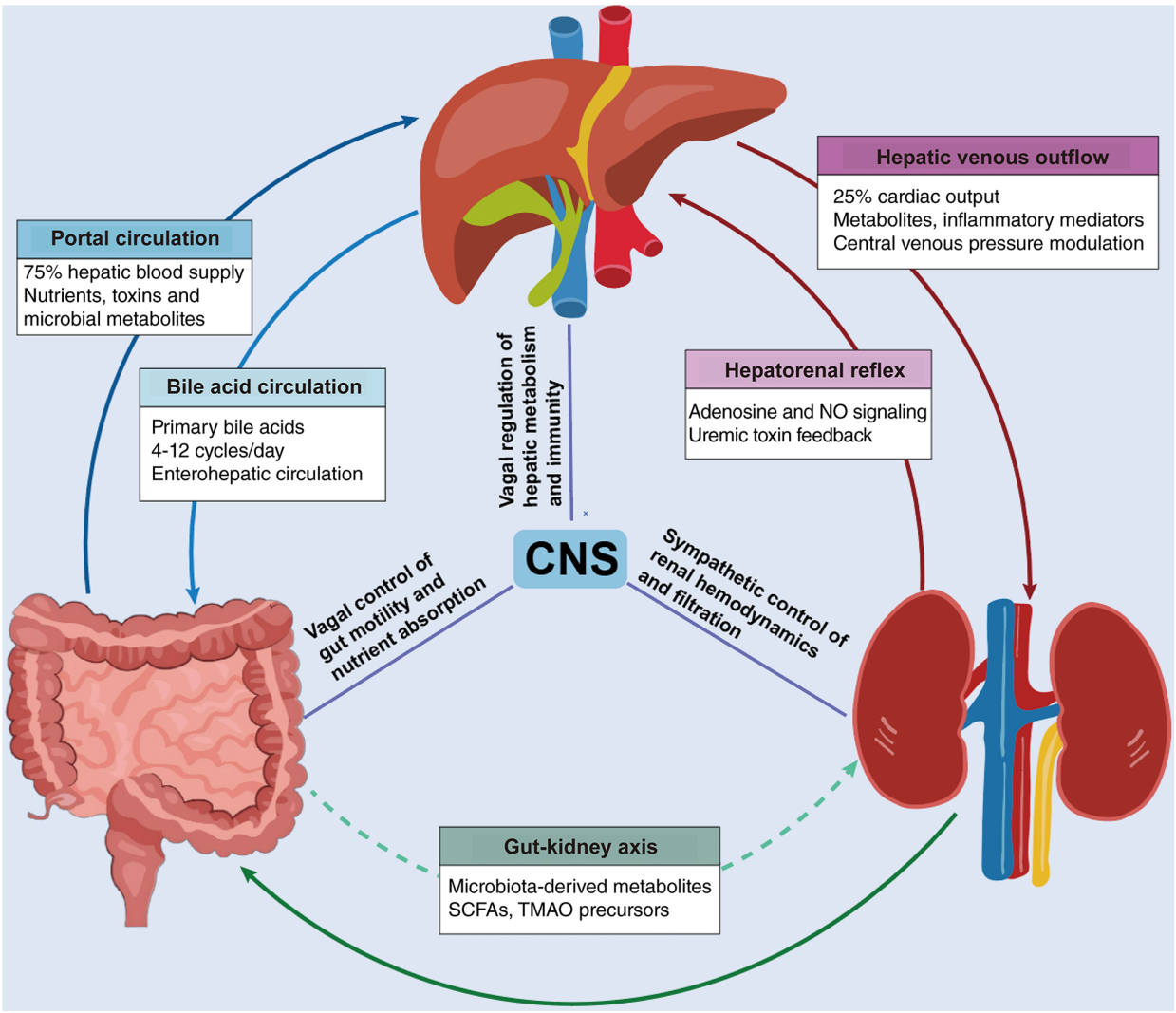

Figure 1. Anatomical and regulatory framework of the gut-liver-kidney axis. CNS-mediated autonomic regulation coordinates gut, liver, and kidney function. CNS, central nervous system; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide.

microcirculation (31,32). Thus, hepatic lymphatics serve a role in fluid homeostasis and contribute to the immune system and lipid metabolism by transferring immune cells, antigens and lipids to the surrounding lymph nodes (31,33). The lymphatic vessels in the kidneys are primarily distributed in the renal cortex. Mapping techniques have indicated that bidirectional crosstalk occurs between the renal, hepatic and lymph nodes (34,35).

Neural connectivity: Autonomic regulation and sensory feedback. Neural regulation of the gut-liver-kidney axis is coordinated by the central nervous system (CNS) through autonomic pathways. The autonomic NS (ANS), comprising the parasympathetic (vagal) and sympathetic branches, mediates bidirectional communication between the brain and peripheral organs (36). Vagal stimulation in the gut influences motility, secretion and stimulation of blood flow, which contribute to the digestion and absorption of nutrients (37). Additionally, intestinal motility and gut-organ communication are regulated by the enteric nervous system and sympathetic innervation, which provide local and systemic neural control, independent of direct vagal input (38). The ANS, particularly its sympathetic portion, controls the renal blood flow, glomerular filtration rate (GFR) and renin secretion (39,40). Sensory feedback loops are key as enteric sensory neurons sense luminal perturbations, such as nutrient content and mechanical stretch, and transmit these signals to the CNS or afferent systems, resulting in CNS-mediated adaptations in gut, liver and kidney function (41-43). In conclusion, the balance between autonomic regulation and sensory feedback within this neural network maintains organ health and its disruption can lead to disease.

Physiological molecular signaling pathways. The gut-liver-kidney axis maintains homeostasis through complex molecular signaling networks (Fig. 2), including endocrine orchestrators, metabolic intermediaries and beneficial microbial metabolites that coordinate bidirectional interorgan communication.

Endocrine orchestrators

Gut-derived hormones. Gut hormones serve as key mediators in the gut-liver-kidney axis, serving as notable endocrine signals that coordinate metabolic, immune and homeostatic balance. Glucagon-like peptide-1 (GLP-1), predominantly synthesized in enteroendocrine L cells of the distal small

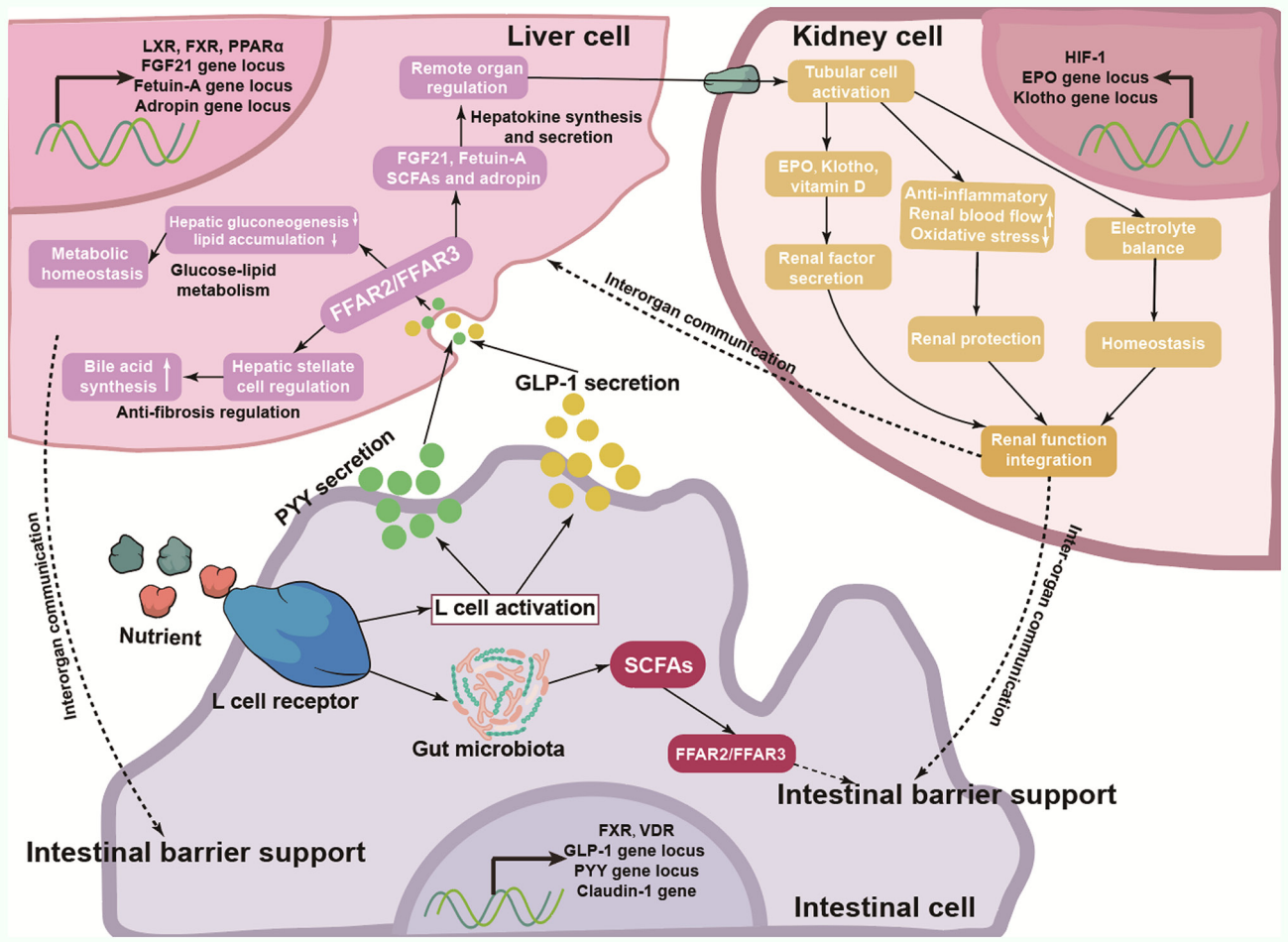

Figure 2. Molecular signaling networks underlying physiological communication within the gut-liver-kidney axis. LXR, liver X receptor; FXR, farnesoid X receptor; FGF, fibroblast growth factor; FFAR, free fatty acid receptor; PYY, peptide YY; GLP, glucagon-like peptide; SCFA, short-chain fatty acid; VDR, vitamin D receptor; EPO, erythropoietin; HIF, hypoxia-inducible factor; PPARα, peroxisome proliferator-activated receptor α.

intestine and colon, stimulates insulin release, improves glucose tolerance and exerts hepatoprotective and nephroprotective properties (44). In the liver, GLP-1 receptor stimulation may minimize decreased hepatic gluconeogenesis and lipid deposition as well as inhibit MASLD development (45). Additionally, GLP-1 attenuates renal inflammation and fibrosis by suppressing inflammatory signaling and antioxidant activity in the kidney (46). Another gut hormone secreted by intestinal L cells, peptide YY (PYY), affects liver metabolism by controlling lipid and glucose homeostasis (47,48). PYY may exert renoprotective effects, possibly through the amelioration of renal hemodynamics and oxidative stress (49). In CKD, and particularly in DKD, progressive enteroendocrine L cell dysfunction and GLP-1 resistance diminish this sustained renoprotective signaling, preventing inhibition of tubulointerstitial inflammation and contributing to the accelerated estimated GFR (eGFR) decline that GLP-1 receptor agonists partially attenuate in clinical trials (50,51).

Hepatokines. Hepatokines serve as key mediators of regulation and communication between organs in the gut-liver-kidney axis. Fibroblast growth factor 21 (FGF21), an endocrine factor primarily produced in the liver, serves a crucial role in regulating global energy metabolism by increasing the hepatic and adipose FA oxidative capacity and modulating glucose homeostasis through activation of FGFR1-βKlotho (52-54). FGF21 plays a key role in systemic metabolic control. Additionally, FGF21, a key index of metabolic adaptation, serves a role in nephroprotection by enhancing renal function, relieving inflammatory response and inhibiting fibrosis progression (55). Similarly, glycoprotein fetuin-A, which paradoxically causes insulin resistance, also controls calcium metabolism (56). Under physiological conditions, fetuin-A is maintained at a level that balances metabolic functions across the hepatorenal compartment (57,58). Furthermore, adropin is a novel hepatokine that maintains cell health by promoting mitochondrial activity and insulin sensitivity (59). In the gut-liver-kidney axis, adropin prevents metabolic crosstalk, enhancing intestinal barrier function and promoting hepatorenal cell protection in an AMPK-dependent manner (60,61). Together, these hepatokines represent diverse interorgan networks that promote systemic metabolic homeostasis and are implicated in orchestrating disease pathogenesis along the gut-liver-kidney axis. Although other liver-derived factors (angiopoietin-like protein family members, leukocyte cell-derived chemotaxin 2) have been implicated in systemic metabolic regulation, FGF21, fetuin-A and adropin have the strongest mechanistic and clinical evidence within the gut-liver-kidney axis (62,63). When these hepatokine networks are disrupted in CKD, as occurs with the FGF21 resistance and elevated fetuin-A characteristic of MASLD-associated DKD,

their renoprotective and anti-fibrotic actions are lost, directly favoring renal lipid accumulation, oxidative injury and fibrosis progression (63,64).

Renal-derived factors. Renal-derived factors are essential for the orchestration of metabolic homeostasis and organ crosstalk that occurs within the gut-liver-kidney axis. Erythropoietin (EPO), a hormone secreted by the peritubular interstitial fibroblasts, exhibits anti-inflammatory and anti-fibrotic properties in addition to its classical function in erythropoiesis (65). EPO contributes to hepatic tissue regeneration and regulates gut immune responses associated with the preservation of intestinal barrier function (66,67). Klotho, a transmembrane protein predominantly found in the kidney, is a key antiaging factor that ameliorates insulin resistance and inhibits oxidative stress in kidney, liver and intestine (68). In the context of the gut-liver-kidney axis, klotho inhibits organ fibrosis and modulates gut microbiota composition, contributing to coordinated metabolic and inflammatory regulation across organs (69,70). Vitamin D is converted to its biologically active form 1,25-dihydroxyvitamin D via renal hydroxylation, which confers pleiotropic protective effects (71). Active vitamin D promotes intestinal barrier function to improve hepatic lipid metabolism and inhibits the progression of renal injury (72,73). Consistent with these protective roles, deficiency or impaired metabolism of active vitamin D is associated with an increased risk of CKD, MASLD and intestinal disease (74-76). Taken together, these renal factors demonstrate complexity that characterizes the endocrine role of the kidney in regulating systemic physiology. Table I summarizes the key signaling molecules mediating the gut-liver-kidney axis communication, including their primary sources, receptor targets, biological function, axis-specific mechanisms and pathological alterations in CKD.

Metabolic intermediaries

Bile acids as signaling molecules. Bile acids, which are important in lipid digestion (77), are signaling molecules that play a key role in the gut-liver-kidney axis. These lipophilic molecules are produced from cholesterol in the liver and undergo enterohepatic circulation, shuttling between the liver, intestine and enterohepatic organs (78,79). Bile acids are also recognized by nuclear receptors, such as farnesoid X receptor (FXR), and membrane-bound receptors, including Takeda G protein-coupled receptor 5 (TGR5) (80). FXR activation in the liver and intestine affects bile acid synthesis, transport and metabolism (81), whereas TGR5 activation in enteroendocrine and immune cells decrease inflammation and regulates energy metabolism (82,83). Under physiological conditions, bile acid signaling functions in metabolic homeostasis and protects organs in the gut-liver-kidney axis. In CKD, impaired renal clearance and altered bile acid composition convert this homeostatic signaling into a driver of injury: Excess and structurally altered bile acids activate pro-inflammatory and pro-fibrotic programs in renal tubular cells, directly linking bile acid dysregulation with interstitial fibrosis and functional decline.

Beneficial microbial metabolites. Microbial metabolites are key mediators of the crosstalk between organs in the gut-liver-kidney axis. Short-chain FAs (SCFAs), such as acetate, propionate and butyrate, are products of gut microbiota fermentation of dietary fiber. SCFAs serve multiple roles in the human body, including acting as an energy source for colonic epithelial cells and modulating gut barrier formation and immune responses (84). SCFAs affect the lipid and glucose metabolism in the liver, thereby decreasing hepatic steatosis and improving insulin sensitivity (85). Additionally, SCFAs exert anti-inflammatory and anti-fibrotic effects that decrease renal injury (86,87). Mechanistically, these SCFAs have distinct receptor-binding profiles and physiological roles. Acetate (2C SCFA), which accounts for ~60% of total SCFAs, mainly stimulates free FA receptor 2 (FFAR2) and FFAR3 and serves a role in metabolism in hepatocytes and renal tubular cells (88,89). Propionate (3C SCFA), which accounts for 20% of the total SCFAs, inhibits histone deacetylases (HDACs), preferentially activates of G protein-coupled receptor 41 (GPR41) and enhances anti-inflammatory and metabolic functions (90,91). However, butyrate (4C SCFA and the most biologically active SCFA), exerts an anti-HDAC effect via GPR109A activation and direct metabolic effects on colonocytes in addition to stellate cells in the human liver, despite accounting for 20% of SCFAs (92,93). The receptor selectivity and metabolic differences of these SCFAs allow coordinated signals throughout the gut-liver-kidney network. These protective metabolites are the health-promoting part of microbe-host crosstalk, which ensures systemic health and balance along the gut-liver-kidney axis. For example, supplementation with SCFAs, particularly butyrate, initiates coordinated anti-inflammatory effects across the gut-liver-kidney axis. At the intestinal level, butyrate enhances epithelial barrier integrity and suppresses pro-inflammatory signaling by inhibiting HDAC (94,95). These effects decrease microbial translocation and the systemic inflammatory burden. In the liver, SCFA-mediated modulation of bile acid signaling and FXR activity contributes to improved metabolic homeostasis and the attenuation of hepatic inflammation (95). Downstream, decreased systemic inflammatory signaling and improved metabolic profiles are associated with decreased renal inflammatory activation and fibrosis, demonstrating a coordinated anti-inflammatory cascade spanning the gut, liver, and kidneys. Conversely, the SCFA depletion characteristic of CKD-associated dysbiosis (most pronounced in DKD, where butyrate-producing taxa are markedly depleted) removes this protective cascade simultaneously at all three organs, thereby accelerating endotoxemia, hepatic inflammation and renal fibrosis (96). Branched-chain amino acids are microbiota-influenced metabolites whose altered profiles are linked to insulin resistance and hepatic steatosis, though their role in CKD is indirect and less well-defined than that of SCFAs (97,98).

3. Systems biology scaffold for gut-liver-kidney axis analysis

The gut-liver-kidney axis is a physically and biochemically coupled system, integrated through portal and systemic vascular networks, enterohepatic bile acid circulation and a shared endocrine and microbial-metabolite signaling milieu. Translating this coupled architecture into a tractable analytical framework capable of supporting causal inference, predictive modeling and rational therapeutic targeting requires explicit

Table I. Key signaling molecules in the gut-liver-kidney axis.

Signaling molecule	Primary source	Receptor/target	Primary biological function	Axis-specific mechanisms	Pathological alterations
A, Gut-derived hormones					
GLP-1	Ileal and colonic L cells	GLP-1R	Promotes insulin secretion, improves glucose tolerance	Liver: Decreases gluconeogenesis and lipid accumulation; kidney: Anti-inflammatory, anti-fibrotic	Decreased secretion and receptor sensitivity in CKD
PYY	Intestinal L cells	Y receptor family	Regulates appetite and energy metabolism	Liver: Modulates lipid and glucose metabolism; kidney: Improves renal hemodynamics	Abnormal secretion during intestinal dysbiosis
B, Hepatokines					
FGF21	Hepatocytes	FGFR1-βKlotho	Regulates systemic energy metabolism	Gut: Improves barrier function; kidney: Anti-inflammatory, anti-fibroticKidney:	Compensatory elevation with diminished efficacy in CKD
Fetuin-A	Hepatocytes	Insulin receptor	Regulates insulin sensitivity and calcium metabolism	Participates in vascular calcification; gut: Affects inflammatory responses	Decreased levels in advanced CKD, deficiency (loss ofcalcification inhibition) associated with vascular calcification
Adropin	Hepatocytes and other tissue	Incompletely defined	Maintains cell homeostasis, improves insulin sensitivity	Promotes cell protection via AMPK pathways	Decreased levels in metabolic disease
C, Renal-derived factors					
EPO	Renal interstitial cells	EPOR	Erythropoiesis, anti-inflammatory, anti-fibrotic	Liver: Promotes tissue repair; gut: Modulates immune responses	Declines early in CKD progression
Klotho	Renal tubular epithelial cells	FGFR1c	Anti-aging, improves insulin sensitivity	Inhibits fibrosis, modulates gut microbiota	Significantly decreased in CKD, accelerates aging
Active VD	Renal 1α-hydroxylase	VDR	Calcium-phosphate metabolism, immune regulation	Enhances intestinal barrier, optimizes hepatic lipid metabolism, renoprotection	Decreased synthesis in CKD, deficiency exacerbates disease
D, Bile acids					
Cholic acid	Hepatic cholesterol synthesis	FXR, TGR5	Lipid digestion, metabolic regulation	Enterohepatic circulation regulates metabolic homeostasis	Impaired clearance in CKD, toxic accumulation

Table I. Continued.

Signaling molecule	Primary source	Receptor/target	Primary biological function	Axis-specific mechanisms	Pathological alterations
D, Bile acids					
Chenodeoxycholic cid	Hepatic cholesterol synthesis	FXR, TGR5	Anti-inflammatory, metabolic regulation	Activates FXR/TGR5 signaling	Decreased enterohepatic recycling; decreased levels with impaired bile acid metabolism in CKD
Lithocholic cid	Gut microbiota metabolism	TGR5	Immune regulation, anti-inflammatory	TGR5-mediated anti-inflammatory signaling	Potentially toxic in pathological states
E, Short-chain fatty acids					
Acetate (C2)	Gut microbiota fermentation	FFAR2, FFAR3	Energy provision, metabolic signaling	Comprises 60% of SCFAs, activates hepatic and renal metabolic receptors	Significantly decreased production in CKD
Propionate (C3)	Gut microbiota fermentation	GPR41, HDAC inhibition	Gluconeogenesis regulation, anti-inflammatory	HDAC inhibition mediates anti-inflammation, GPR41 regulates renal blood flow	Decreased with insufficient fiber intake
Butyrate (C4)	Gut microbiota fermentation	GPR109A, HDAC inhibition	Colonic cell energy source, anti-inflammatory, anti-fibrotic	Comprises 20% of SCFAs but exhibits the highest bioactivity, multi-pathway protection	Sharp decrease during dysbiosis
F, Uremic toxins					
Indoxyl sulfate	Tryptophan microbiota metabolism	AhR	Pro-inflammatory, pro-fibrotic	Activates AhR pathway, accelerates multi-organ aging	Significant accumulation in CKD, enhanced toxicity
p-Cresyl sulfate	Tyrosine microbiota metabolism	Endothelial cell receptors	Vascular toxicity, pro-inflammatory	Inhibits eNOS, activates oxidative stress	High protein binding, difficult to clear
TMAO	Choline/carnitine microbiota metabolism, hepatic FMO3	Incompletely defined	Cardiovascular toxicity, nephrotoxicity	Activates NLRP3 inflammasome, promotes atherosclerosis	10-100-fold elevation in CKD
Hippuric acid	Phenylalanine microbiota metabolism	Organic anion transporters	Potential neurotoxicity	Competitive inhibition of organic anion transport	Accumulates with declining renal function

AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; CKD, chronic kidney disease; eNOS, endothelial nitric oxide synthase; EPOR, erythropoietin receptor; FFAR2, free fatty acid receptor 2; FGFR1, fibroblast growth factor receptor 1; FMO3, flavin monooxygenase 3; FXR, farnesoid X receptor; GLP-1R, glucagon-like peptide-1 receptor; GPR41, G protein-coupled receptor 41; HDAC, histone deacetylase; NLRP3, NLR family pyrin domain-containing 3; PYY, peptide YY; SCFA, short-chain fatty acid; TGR5, Takeda G protein-coupled receptor 5; TMAO, trimethylamine N-oxide; VDR, vitamin D receptor.

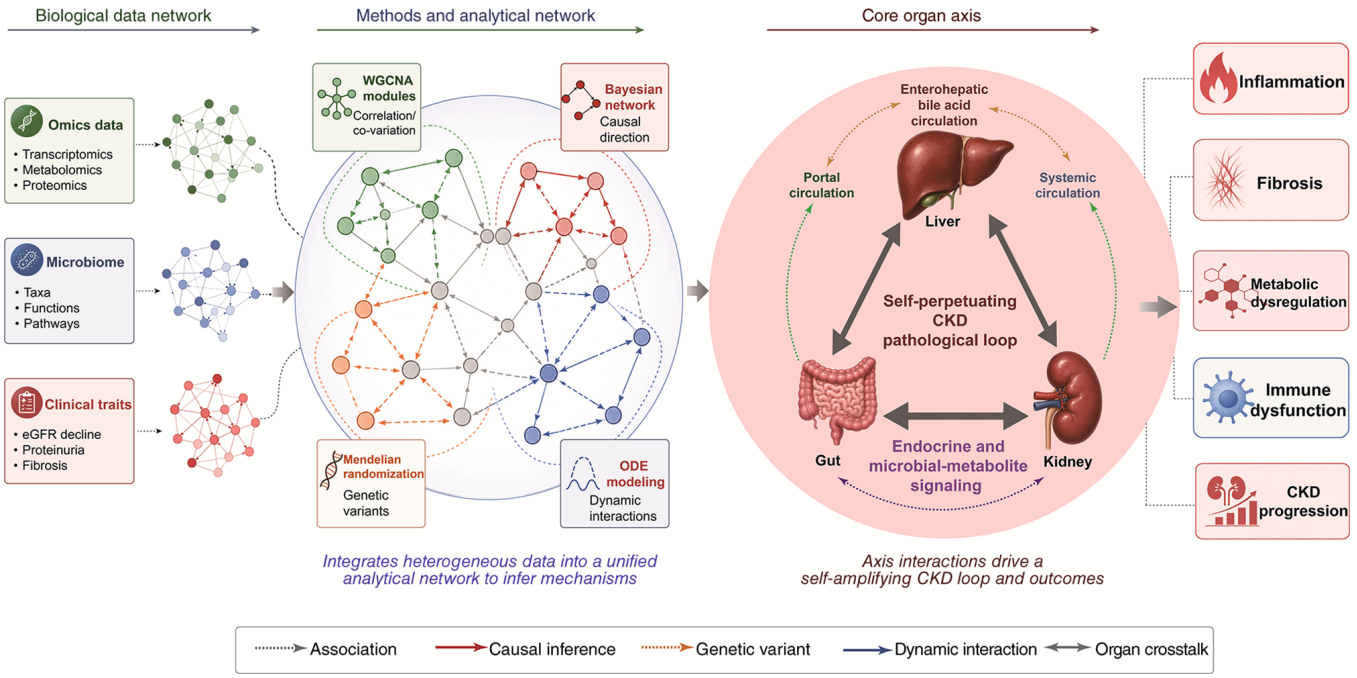

Figure 3. Systems biology framework for gut-liver-kidney axis analysis in CKD, integrating multidimensional biological data, network-based and causal analytical methods. CKD, chronic kidney disease; ODE, ordinary differential equation; WGCNA, weighted gene co-expression network analysis; eGFR, estimated glomerular filtration rate.

systems biology methodology. The molecular signaling network underlying this axis operates across multiple biological scales from intracellular receptor cascades to interorgan metabolite shuttling and cannot be adequately captured by reductionist, single-pathway analyses. A systems biology scaffold provides the analytical apparatus required to translate this complexity into causal, predictive and dynamic models of CKD progression. This framework is organized as a multi-layer analytical pipeline spanning biological data, analytical methods and the core organ axis that converges on causal and dynamic modeling of the gut-liver-kidney axis (Fig. 3).

Network-based module identification. Weighted gene co-expression network analysis (WGCNA) (99) and its multi-omics extensions (100,101) identify clusters of transcripts, metabolites and microbial taxa whose levels change in a coordinated manner across the gut, liver and kidney, revealing functional modules whose coordinated dysregulation is associated with clinical traits including eGFR decline, proteinuria and fibrosis scores. Consensus and module-preservation approaches enable identification of modules conserved across species and cohorts, addressing the cross-species translational gap that limits axis research. Applied to CKD cohorts with multi-tissue sampling, this approach may define axis modules (composite signatures) that may replace the current single-marker diagnostic paradigm (102).

Causal inference. Co-expression analyses identify associations but not directionality. Bayesian network frameworks, including dynamic Bayesian networks applied to longitudinal multi-omics microbiome data, prioritize candidate causal drivers and have been validated in inflammatory bowel disease and associated axis-pathology contexts (103). Mendelian randomization (MR), using genetic variants as instrumental variables, has been applied to test causal links between gut microbiota composition and renal traits in large biobank cohorts, identifying specific taxa (such as Bacteroidia) with strong causal associations with eGFR decline (104) and revealing gut microbiota-immune system-kidney mediating pathways that operationalize the axis at the genetic-causal level (105). Notably, bidirectional MR analyses indicate that elevated circulating trimethylamine N-oxide (TMAO) in CKD may partly reflect decreased renal clearance rather than upstream causation, with type 2 diabetes and kidney disease shown to causally increase TMAO levels; this has implications for whether TMAO-targeted interventions can modify renal outcomes (106).

Dynamic simulation. Ordinary differential equation (ODE) models capture the temporal cyclicity that defines axis pathology. Multi-compartment ODE frameworks of bile acid enterohepatic circulation, incorporating FXR-mediated autoregulation and selective transport mechanisms across hepatic, intestinal and systemic compartments, have been developed and calibrated against human pharmacokinetic and physiological datasets (107,108). By encoding production, degradation and interaction kinetics across organ compartments, integrated ODE models enable *in silico* screening of interventions, such as SCFA supplementation, FXR agonism and fecal microbiota transplantation (FMT), before initiating costly clinical trials, and can identify tipping points at which compensatory mechanisms form a self-perpetuating pathological loop.

Integration and outlook. Together, network-based module identification, causal inference and dynamic simulation constitute the quantitative scaffold on which the systems

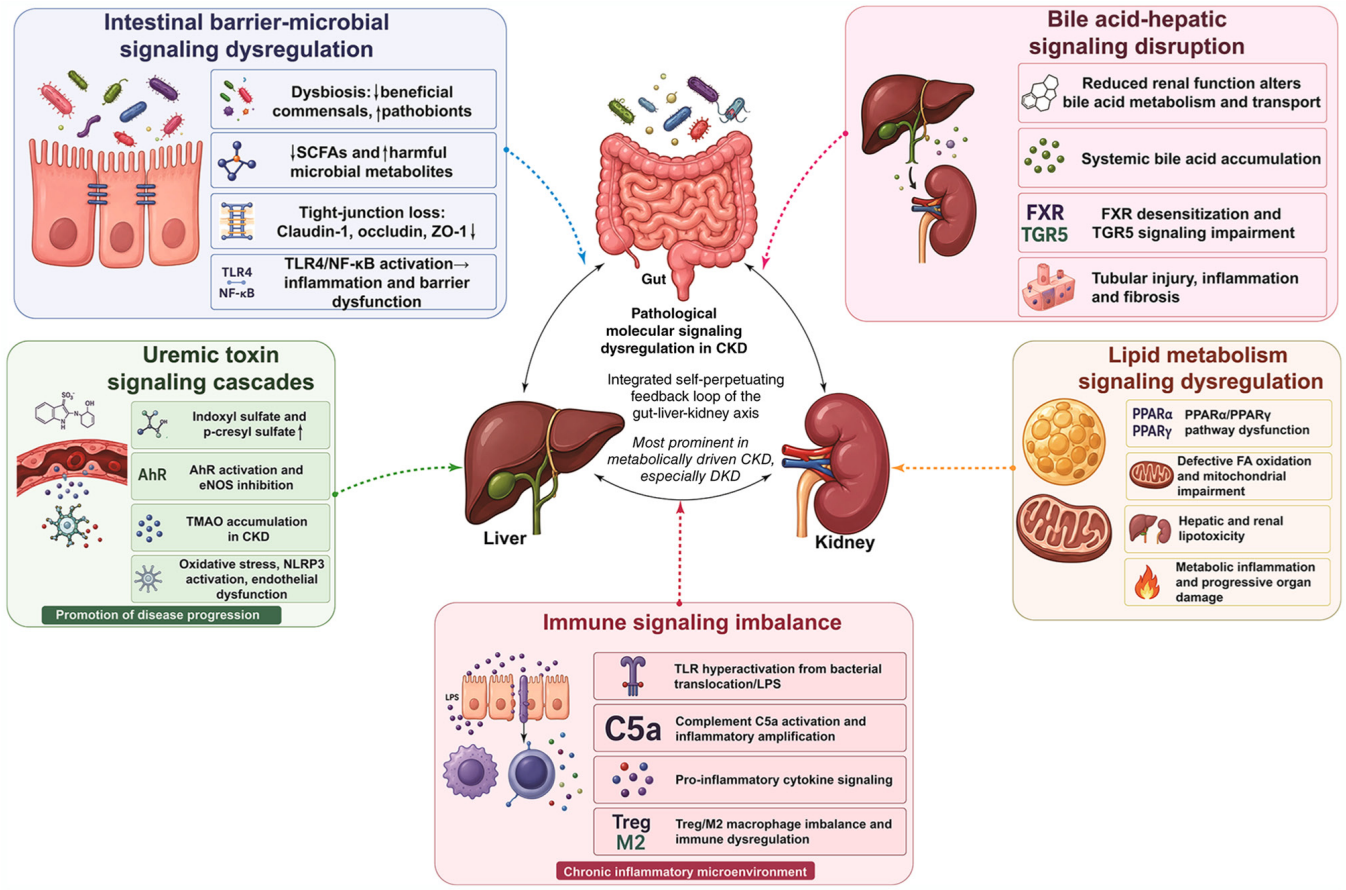

Figure 4. Multiscale pathological signaling dysregulation across the gut-liver-kidney axis in CKD, spanning molecular, cell, organ-level and systemic interactions. SCFA, short-chain fatty acid; ZO, zonula occludens; TLR, toll-like receptor; AhR, aryl hydrocarbon receptor; eNOS, endothelial nitric oxide synthase; TMAO, trimethylamine N-oxide; CKD, chronic kidney disease; DKD, diabetic kidney disease; LPS, lipopolysaccharide; C5a, complement component 5a; Treg, regulatory T cell; FXR, farnesoid X receptor; TGR5, Takeda G protein-coupled receptor 5.

biology framework rests, integrating heterogeneous biological data into a unified network that links molecular perturbations with the self-perpetuating organ-axis loop and downstream CKD outcomes (Fig. 3). Their integration into routine gut-liver-kidney axis research remains in its early stages, with most studies applying individual tools rather than the unified pipeline (109-111). The development of standardized multi-organ, multi-omics CKD datasets, together with computational platforms supporting joint analysis, represents both the principal bottleneck and the most promising direction for axis research.

4. Pathological molecular signaling dysregulation

In CKD, dysregulation of gut-liver-kidney communication is an integrated, self-perpetuating loop in which each module amplifies the others across organ boundaries (Fig. 4). Intestinal barrier failure releases endotoxins and uremic toxin precursors into the portal circulation; hepatic exposure to these signals exacerbates bile acid dysregulation, lipotoxic signaling and acute-phase inflammation; the resulting systemic milieu (elevated TMAO, indoxyl sulfate, pro-inflammatory cytokines and dysregulated peroxisome proliferator-activated receptor (PPAR)/FXR signaling) precipitates renal tubular injury and fibrosis; the consequent decline in renal clearance feeds back to alter gut microbial composition, bile acid pool homeostasis and tight junction integrity, completing the cycle. The intestinal barrier, microbial signaling dysregulation, bile acid-hepatic signaling pathway disruption, uremic toxin signaling cascades, lipid metabolism signaling network dysregulation and immune signaling imbalance are not parallel disease mechanisms but interlocking nodes of a positive-feedback network whose collective dynamics, rather than any single component, drive CKD progression across multiple biological scales, from intracellular signaling to organ-level dysfunction and systemic inflammation.

The gut-liver-kidney axis does not operate uniformly across CKD etiologies; its dysfunction is most pronounced and most therapeutically tractable in DKD, where metabolic, hepatic and renal compartments are tightly coupled. In DKD, all three arms of the axis are simultaneously engaged. Hyperglycemia and insulin resistance drive hepatic steatosis, with MASLD affecting the majority of patients with type 2 diabetes and increasing CKD risk (14,112). The gut microbial signature of DKD is distinctive, differing from that of diabetes without nephropathy in both the expansion of pathobionts and the depletion of butyrate-producing taxa (113,114). Together, these shifts amplify SCFA depletion, endotoxemia and uremic toxin generation, situating DKD as the prototypical setting in which gut dysbiosis, hepatic lipotoxicity and renal injury

Table II. Subtype specificity of gut-liver-kidney axis dysfunction.

Dimension	DKD	Non-DKD CKD (IgAN, hypertensive, ADPKD)
Primary driver	Hyperglycemia, insulin resistance, lipotoxicity	Immune, hemodynamic, or genetic
Hepatic-metabolic arm	Strongly engaged; high MASLD comorbidity (55-70%)	Weakly engaged; low MASLD prevalence
Gut microbial signature	Increased *Hungatella, Escherichia*; decreased butyrate producers	Dysbiosis present but distinct in composition/ magnitude
Dominant uremic toxins	TMAO, indoxyl sulfate, p-cresyl sulfate (high)	Uremic toxin accumulation shared, etiology-modulated
Bile acid-FXR-TGR5 axis	Prominent dysregulation	Secondary involvement
Axis-targeted therapeutic potential	High (GLP-1RA, FXR agonists, SCFA, FMT)	Limited; etiology-specific treatment dominates

DKD, diabetic kidney disease; CKD, chronic kidney disease; IgAN, immunoglobulin A nephropathy; ADPKD, autosomal dominant polycystic kidney disease; MASLD, metabolic dysfunction-associated steatotic liver disease; TMAO, trimethylamine N-oxide; GLP-1RA, glucagon-like peptide-1 receptor agonist; FXR, farnesoid X receptor; SCFA, short-chain fatty acid; FMT, fecal microbiota transplantation; TGR5, Takeda G protein-coupled receptor 5.

reinforce one another. In non-DKD CKD, including IgA nephropathy, hypertensive nephrosclerosis and autosomal dominant polycystic KD, the axis is engaged more selectively. Intestinal dysbiosis and uremic toxin accumulation accompany advanced renal dysfunction regardless of etiology, but the hepatic-metabolic arm is less prominent in the absence of insulin resistance and MASLD (113). Consequently, the gut-liver-kidney framework carries greatest explanatory and therapeutic weight in metabolically driven CKD, whereas in non-DKD subtypes, axis-directed interventions remain more speculative and etiology-dependent. This underscores the need for subtype-stratified evaluation of axis-targeted therapies (Table II).

Intestinal barrier-microbial signaling dysregulation

Dysbiosis-mediated signaling alterations. At the organ and systemic levels, dysbiosis-mediated signaling alterations emerge in CKD, characterized by notable changes in the gut microbiota composition that reshape molecular signaling at the gut-liver-kidney interface. For example, accumulation of uremic toxins creates a toxic intestinal milieu that selectively favors the expansion of unfavorable microbial species at the expense of beneficial commensals (115,116). Key mechanisms of dysbiosis include a shift in microbial composition toward proteolytic bacteria, resulting in decreased SCFA production and increased generation of indoles, phenols and amines (117-119) and activation of toll-like receptor (TLR) signaling, particularly TLR4 stimulation by lipopolysaccharide (LPS) derived from Gram-negative bacteria, which initiates and propagates inflammatory responses along the gut-liver-kidney axis (120).

Loss of tight junction adhesion and barrier signaling. Impairment of the intestinal barrier is a key molecular signaling failure that plays a notable role in CKD. Uremic toxins and pro-inflammatory cytokines directly impair tight junction proteins, such as claudin-1, occludin and zonula occludens-1 via several signaling pathways (121,122). At the molecular and cell levels, uremic toxins and pro-inflammatory cytokines activate NF-κB signaling and increase myosin light-chain kinase activity, leading to reduced expression of tight junction proteins and cytoskeletal reorganization, compromising intestinal barrier integrity (123-125). Disruption of the barrier permits the transit of bacteria and endotoxins, which leads to systemic inflammation via activation of the complement system and the release of cytokines. This forms a feed-forward loop in which the inflammatory signals exacerbate barrier function, which is defective.

Bile acid-hepatic signaling pathway disruption

Bile acid metabolism changes in renal dysfunction. In KD, disordered bile acid metabolism disrupts gut microflora homeostasis and promotes intestinal barrier dysfunction, thereby facilitating kidney inflammation (126-128). High concentrations of bile acids induce proinflammatory pathways in the renal tubules, leading to fibrosis-based CKD (129). Additionally, impaired renal function affects bile acid elimination by decreasing GFR and altering tubular transport systems, with accumulation of bile acids in the systemic circulation and modification of their composition (130). The decreased renal elimination establishes a cycle, wherein accumulated bile acids harm renal tubular cells, resulting in a decrease in kidney function and maintenance of the cycle.

FXR/TGR5 receptor signaling pathway dysregulation. Notably, high bile acid levels lead to paradoxical FXR desensitization and downregulation, interfering with normal metabolic control through receptor systems (80). This results in a state of bile acid resistance similar to that observed in insulin resistance with high levels of circulating bile acids, while the protective signaling effects are attenuated due to receptor dysfunction and loss of downstream effectors. Disruption of TGR5 signaling in immune cells leads to a decreased anti-inflammatory response and results in chronic

inflammation in the gut, liver and kidney (131,132). Altered signaling through FXR in hepatocytes results in the disturbance of bile acid synthesis enzymes, transporters and metabolic genes. Diminished TGR5-mediated signaling in enteroendocrine cells decreases incretin hormone production and metabolic synchronization between the gut and liver across the axis (133,134).

Uremic toxin signaling cascades

Protein-bound uremic toxin receptor signaling. Protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate accumulate during CKD and exert toxic effects via receptor-mediated signaling pathways (135,136). Uremic toxins, the end products of gut microbiota metabolism, accumulate in the blood owing to renal malfunction. Toxins, such as indoxyl sulfate and p-cresyl sulfate, are inflammatory and oxidative stress triggers that damage various organs, including the liver and kidney (137). For example, indoxyl sulfate induces aryl hydrocarbon receptor (AhR) activation resulting in the upregulation of pro-inflammatory genes and pro-fibrotic factors (138). Activation of AhR leads to endothelial cell infiltration, oxidative stress and degeneration in various organs. The p-Cresyl sulfate impairs cell signaling by suppressing endothelial nitric oxide synthase and stimulating NADPH oxidase, resulting in vascular dysfunction and inflammation (139,140).

TMAO-mediated renal toxicity signaling. TMAO, a gut microbiota-derived metabolite generated by hepatic flavin monooxygenase 3-mediated oxidation of TMA, is a key pathogenic factor in the gut-liver-kidney axis (141-143). Choline, carnitine and betaine are dietary precursors that are metabolized by the gut microbiota to form TMA, which is converted to TMAO in the liver. TMAO accumulates at high levels in CKD because of the combined effects of production from aberrant gut microbiome and decreased elimination by the kidney, forming a pathological store that promotes cardiovascular-renal disease (144). TMAO directly affects the renal tubules via NLRP3 inflammasome activation in renal tubular cells, resulting in increased production of IL-1β and IL-18 as well as an acceleration of tubulointerstitial fibrosis (145,146). Moreover, TMAO induces endothelial dysfunction via oxidative stress and decreases nitric oxide bioavailability, which lead to premature atherosclerotic changes and cardiovascular events in patients with CKD (147). Notably, TMAO disrupts hepatic lipid homeostasis by blocking ATP-binding cassette transporter A1-dependent reverse cholesterol transport while suppressing cholesterol 7α-hydroxylase (CYP7A1) expression, which encodes the rate-limiting enzyme for bile acid synthesis (148,149). This disruption of hepatic cholesterol handling leads to a feed-forward pathological loop in which impaired liver lipid metabolism amplifies systemic inflammation and worsens hepatic steatosis and renal lipotoxicity. Together, these effects position TMAO as a key link connecting gut dysbiosis with coordinated liver-kidney dysfunction during the progression of cardiovascular disease. Collectively, accumulating evidence from experimental models and clinical cohorts indicates that elevated circulating TMAO is associated with CKD progression and cardiovascular risk, reinforcing its role as a key molecular nexus within the gut-liver-kidney axis (150,151).

Oxidative stress signaling networks. Uremic toxins and their transduction pathways induce oxidative stress, trigger mitochondrial breakdown, block respiratory chain complexes, activate NADPH oxidase via protein kinase C pathways and disrupt intracellular antioxidant mechanisms, such as depleting glutathione and decreasing antioxidant enzyme activity (137). Concurrently, uremic toxins disrupt Nrf2 signaling, thereby promoting cytoplasmic entrapment and inhibiting nuclear Nrf2 translocation, decreasing cellular antioxidant reserves and impairing the counter-regulative response to oxidative stress (137,152). Consequently, oxidative stress extends across the gut-liver-kidney axis, leading to cell damage and pro-inflammatory signaling which promotes disease progression (153).

Lipid metabolism signaling network dysregulation

PPAR signaling pathway dysfunction. CKD has effects on PPAR signaling, especially for PPARα and PPARγ pathways in the gut-liver-kidney axis. In DKD, PPARα expression and activity decreases in the liver and kidney, resulting in FA oxidation impairment and lipid accumulation (154,155). This dysfunction promotes hepatic steatosis and renal lipotoxicity thus creating pro-inflammatory microenvironments that potentiate organ damage. Concurrently, PPARγ expression becomes dysfunctional in adipose tissue and immune cells and results in insulin resistance and inflammation activation (156,157). Thus, the combined alteration of PPAR signaling leads to a systemic metabolic disarray that fuels CKD progression.

FA oxidation signaling defects. Fat oxidation machinery at the molecular level is repeatedly disrupted over time in patients with CKD. Long-term inflammation and oxidative stress disrupt AMPK signaling, a central regulator of cellular energy metabolism (158,159). This impairment depresses acetyl-CoA carboxylase phosphorylation and enhances malonyl-CoA content to prevent carnitine palmitoyltransferase 1 (CPT1)-mediated inhibition of FA transfer into the mitochondria (160). Simultaneously, the expression of PPARγ coactivator-1α decreases, thereby leading to decreased mitochondrial biogenesis and oxidative capacity (161,162).

Lipotoxicity signaling cascades. Excessive lipid storage in the liver and kidney leads to complex lipotoxicity signaling pathways that result in systematic multi-organ dysfunctions through the gut-liver-kidney axis. Saturated fat increases ceramide formation via *de novo* biosynthesis and/or the salvage routes, leading to ceramide accumulation. These elevated ceramides directly activate the protein kinase C (PKC) and JNK signaling cascades, which modulate hepatocyte and tubular cell apoptosis (163,164), amplify inflammatory cytokines and alter fibroblasts so they are activated by collagen deposition (165,166). Concurrently, accumulation of diacylglycerol selectively activates novel PKC isoforms (PKCδ, PKCε, PKCθ), thereby causing phosphorylation of insulin receptor substrate/activation of transcription factors such as NF-κB, resulting in hepatic and renal insulin resistance/inflammation (167). This lipotoxic microenvironment creates a self-perpetuating cycle, wherein lipid-induced inflammation may disrupt cell lipid metabolism and mitochondrial function (168,169), leading to progressive organ dysfunction combined with worsening metabolic disarray through the gut-liver-kidney network.

Immune signaling imbalance

TLR signaling hyperactivation. CKD engenders a sustained immune hyperactivation reflected by abnormal TLR signaling escalation along the gut-liver-kidney axis. The leakage of bacterial components, particularly from LPS from Gram-negative bacteria, across the partially damaged intestinal barrier activates a series of TLR4 signaling cascades in hepatic Kupffer cells, renal resident macrophages and recruitment immune cell (170,171). This translocation of bacteria at TLR4 exacerbates NF-κB nuclear translocation and transcription, resulting in continuous release of pro-inflammatory cytokines and progressive organ damage (172,173). Concomitantly, TLR2 and TLR9 are overactivated by an increasingly large pool of damage-associated molecular patterns, such as high mobility group box 1 and heat shock proteins, which are lost mainly from necrotic hepatocytes and renal proximal tubular cells (174-176). Chronic TLR activation induces the reprogramming of innate immune cells into a trained state via epigenetic changes and metabolic rewiring (176). This leads to pathological immune memory, biased inflammatory responses and tissue damage in the absence of continuous pathogen exposure. Consequently, a self-perpetuating cycle of sterile inflammation is induced by the gut-liver-kidney loop.

Complement system dysregulation. The complement cascade in CKD is dysregulated and induces an inflammatory pattern that amplifies organ destruction and malfunction in the gut-liver-kidney axis. Hyperactivation of the alternative complement pathway is the primary mechanism, with multiple pathways contributing to the downregulation of key complement regulatory proteins (factor H, CD55, CD46) and increased stability of the C3 convertase due to decreased decay accelerating factor activity (177-179). Aberrant activation of this downstream cascade results in the overproduction of C5a anaphylatoxin, which is a chemotaxin and neutrophil priming factor that activates tissue-resident macrophages and induces degranulation-mediated tissue damage along the hepatic sinusoids and renal interstitium (180,181). In the intestine, the complement system is activated by bacterial translocation-induced classical pathway activation and regional C3 deposition in gut epithelial cells. The classical complement pathway is compromised via autoactivation by deposited circulating immune complexes and binding of acute-phase proteins (C-reactive protein and serum amyloid P), resulting in further amplification loops of inflammation (182). Notably, unregulated systemic activation of complement has several pathological implications. These include complement-mediated glycocalyx degradation, increased platelet activation, phospholipid surface stimulation of the coagulation cascade and the ulceration of atherosclerotic plaques (183,184). Together, these effects may contribute to the increased cardiovascular morbidity observed in patients with CKD.

Cytokine signaling network disruption. CKD leads to a striking dysregulation in the cytokine signaling network, characterized by sustained elevation of pro-inflammatory mediators along with impaired anti-inflammatory regulatory mechanisms at the gut-liver-kidney axis level (185). IL-6 signaling is constitutively active because of sustained phosphorylation and nuclear translocation of STAT3, which promotes hepatic acute-phase protein synthesis (C-reactive protein, fibrinogen and serum amyloid A), while simultaneously coordinating systemic inflammatory responses that disseminate along the entire axis (186,187). Simultaneously, chronic elevation of TNF-α activates sustained canonical NF-κB (p65/p50) and stress signal MAPK pathways (JNK, p38, ERK1/2), all of which result in hepatocyte apoptosis, injury to renal tubular cells, gut barrier failure and step-wise fibroblast activation for multi-organ fibrosis (188,189). Notably a paradoxical dysregulation of the anti-inflammatory cytokine network is observed, wherein IL-10 production declines following suppression of T regulatory cell activity and M2 macrophage polarization deficiency (190,191). TGF-β signaling undergoes pathological reprogramming from its protective tissue-healing role toward profibrotic action with increased Smad2/3 phosphorylation and diminished Smad7 inhibitory capacity (192,193). Dysregulation of this cytokine network contributes to a vicious cycle of chronic inflammation, which leads to progressive organ damage. Furthermore, it generates cytokine resistance signatures that compromise the ability of the host to resolve inflammation and repair tissue. This, in turn, maintains the spread of the disease within the gut-liver-kidney network.

5. Therapeutic targeting of the gut-liver-kidney axis

The therapeutic strategies span a spectrum of clinical maturity, from mechanistic preclinical studies to late-phase randomized controlled trials (RCTs). Notably, the majority of gut-liver-kidney axis-targeted interventions remain at the preclinical or early-phase stage, and the few therapies supported by Phase III renal-outcome evidence (SGLT2 inhibitors, finerenone, GLP-1 receptor agonists) act predominantly through direct renal or systemic metabolic mechanisms rather than through the gut-liver axis.

Microbiome-targeted therapy. The gut microbiome is a key therapeutic target in the gut-liver-kidney axis, as dysbiosis initiates pathological cascades ranging from barrier dysfunction to multi-organ injury. Recent microbiome-based interventions, such as prebiotics, probiotics, synbiotics and engineered live biotherapeutics (194), present an upstream therapeutic window for combating the pathophysiological causes of KD and deliver parallel hepatic and systemic benefits by restoring commensal microbial populations and their protective metabolic functions.

Probiotics and prebiotics

Targeted probiotic interventions. The strategy behind probiotic supplementation is based on the re-establishment of a balanced ecosystem of beneficial microorganisms, necessary to balance gut-liver-kidney cross-talk. Microorganisms such as *Bifidobacterium longum* and *B. bifidum* are cornerstone treatment modalities owing to their ability to produce SCFAs, particularly butyrate, which has an anti-inflammatory effect on the renal tubular cells and hepatocytes and improves intestinal barrier integrity through the induction of tight junction proteins (195,196). Other studies in CKD cohorts have also demonstrated that *Bifidobacterium* supplementation leads to a decrease in serum inflammatory markers (IL-6, TNF-α) and suggests a trend toward improved eGFR (197,198). *Akkermansia muciniphila* is another target, especially in view of its role as a barrier to metabolic function. This mucin-digesting gut bacterium serves a direct role in the mucin

layer thickness and intestinal permeability, modulates the production of beneficial metabolites and reverses hepatic insulin resistance with nephroprotective effects (199). In overweight and obese patients, *Muciniphila* markedly decreases markers of liver dysfunction and systemic inflammation, with its effects associated with gut microbiota metabolic pathways involved in FA production, branched-chain amino acid metabolism and bile acid signaling (200). *Lactobacillus spp*., especially *L. casei* and *L. rhamnosus*, provide benefits through immune modulation and competitive exclusion of pathogenic bacteria. Such strains stimulate the development of regulatory T cells, decrease pro-inflammatory cytokine secretion and maintain enteric pH at levels that are conducive to the growth of healthy microbiota while suppressing urease-producing bacteria required for ammonia production, leading to systemic toxicity (201-203).

Precision prebiotic strategies. Prebiotic interventions modulate discrete health-associated bacterial populations using deliberately chosen fiber substrates and resistant starches (RSs). Inulin-type fructans are selective factors for *Bifidobacterium* growth and SCFA production and clinical trials have shown decreased levels of uremic toxins and ameliorated renal function following supplementation in patients with CKD (204-206). RS type 2 and RS type 4 formulations selectively stimulate butyrate-producing bacteria (*Faecalibacterium prausnitzii, Roseburia spp*.), while lowering colonic pH and decreasing protein fermentation, resulting in a decrease in the generation of nephrotoxic metabolites (207). Additionally, novel galacto- and fructo-oligosaccharide combinations exert a combined effect in terms of stimulatory bacteria favoring multiple beneficial viable counts and deteriorating pathogenic species levels (208). Superior multimodular synbiotic formulations with designed probiotics and substrates exert a better therapeutic effect than monotherapy by significantly increasing SCFA production, decreasing uremic toxins and displaying enhanced multi-organ protection over 12 weeks (209).

Microbiome modulation

FMT and beyond. FMT has been proposed as an advanced formulation for the overall restoration of the gut microbiome in patients with CKD with extreme dysbiosis. Selective donors, who have been screened amongst metabolically healthy individuals with strong SCFA-producing microbiota, provide the opportunity for rapid ecosystem recovery and access to therapeutic benefits. Studies using frozen encapsulated FMT products have demonstrated efficacy in lowering uremic toxin levels, improving kidney function and preserving the intestinal barrier (210). In FMT, donors are screened for beneficial bacteria (including *Akkermansia, Faecalibacterium* and *Bifidobacterium*) and the absence of pathogens prior to treatment, which is necessary to optimize the therapeutic effect (211). Studies on FMT have suggested improvements in microbial diversity, SCFA production and inflammatory markers along the gut-liver-kidney axis over follow-up periods of 6-12 weeks (211-213). However, the durability and long-term stability of microbiome remodeling remain incompletely defined and require confirmation in larger studies with extended follow-up periods (214).

Engineered therapeutic microorganisms. Emerging therapeutic modalities use genetically manipulated bacterial strains targeting specific disease pathways in the gut-liver-kidney axis. For example, *Lactobacillus* strains have been designed to express urease inhibitors aiming to decrease intestinal ammonia production, and engineered *Bifidobacterium* species containing indole-metabolizing enzymes have been proposed to target uremic toxin precursors (215,216), however, these remain proof-of-concept designs at the preclinical stage. Synthetic biology enables the design of chassis organisms (engineered host microbes serving as programmable platforms) programmed to deliver therapies to the gut. These designer therapeutic microbes produce protective metabolites, neutralize harmful bacterial products and sustain drug release at the site of interest within the gut. For example, preclinical studies using modified *E. coli* Nissle 1917 strains engineered to metabolize excess ammonia have shown promising results in mouse models of hyperammonemia and associated neurological disorder (217-219); to the best of our knowledge, these constructs have not yet been evaluated in patients with CKD. The precision microbiome transfer approach is based on the administration of characterized bacterial communities that are selected because of their therapeutic potential in KD, thus circumventing the limitations of whole-microbiome transplantation without compromising its therapeutic efficacy. Microbiome-targeted therapeutic strategies for nephroprotection are summarized in Fig. 5.

Metabolic pathway interventions

Bile acid modulators

FXR-targeted therapeutic interventions. FXR agonists are recognized as a complex option to treat the disrupted bile acid signaling network through the gut-liver-kidney axis (80). Obeticholic acid (OCA), a semi-synthetic bile acid analog and selective FXR agonist, exerts hepatoprotective and nephroprotective effects through several integrated mechanisms (220,221). OCA-mediated activation of FXR markedly suppresses CYP7A1 expression, the rate-limiting enzyme in bile acid synthesis, thereby decreasing the total size of the bile acid pool and protecting the liver from accumulation (222). Concomitantly, FXR activation increases the expression of bile salt export pump and multidrug resistance-associated protein 2, promoting the efficient efflux of bile acids from hepatocytes and decreasing intracellular lipotoxicity (223,224). In the renal compartment, FXR activation confers direct protection to the kidney by inhibiting inflammatory cytokines (TNF-α, IL-1β and IL-6) in tubular epithelial cells, downregulating fibroblast activation and decreasing collagen deposition (225). Novel FXR modulators, such as tropifexor and nidufexor, have shown improved tissue selectivity and, in early-phase clinical studies, more favorable side-effect profiles than first-generation compounds, although dose-dependent pruritus persists and renal outcome data in CKD are lacking (226-228). Tropifexor, an extremely potent full agonist of FXR, exhibits strong anti-fibrotic activity owing to its selective activation in the liver and gut with minimal off-target engagement in other tissue. Nidufexor, a tricyclic dihydrochromenopyrazole structure with partial FXR agonism, mediates specific modulation of the FXR-gene network that results in significantly decreased steatosis, inflammation and fibrosis in preclinical MASLD models (228-230). These two compounds have proceeded to phase II clinical trials, where they are under evaluation for MASLD and DKD, suggesting their potential as

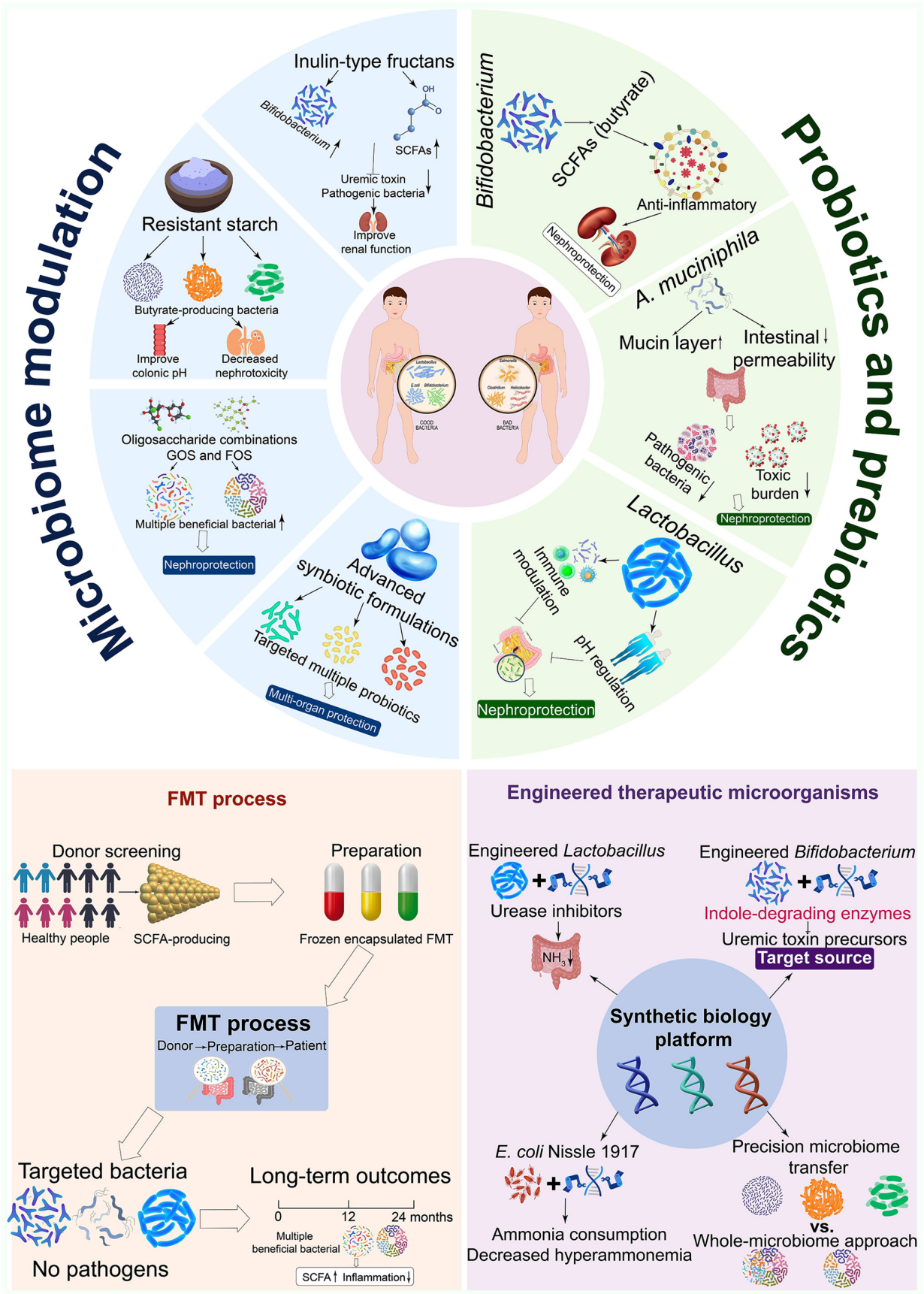

Figure 5. Therapeutic strategies targeting the gut microbiome to achieve nephroprotection within the gut-liver-kidney axis. GOS, galacto-oligosaccharide; FOS, fructo-oligosaccharides; SCFA, short-chain fatty acid; FMT, fecal microbiota transplantation.

dual therapeutic interventions against metabolic, hepatic and renal complications (231,232). These second-generation FXR agonists retain therapeutic activity at lower doses to minimize bile acid synthesis suppression and dyslipidemia.

TGR5-mediated therapeutic pathways. TGR5 agonists exert additional therapeutic effects through unique mechanisms, promoting metabolic health and anti-inflammation along the gut-liver-kidney axis. INT-777, a selective TGR5 agonist, stimulates adenylyl cyclase and intracellular cAMP generation in enteroendocrine cells to increase GLP-1 and PYY secretion (233,234). This incretin response contributes to glucose homeostasis, increases insulin sensitivity and exerts nephroprotective effects through the activation of the GLP-1 receptor in renal tubular cells (235,236). Immune cell activation of TGR5 induces anti-inflammatory signaling cascades via cAMP-dependent PKA and phosphorylation of cAMP response element-binding protein, resulting in decreased pro-inflammatory cytokine production and increased synthesis of anti-inflammatory mediators (237). Derivatives of lithocholic acid, especially lithocholic acid acetate and 3-keto lithocholic acids, are endogenous TGR5 ligands with the potential for CKD treatment. These compounds exert anti-inflammatory and metabolic effects via TGR5 signaling in hepatic Kupffer cells and renal macrophages (238,239). More recently, preclinical studies have shown that selective TGR5 agonism attenuates renal fibrosis and improves GFR and survival in experimental mouse) models of CKD (240,241); to the best of our knowledge, these findings have not yet been confirmed in clinical trials.

Dual FXR/TGR5 modulation strategies. Combinations of the FXR and TGR5 modulators may have synergistic effects, where the effect of using both drugs is greater than the sum of their individual effects. BAR502, a dual FXR/TGR5 agonist, controls metabolism by concomitantly activating both signaling pathways (230,242). This combination strategy achieves bile acid homeostasis and generates more effective anti-inflammatory and metabolic benefits in the gut-liver-kidney axis. Clinical development programs for dual modulators may be promising strategies for the complex pathophysiology of CKD-associated metabolic dysregulation through the restoration of whole-body bile acid-triggered signaling (80).

SCFA supplementation

Direct SCFA therapeutic administration. SCFA restoration may be a personalized treatment strategy for selective compensation of disordered microbial metabolite production in CKD dysbiosis. Sodium butyrate, the most commonly studied therapeutic SCFA, exerts combined beneficial effects on the gut-liver-kidney axis by inhibiting HDACs and activating GPR43 (86,243). SCFA butyrate administration suppresses the expression of an inflammatory gene program in renal tissue that is associated with NF-κB suppression and increased regulatory T cell numbers (86). Additionally, preclinical studies have shown that sodium butyrate exerts renal protective effects through multiple mechanisms, including decreasing the levels of oxidative stress and inflammation markers, improvement of mitochondrial function and regulating cell metabolic pathways in several experimental models of kidney disease, with increasing interest in DKD research (244,245). Supplementation with propionate yields metabolic benefits through independent signaling pathways associated with GPR41 activation and regulation of hepatic gluconeogenesis. Propionate promotes hepatic gluconeogenesis and enhances insulin sensitivity through olfactory receptor 78 in renal juxtaglomerular cells (246,247). This dual action is beneficial not only for the optimization of glucose homeostasis but also offers direct nephroprotection by improving renal perfusion and lowering oxidative stress. Acetate administration supports systemic energy metabolism and promotes the growth of beneficial bacteria through cross-feeding mechanisms that enhance endogenous SCFA production (248-250).

Enhanced SCFA production strategies. RS supplementation is an upstream therapeutic strategy that stimulates endogenous SCFA production by selectively stimulating the beneficial bacteria. With the ability to specifically promote the growth of *Bifidobacterium* and *Faecalibacterium prausnitzii*, high-amylose maize starch may be a human non-digestible carbohydrate source from RS2 that causes sustained butyrate production and improves the intestinal health (251). RS type 4 resistant starch compositions exhibit improved stability and selective colonic delivery, allowing maximal availability of the substrate for the fermentation of beneficial bacteria (252). Trials in CKD populations have shown that RS supplementation notably lowers inflammation and oxidative stress, attenuates symptoms caused by the retention of uremic toxins and improves renal function in patients with CKD (253,254). Arabinoxylan oligosaccharides (AXOS) and β-glucan supplementation demonstrate specific prebiotic responses that selectively enrich SCFA-producing bacteria while promoting other immunomodulatory effects (255). AXOS stimulates the proliferation of *Roseburia* and *Eubacterium rectale*, leading to increased butyrate production and improved intestinal barrier function by increasing the expression of tight junction proteins (256). β-glucan supplementation exerts dual actions by improving SCFA production and directly modulating the immune system through activation of dectin-1 receptor in the intestinal macrophages (257).

Synbiotic SCFA enhancement protocols. Complex or advanced synbiotic compositions, comprising specific probiotic strains combined with selected prebiotics that are SCFA-inducing, are more effective compared with mono-intervention (258). These pathways promote sustained SCFA levels over the duration of treatment, and demonstrate durable clinical responses beyond the period of active supplementation. Synbiotic preparations containing multiple strains, including *A. muciniphila* with *B. longum* and *L. casei* on a galacto-oligosaccharide substrate, exert a notable metabolic effect, increase SCFA production, strengthen barrier function and decrease inflammatory signaling along the gut-liver-kidney axis (259).

Lipid metabolism correction

PPARα-targeted therapeutic interventions. PPARα agonists, such as fibrates, are the mainstay therapies for treating severe disturbances of lipid metabolism observed with CKD development. Fenofibrate, a selective PPARα agonist exert a nephroprotective effects via induction of FA oxidation, suppression of renal lipid accumulation and inhibition of inflammatory signaling pathways (260). In renal tubular cells, PPARα activation upregulates the transcription of FA oxidation enzymes (such as CPT1 and acyl-CoA oxidase), leading to a decrease of lipid overload, which prevents lipotoxic nephrotoxicity (261). Hepatic PPARα activation decrease very low-density lipoprotein production, and improves systemic lipid profiles,

thereby conferring metabolic benefits in extra-hepatic tissue, including the kidney (262). Clinical evidence has shown that fenofibrate therapy decreases cardiovascular events, increases the eGFR and decreases albuminuria in patients with CKD over 5-year period (263). Pemafibrate, a selective PPARα modulator (SPPARMα), is associated with decreased renal function decline and better safety profile than conventional fibrates (264). This next-generation PPARα agonist decreases the prevalence of MASLD with better safety in patients with CKD. The drug is metabolized in the liver and excreted via bile, resulting in minimal changes in systemic exposure, even in patients with CKD, thereby minimizing the risk of drug accumulation and supporting its safety as a therapeutic option (265).

PPARγ modulation and insulin sensitivity enhancement. Therapeutic benefits of PPARγ agonists are achieved by improvements in insulin sensitivity, inflammation and adipocyte function in the gut-liver-kidney axis. The thiazolidinedione PPARγ agonist pioglitazone exerts numerous pleiotropic effects on the kidney, such as improving insulin sensitivity, decreasing oxidative stress and inhibiting inflammatory cytokine production (266,267). In the kidney, PPARγ activation induces macrophage anti-inflammation and polarization, inhibits fibroblast activation and extracellular matrix deposition, and enhances podocyte survival by boosting mitochondrial function (268). Activation of hepatic PPARγ ameliorates hepatic insulin sensitivity, decreases hepatic glucose output and increases adiponectin secretion, all of which improve systemic metabolism and kidney function (269,270). SPPARMs such as telmisartan, have advantages over thiazolidinediones as they provide the beneficial effects of PPARγ activation without fluid retention and weight gain (271). These compounds exhibit a notable nephroprotective effect mediated by combined angiotensin receptor blocking and PPARγ activation, providing dual mechanisms of action.

FA oxidation enhancement strategies. Carnitine replacement can partially restore FA oxidation capacity in patients with CKD, in whom decreased dietary intake, impaired synthesis and increased carnitine loss are common (272). L-carnitine supplementation has been shown to improve FA oxidation and dialysis-associated symptoms (273,274). As these effects are primarily systemic rather than specific to gut-liver-kidney axis signaling, carnitine strategies are considered adjunctive within the present framework.

Integrated multi-organ protection in the gut-liver-kidney axis. Emerging insights into the pathophysiology of the gut-liver-kidney axis have spurred interest in integrated multi-organ protection interventions, expanding beyond traditional organ-centric treatment modalities (17,275). Data remain scarce, but combined intervention of different organs in this axis may show better outcomes than mono-target therapy (276). The preliminary CONFIDENCE trial supported this approach, however, further confirmation of long-term kidney disease progression is required (276). This represents an initial step toward multitarget therapy in nephrology, pending confirmation from larger longer-term studies.

Renal-targeted combination therapy as complementary approaches. In addition to therapeutic interventions that target the gut-liver-kidney axis by modulation of the microbiome, restoration of metabolic pathways or axis-selective apoptosis, renal-targeted therapies act through other mechanisms. SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists (MRA) have shown promising nephroprotective properties against CKD with increased renal risk, especially in patients with type 2 diabetes (277). However, these agents act almost exclusively via direct hemodynamic and tubular effects on the kidney, rather than by altering the intestinal-hepatic-renal signaling pathways emphasized in the present axis. Recent clinical evidence, including that from the CONFIDENCE trial, suggests potential benefits of combination therapy with empagliflozin and finerenone in decreasing albuminuria (278). Although these effects appear promising, their mechanisms of action are primarily focused on the kidney and include glomerular hemodynamic changes, inhibition of tubular sodium-glucose transport and antagonism of mineralocorticoid receptors in renal tissue (279). The association between these therapeutic targets and gut-derived metabolites, hepatic metabolic dysfunction and microbiome-mediated signaling pathways is indirect and largely undefined. Accordingly, although SGLT2 inhibitors and MRAs are emerging as important additions for the treatment of CKD in nephrology and may be combined with gut-liver-kidney axis-targeted therapies, a detailed discussion of their mechanisms is beyond the scope of the present review. Clinicians treating individuals with DKD should consider complementary rather than mutually exclusive axis-targeted therapies and other renoprotective agents, however, the best approach to integrate these potent yet distinct therapeutic strategies awaits further evaluation. Table III provides an overview of the therapeutic approaches targeting the gut-liver-kidney axis, categorizing interventions by mechanism of action, study design, key findings and current limitations. These include microbiome-directed strategies such as prebiotic-probiotic supplementation and resistant starch (280,281), bile acid-based FXR agonists (282), PPARα modulators including fibrates and pemafibrate (283,284), direct SCFA administration with sodium butyrate and propionate (285,286), and carnitine-based interventions (287,288).

Microbiome-metabolic axis combination interventions

Multi-level microbiome modulation. Microbiome-based therapies offer an experimental therapeutic scheme by which potential upstream contributors to gut-liver-kidney axis dysfunction can be addressed. Early interventional approaches have associated precision probiotics with tailored pre- and postbiotic supplementation to restore the entire ecosystem. Synbiotic formulations composed of multiple strains demonstrate the potential for greater therapeutic efficacy compared with single-agent probiotic strategies in cholesterol control, blood pressure regulation and anti-inflammatory activity based on small studies (289,290). In a small but well-designed SYNERGY randomized controlled clinical trial, a 6-month intervention with synbiotic therapy resulted in significantly lower levels of p-cresyl sulfate compared with placebo among patients with stage 3-4 CKD (291). However, the trial was small (37 patients) and examined biochemical markers rather than clinical measures. Serum indoxyl sulfate reduction was not the primary endpoint, however, secondary improvements

Table III. Therapeutic approaches targeting the gut-liver-kidney axis.

Intervention	Study type	Mechanism of action	Condition	Key findings	Limitations	(Refs.)
A, SGLT2i + MRA						
Empagliflozin + finerenone	Phase 2 RCT (CONFIDENCE trial)	Dual SGLT2 inhibition + selective MRA	CKD + T2D	29% greater UACR reduction vs. finerenone-alone; 32% greater vs. empagliflozin-alone	Surrogate endpoint; short-term (6-month) follow-up; insufficient duration to assess cardiovascular/ kidney outcomes	(277)
B, Microbiome						
Prebiotic + probiotic	Feasibility RCT	Gut microbiome modulation to decrease uremic toxin production	Stage 3-4 CKD	No effect on uremic toxins; notable eGFR decline	n=68; feasibility study; underpowered for clinical outcomes	(280)
Resistant starch	Pilot RCT (double-blind, placebo-controlled)	Enhanced SCFA production	CKD patients	Decreased inflammation markers	Small sample size (n=16); short follow-up (4 weeks); high individual variability; pilot study design	(281)
Akkermansia muciniphila	Proof-of-concept exploratory	Intestinal barrier enhancement +TLR2-mediated immune modulation	Metabolic disorders	Improved insulin sensitivity, decreased liver enzymes, modest weight loss	No CKD-specific data, small sample size (n=32 completed), short-term	(200)
C, Bile acid modulators						
Obeticholic acid (FXR agonist)	Phase 3 trial	FXR activation	NASH	Decreased liver fibrosis	Dose-dependent pruritus (51%); elevated LDL; high discontinuation rate; interim analysis	(282)
Tropifexor (LJN452)	Preclinical	Selective FXR modulation	NASH	Anti-fibrotic effects	Rodent studies only	(231)
Nidufexor (LMB763)	Phase 2, multicenter, randomized, double-blind	Partial FXR agonist	DKD	Good safety and tolerability with dose-proportional pharmacokinetics when added to standard ACEI/ARB therapy	Non-confirmatory design with limited patient population. Requires long-term validation data	(228)

Table III. Continued.

C, Bile acid modulators						
Intervention	Study type	Mechanism of action	Condition	Key findings	Limitations	(Refs.)
Nidufexor (LMB763)	Phase 2, multicenter, randomized, double-blind	Partial FXR agonist	NASH	12-week proof-of-concept study; compared with placebo, nidufexor decreases ALT, hepatic fat and body weight	Proof-of-concept only; efficacy data reported in a conference abstract (not peer-reviewed); nidufexor development subsequently discontinued	(228)
D, PPAR modulators						
Fibrates	Systematic review and meta-analysis of RCTs	PPARα activation	CKD + dyslipidemia	Fibrates improve lipid profile, reduced albuminuria progression and cardiovascular events, with a reversible rise in serum creatinine	Limited data on advanced CKD	(283)
Pemafibrate	Phase 3	Selective PPARα modulation	Dyslipidemia	Favorable safety profile with fewer hepatic/renal laboratory abnormalities and adverse events vs. fenofibrate	Limited CKD-specific data	(284)
E, SCFA supplementation						
Sodium butyrate	Animal	HDAC inhibition; anti-inflammatory	DKD	Reduced kidney inflammation	Preclinical only	(285)
Propionate	Small human	GPR41 activation	Metabolic syndrome	Improved insulin sensitivity	No CKD-specific trials	(286)
F, Carnitine therapy						
L-carnitine	Large multicenter RCT	Enhanced fatty acid oxidation	Dialysis	Decreased muscle cramps, improved exercise capacity, increased muscle mass	Limited long-term follow-up, potential selection bias	(287)

Table III. Continued.

F, Carnitine therapy						
Intervention	Study type	Mechanism of action	Condition	Key findings	Limitations	(Refs.)
Acetyl-L-carnitine	RCT	Mitochondrial function	Diabetic neuropathy	Potential neurological benefits	No effect on nerve conduction velocity, requires early intervention, limited to diabetic patients	(288)

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FXR, farnesoid X receptor; GPR41, G protein-coupled receptor 41; HDAC, histone deacetylase; LDL, low-density lipoprotein; MRA, mineralocorticoid receptor antagonist; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RCT, randomized controlled trial; SCFA, short-chain fatty acid; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TLR2, toll-like receptor 2; UACR, urine albumin-to-creatinine ratio.

were observed. The SYNERGY II feasibility trial demonstrated synbiotic supplementation may modulate the stool microbiome and is feasible in patients with CKD, achieving acceptable retention rates and potential benefits for specific secondary outcomes (280). Both of the aforementioned studies had limited sample sizes and short-to-medium-term follow-up periods, however, as proof-of-concept reports, these trials demonstrate the need for other larger-scale validation studies.

Metabolic pathway restoration strategies. Interventions in combination that aim to positively alter the disrupted gut-liver-kidney metabolic axis seem promising based on an improved restoration of coordinated pathways. To the best of our knowledge, few clinical studies in metabolic syndrome populations have demonstrated that the combined supplementation of specific probiotic strains and (prebiotic) fibers improve insulin sensitivity and lipid profiles compared with the effects produced by compounds alone, with some effects remaining for ≥16 weeks after treatment cessation (234,292). Bile acid modulation-based combination therapies that pair FXR agonists with microbiome-targeted prebiotics may simultaneously address upstream gut dysbiosis and downstream metabolic disturbances, leading to normalization of bile acid profiles and enrichment of beneficial bacterial populations through bile acid-microbiome cross-talk (293,294). However, these methods are experimental and have limited clinical applications.

Advanced multi-modal therapeutic platforms

Nanotechnology-enhanced delivery systems. Through experimental therapeutic platforms, nanotechnology approaches are being evaluated and developed that may result in targeted multi-organ delivery with improved specificity and decreased systemic toxicity (295,296). However, these strategies remain largely in the preclinical development stage and pose translational hurdles. Emerging technologies, including drug delivery systems targeting the gut-brain-microbiome axis, suggest therapeutic potential for chronic disease intervention, however, studies in patients with CKD remain scarce and are often constrained by regulatory issues (297). Nanotechnology also aims to create lipid-based nanocarriers that may, in principle, deliver probiotics, prebiotics and bioactive compounds to target locations in the gut-liver-kidney axis; to the best of our knowledge, these remain conceptual designs without *in vivo* validation in CKD models, where therapeutic dose exposures can be maximized and off-target effects can be minimized (298,299). Smart polymer systems are also being developed to respond to specific tissue pH and enzymatic environments with the ability to deliver therapeutic compounds in a spatially and temporally controlled manner (300). Although conceptually attractive, such formulations have shown the early potential to deliver SCFA precursors *in vitro* for colon targeting, bile acid modulators to liver tissue and antioxidant compounds to renal tubular cells through selective release. Nevertheless, clinical impact, production scalability, cost-effectiveness and regulatory approval processes are impediments to clinical application.

Superior targeting mechanisms and biological barriers. Nanotechnology platforms are investigating advanced targeting approaches that can be applied to overcome the

biological obstacles present in the gut-liver-kidney axis. Active targeting strategies include evolving surface-functionalized nanoparticles with attached organ-specific ligands such as megalin-targeting peptides for delivery to proximal tubular cells, hepatocyte-selective asialoglycoprotein receptor ligands and gut epithelial cell-binding lectins (301,302). Although these molecularly targeted platforms exhibit increased cell uptake *in vitro*, clinical translation faces obstacles related to their synthetic complexity, potential immunogenicity and heterogeneous pharmacokinetics in patients with CKD. Passive targeting strategies theoretically exploit the enhanced permeability and retention (EPR) effect observed in inflamed renal and hepatic tissue, wherein compromised endothelial integrity may facilitate preferential nanoparticle accumulation (303). However, the EPR effect is heterogeneous among patients and diseases and its clinical predictability remains poor. Stimuli-responsive components are added to next-generation nanocarrier constructs that may, in principle, respond to disease-specific changes in the tissue microenvironment, such as altered pH of the inflamed tissue, increased levels of reactive oxygen species or altered enzyme activity patterns characteristic of CKD progression (304). To the best of our knowledge, these measures are in the early stages of development and have not yet been clinically validated in patients with CKD.

Clinical translation bottlenecks. Despite mechanistic promise, the translation of gut-liver-kidney axis-targeted therapies into clinical nephrology faces barriers in safety, tolerability, durability and regulatory pathways.

FXR agonists. The bile acid-based FXR agonist OCA has advanced to Phase III in metabolic dysfunction-associated steatohepatitis but has not been approved, as its moderate hepatic benefit does not outweigh dose-dependent adverse effects (305). The most frequent adverse effect is pruritus, occurring in ~23% of OCA-treated patients vs. 6% of placebo-treated patients, and is typically severe at higher doses (306). OCA also induces a pro-atherogenic lipid shift, raising low-density and lowering high-density lipoprotein cholesterol, typically requiring concomitant statin therapy, alongside risks of cholelithiasis and hepatotoxicity (305,307). These liabilities are concerning in CKD, where cardiovascular risk is already markedly elevated. Non-bile acid and intestine-restricted FXR agonists (tropifexor, nidufexor, cilofexor) aim to dissociate efficacy from these effects, but dose-dependent pruritus persists and, to the best of our knowledge, no agent has yet demonstrated renal outcome benefit in CKD; CKD-specific efficacy and safety datasets do not currently exist.

FMT. FMT has shown encouraging preliminary results in CKD: In a 6-month double-blind RCT in CKD stages 2-4, fewer FMT recipients demonstrated CKD progression (13.3%) than placebo recipients (53.8%), with stable renal parameters and only mild-to-moderate gastrointestinal adverse events and an exploratory trial in IgA nephropathy reported acceptable safety (308). However, the evidence base is limited by small sample sizes, heterogeneous protocols, absence of standardization and undefined long-term durability and safety, including donor-dependent variability and theoretical infection transmission risk (213,309). To the best of our knowledge, no Phase III renal outcome trial exists, and regulatory frameworks for microbiome therapeutics in chronic, non-infectious indications remain immature.

Other modalities. Engineered therapeutic bacteria and nanotechnology-based delivery systems remain preclinical, facing barriers of manufacturing scalability, immunogenicity, heterogeneous pharmacokinetics in CKD and the absence of regulatory precedent for multi-organ, axis-targeted agents. Across all modalities, the key bottleneck is the absence of adequately powered, CKD-specific RCTs with hard renal endpoints and long-term safety follow-up.

6. Future perspectives

The evolution of nephrology toward a system-based paradigm represents a fundamental transformation in the conceptualization, diagnosis and treatment of CKD. Fig. 6 illustrates the integrated framework for future gut-liver-kidney axis research and clinical translation, encompassing systems biology approaches, personalized medicine strategies and novel clinical trial designs that collectively advance precision nephrology.

Systems biology approaches to redefine nephrology. Nephrology may approach toward systems medicine beyond the current multi-omics integration efforts. Such advances could feature the availability of organ-specific biosensors that allow real-time monitoring of gut-liver-kidney axis activity. However, current biosensor technology has limitations in operational accuracy, biocompatibility and long-term stability. Additionally, new systems of disease classification, in which the molecular associations in the network space replace organ regions (or traditional pathology), may be developed over time, which will require validation prior to community acceptance.

Personalized medicine targeting the gut-liver-kidney axis. The future of precision nephrology may involve the creation of a full individual 'axis fingerprint' that includes genomic, epigenomic, microbiome, metabolomic and environment exposure information, which can be used to develop personalized treatment algorithms. In this regard, machine learning-based clinical decision support systems have already been developed. Continuous wearable monitoring systems may be integrated into future clinical practice; however, currently available wearables have low accuracy for most clinically relevant biomarkers and potential issues with patient use and data interpretation.

Novel clinical trial designs with composite endpoints. The changing face of trial design may increasingly incorporate adaptive, platform-oriented designs that may assess several interventions over the gut-liver-kidney axis once patient heterogeneity is considered. Table IV compares traditional nephrology trial designs with emerging gut-liver-kidney axis approaches, highlighting key differences in the study focus, endpoints, temporal framework, trial design, sample size consideration, statistical methods, inclusion criteria, intervention strategies, biomarker strategies and regulatory pathways.

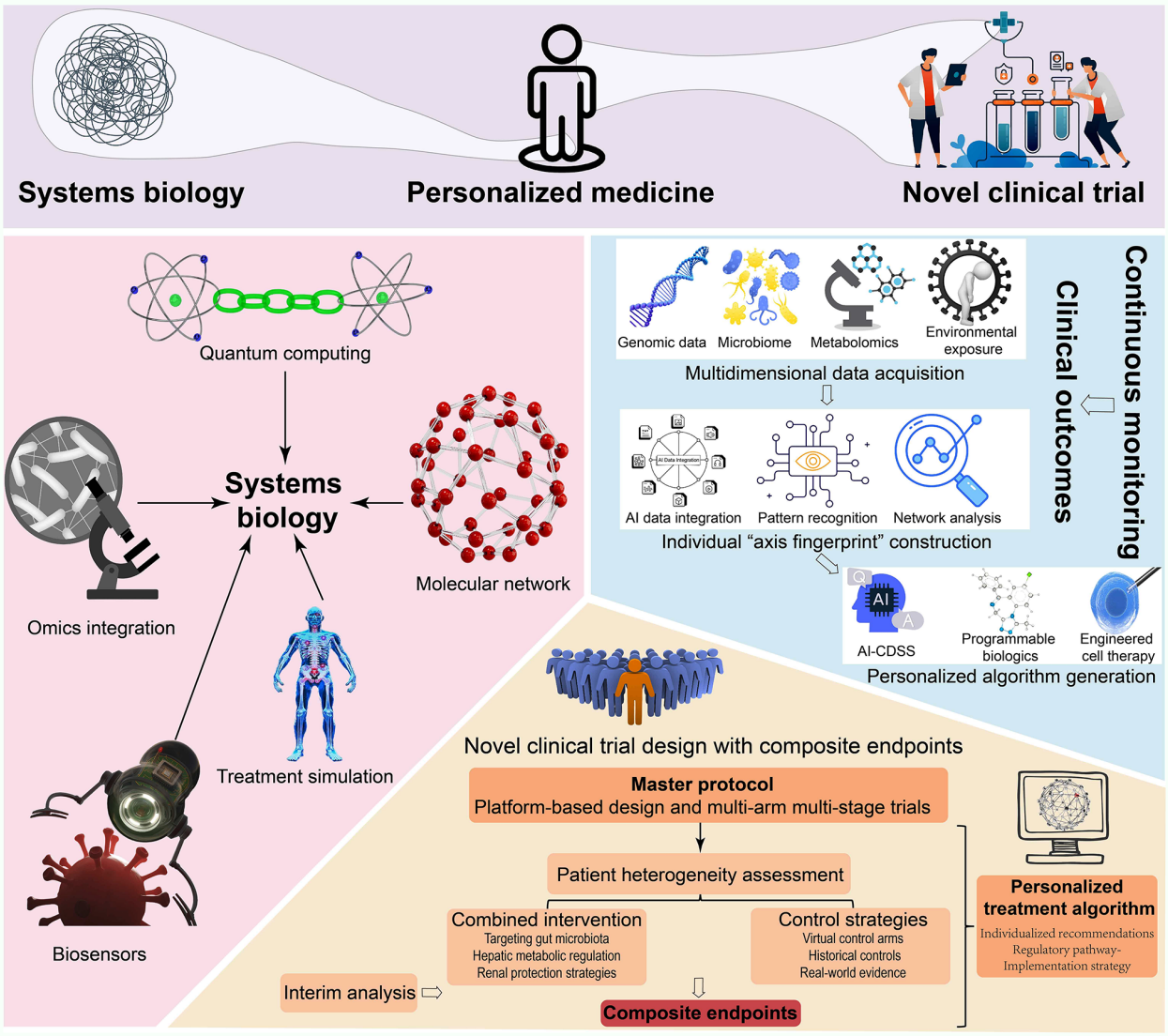

Figure 6. Integrated conceptual framework for advancing research and clinical translation of the gut-liver-kidney axis. AI, artificial intelligence; CDSS, clinical decision support system.

Future trials should include master protocols that allow integration of combination therapies, however, these designs are complex (requiring statistical and regulatory expertise). Further development of endpoints may also be directed toward composite endpoints incorporating patient-reported outcomes, biomarker changes and functional testing, following an extensive research process and validation, as well as answerability from regulators. The continuous progress in regulatory science may permit the acceptance of surrogate endpoints using validated molecular signatures, however, this may require extensive evidence generation and might take years.

Challenges and opportunities in translational research. The future landscapes of translation in gut-liver kidney axis therapeutics may be influenced by the need to overcome fundamental hurdles that include cross-species translational gaps as well as regulatory complexity for multi-organ intervention and growth realistic preclinical models that more closely mimic human physiology (310,311). In this regard, the establishment of international research consortia may facilitate access to resources and standardized methodologies. Regulatory guidelines need to be revised to meet and support multi-organ therapeutics that are different from traditional approval pathways. Value-for-money assessments in relation to comprehensive axis-targeted strategies are key for health economics research; to the best of our knowledge, however, evidence of the effectiveness and economic efficiency of these interventions is lacking.

Implications for the 2024 KDIGO guidelines. The 2024 KDIGO Clinical Practice Guideline for CKD represents a notable advance, incorporating SGLT2 inhibitors, finerenone and GLP-1 receptor agonists and emphasizing a comprehensive approach to slowing progression (12). Notably, several of these endorsed agents, particularly GLP-1 receptor agonists, whose enteroendocrine origin places them within the axis, intersect mechanistically with gut-liver-kidney signaling, even though the guideline does not frame them in these terms. The axis framework suggests directions for future guideline refinement: First, incorporation of validated gut-derived metabolite biomarkers (TMAO, p-cresyl sulfate, indoxyl sulfate) into CKD risk stratification, complementing eGFR

Table IV. Clinical trial design elements: Traditional vs. gut-liver-kidney axis approaches.

Traditional nephrology trials	Gut-liver-kidney axis trials	Key differences	Implementation challenges
A, Study focus			
Kidney-centric intervention	Multi-organ system interventions	Expanded scope from single organ to integrated axis	Requires multidisciplinary expertise and coordination
Primary renal endpoints	Composite multi-organ outcomes	Broader therapeutic targets	Increased complexity in trial management
Renal function preservation	Systemic homeostasis restoration	Paradigm shift from organ protection to network optimization	Need for novel regulatory frameworks
B, Primary endpoint			
Single renal outcome (eGFR, UACR)	Composite endpoints across organs	Multiple simultaneous targets	Complex statistical powering and interpretation
Kidney-specific biomarkers	Integrated biomarker panels	Expanded measurement scope	Increased cost and analytical complexity
Traditional progression measures	Network dysfunction indices	Novel outcome definitions	Lack of validated composite
C, Secondary endpoint			
Cardiovascular events, mortality	Microbiome diversity, metabolic profiles	Addition of mechanistic biomarkers	Limited understanding of clinical relevance
Dialysis initiation, transplant	Gut barrier function, hepatic metabolism	Multi-system functional assessment	Standardization challenges across centers
Quality of life	Inflammatory markers, metabolite levels	Expanded biological monitoring	Higher analytical costs and complexity
D, Temporal framework			
Short-term surrogate endpoints (6-24 months)	Long-term clinical endpoints (3-5 years)	Extended follow-up requirements	Increased study duration and cost
Rapid biomarker changes	Sustained multi-organ benefits	Different kinetics of response	Need for adaptive interim analyses
Early stopping for efficacy/ futility	Delayed treatment effects recognition	Longer timeframe needed for gut microbiome/multi-organ ecosystem restoration	Risk of premature trial termination
E, Trial design			
Standard parallel-group RCT	Adaptive platform trials	Dynamic protocol modifications	Regulatory approval complexity

Table IV. Continued.

Traditional nephrology trials	Gut-liver-kidney axis trials	Key differences	Implementation challenges
E, Trial design			
Fixed treatment protocols Single intervention testing	Master protocols with multiple arms Combination therapy evaluation	Flexible intervention strategies Simultaneous multi-target assessment	Sophisticated statistical methodology required Interaction effect analysis challenges
F, Sample size			
Moderate (500-2,000 patients) Single primary endpoint powering	Large (2,000-10,000 patients) Multiple endpoint adjustment	Increased power requirements Complex statistical considerations	Higher recruitment and retention challenges Inflated type I error risk
Traditional effect size expectations	Modest multi-organ effects	Different magnitude of expected benefits	Realistic effect size estimation difficulties
G, Statistical methods			
Standard survival analysis Cox proportional hazards	Network-based analysis methods Multi-state modeling	Systems-level statistical approaches Complex transition probabilities	Limited methodological precedent Specialized statistical expertise required
Time-to-event analysis	Joint modeling of multiple outcomes	Associated endpoint handling	Advanced computational requirements
H, Inclusion criteria			
CKD stage-based	Multi-organ dysfunction profiles	Broader patient phenotyping	More complex eligibility assessment
eGFR and albuminuria thresholds	Microbiome and metabolic signatures	Biomarker-driven enrollment	Standardization of novel biomarkers
Comorbidity exclusions	Integrated risk assessment	Inclusive multi-morbidity approach	Higher patient heterogeneity
I, Intervention strategy			
Single drug/device Dose optimization studies Monotherapy focus	Multi-modal interventions Systems-level modulation Synergistic combination therapy	Coordinated treatment approaches Personalized intervention intensity Network effect optimization	Complex protocol adherence monitoring Individualized treatment challenges Drug-drug interaction considerations
J, Biomarker strategy			
Traditional renal markers	Multi-omics integration	Comprehensive molecular profiling	High-throughput analytical requirements

Table IV. Continued.

J, Biomarker strategy			
Traditional nephrology trials	Gut-liver-kidney axis trials	Key differences	Implementation challenges
Serum creatinine, UACR	Microbiome, metabolomics, proteomics	Systems biology approach	Data integration and interpretation complexity
Single time point assessment	Longitudinal multi-marker tracking	Dynamic biomarker evolution	Increased sampling and analytical burden
K, Regulatory path			
Established FDA/EMA guidance	Novel regulatory frameworks	Pioneering approval pathways	Uncertain regulatory acceptance
Precedent-based review	Multi-agency coordination	Cross-specialty regulatory input	Extended review timelines
Standard safety monitoring	Complex multi-organ safety assessment	Expanded safety surveillance	Resource-intensive monitoring requirements

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; RCT, randomized controlled trial; UACR, urine albumin-to-creatinine ratio.

and albuminuria; second, explicit recognition of MASLD as a modifiable comorbidity in CKD risk assessment, given the 38% increased CKD risk in MASLD populations and the axis coupling in DKD; third, structured dietary fiber and microbiome-directed nutritional recommendations, building on the existing nutritional framework; and fourth, adoption of composite endpoints integrating microbiome signatures and metabolite panels in future axis-targeted trials, to generate the high-level evidence that current guidelines require.

7. Conclusion

The present review repositions CKD from an isolated renal disorder to a manifestation of gut-liver-kidney axis dysfunction. The present study defines the gut-liver-kidney axis in CKD through a systems biology framework. By integrating anatomical foundations (portal circulation, hepatic lymphatics, renal innervation), molecular mediators (gut-derived hormones, hepatokines, renal-derived factors) and quantitative methodologies (WGCNA-based module identification, Bayesian causal inference and ODE-based dynamic modeling), the axis is positioned as a tractable, analyzable systems-level entity. This framework reconciles the clinical comorbidity of CKD, MASLD and intestinal dysbiosis under a unified mechanistic architecture, and is most explanatory in metabolically driven CKD, such as DKD. Second, the present review integrates multiple pathological pathways into a single self-perpetuating cycle. Intestinal barrier failure, bile acid-FXR-TGR5 receptor dysregulation, protein-bound uremic toxin and TMAO signaling, PPAR/AMPK-mediated lipid metabolic dysfunction and TLR-complement-cytokine immune hyperactivation are not parallel processes but interlocking nodes of a positive-feedback network. Each module amplifies the others across organ boundaries (gut dysbiosis fueling hepatic lipotoxicity, hepatic lipotoxicity precipitating renal injury and renal failure feeding back to reshape gut microbiota and bile acid composition) creating the pathological inertia that characterizes CKD progression. Third, the present review summarizes precision therapy and novel trial designs along a preclinical/Phase I/II/Phase III spectrum, explicitly acknowledging clinical translation bottlenecks (FXR agonist-associated pruritus and dyslipidemia, FMT donor variability and durability and nanotechnology scalability) and propose concrete directions for incorporating gut-derived biomarkers and composite endpoints into future KDIGO guideline refinement and adaptive trial designs. Translating this framework into practice requires rigorous validation, multi-center axis-targeted trials and regulatory pathways capable of evaluating combination interventions. Evidence-based standard therapies remain foundational; the gut-liver-kidney axis framework supplements rather than displaces current practice, while offering a route to address the upstream pathology that organ-centric strategies cannot reach.

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Authors' contributions

JYH, YXW, LP, ZW and YTL conceived the study. JYH, YTL and SJL performed the literature review, constructed the figures and wrote the manuscript. QQL, WJL and HJZ wrote the manuscript. YXW, LP and ZW revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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