Journal of Renal and Hepatic Disorders
jrenhep.com
TROIKA PUBLISHER

REVIEW

Microbiome interactions in liver and kidney diseases: pathophysiology, clinical management, and novel therapeutic approaches

Melike Yakut Suner[1,*]

[1]Department of Internal Medicine, Çifteler State Hospital, 26700 Eskişehir, Turkey

Abstract

The gut microbiome participates in the regulation of metabolic and immunological processes that are closely linked to hepatic and renal physiology. Its composition and function change in metabolic dysfunction-associated steatotic liver disease, cirrhosis, chronic kidney disease (CKD), and after organ transplantation. Although these conditions differ clinically, several microbiome-related mechanisms are observed across all of them, including loss of intestinal barrier integrity, translocation of microbial products, altered bile acid metabolism, reduced short-chain fatty acid production, and accumulation of gut-derived uremic toxins. These observations have increased interest in the gut-liver and gut-kidney axes and have strengthened the view that the two axes interact to form a broader, interconnected gut-liver-kidney network. This review examines the relationships between intestinal dysbiosis and liver and kidney diseases and evaluates the clinical evidence for microbiome-based interventions. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation are the most widely investigated approaches; however, frequent investigation does not mean that their clinical effects have been proven. Because the strength of the evidence varies with the disease and the type of intervention, the generalizability of the findings and their transfer into daily practice should be judged with caution. Reliable evidence for the clinical efficacy of microbiome-based therapies in CKD is limited. Current findings support the biological importance of microbiome-organ interactions. Nevertheless, methodological heterogeneity and the scarcity of large randomized trials make it difficult for these findings to become routine clinical practice.

Keywords: Chronic kidney disease; Dysbiosis; Gut-kidney axis; Gut-liver axis; Microbiome

Submitted: 17 April, 2026; *Accepted:* 23 October, 2026; *Published:* 27 November, 2026

Author for correspondence: melike.yakut@saglik.gov.tr (Melike Yakut Suner)

How to cite: Melike Yakut Suner. Microbiome interactions in liver and kidney diseases: pathophysiology, clinical management, and novel therapeutic approaches. Journal of Renal and Hepatic Disorders. 2026; 10(2): 23-37. doi: 10.63268/jrenhp.v10i2.268.

Doi: 10.63268/jrenhp.v10i2.268

Copyright: 2026 The Author(s). Published by Troika Publisher.

License: This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

Introduction

Chronic liver and kidney diseases constitute a major public health problem whose burden continues to grow worldwide [1, 2]. Despite all advances in disease-specific treatment, inflammation, metabolic dysfunction, and fibrosis contribute to organ damage [3]. The gut microbiome can amplify this damage through microbial metabolites and gut-derived immune effects, and for this reason it has become a prominent focus of research [4, 5]. Sequencing technologies now make it possible to study the host-microbiome relationship at both the compositional and the functional level [6, 7].

The gut-liver axis is an anatomically direct relationship [8]: approximately 70% of hepatic blood flow is supplied through the portal circulation. The liver is therefore directly exposed to nutrients, microbial metabolites, and bacterial products [8, 9]. The transport of bile acids and antimicrobial mediators from the liver to the intestine makes the gut-liver pathway bidirectional [10, 11]. In chronic liver disease, dysfunction of the intestinal barrier increases the passage of lipopolysaccharide (LPS) into the portal circulation [12]. Changes in the bile acid pool, in turn, contribute to the relationship between intestinal dysbiosis and hepatic inflammation [12].

The gut-kidney axis, although not an anatomically direct relationship, is clinically important [13]. Microbial metabolites such as indoxyl sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine N-oxide (TMAO) are excreted by the kidneys and thus accumulate in the body as renal function declines [13, 14]. Conventional dialysis has limited efficacy in removing protein-bound metabolites [14]. Chronic kidney disease (CKD) reshapes the composition of the intestinal microbiota [13]. Increased urea in the intestinal lumen and loss of barrier integrity, together with dietary restrictions and medication use, favor the expansion of toxin-producing microorganisms while reducing commensal bacteria that produce short-chain fatty

acids (SCFAs) [15, 16]. Declining renal function can therefore alter the gut microbiota, while gut-derived metabolites can in turn influence CKD-related inflammation [13].

Evaluating the liver and kidney axes together is clinically important, because intestinal barrier dysfunction, microbial translocation, systemic inflammation, and altered metabolite handling are mechanisms common to both [6]. These interactions become particularly evident in cirrhosis accompanied by renal dysfunction and in patients in whom metabolic liver disease and CKD coexist [6]. Considering the gut-liver-kidney axis as a whole does not imply that a single microbial mechanism explains all of these pathologies. The influence of dysbiosis varies with the disease, its stage, medication use, and host characteristics [6].

Microbiome research has prompted clinical studies of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) [17–19]. Translation of these interventions into practice, however, differs between diseases. The strongest evidence concerns hepatic encephalopathy, whereas findings in other liver and kidney diseases rest largely on small clinical trials or experimental studies. Differences in microbial sampling methods, treatment formulations, and measured outcomes further complicate comparisons between studies.

This review examines the physiological basis of the gut-liver and gut-kidney relationships, disease-specific microbiome changes, immune mechanisms, and microbiome-based therapies. It also assesses the clinical validity of the evidence from microbiome studies and identifies the areas in which that evidence remains largely conceptual, focusing on the gap between biological plausibility and clinical applicability.

The literature search was conducted in the PubMed, Scopus, and Web of Science databases using different combinations of the terms “gut microbiome”, “dysbiosis”, “liver disease”, “kidney disease”, “fecal microbiota transplantation”, and “uremic toxins”. The search covered studies published between January 2012 and September 2026; earlier landmark studies were also included for context in order to trace the development of the field. Priority was given to randomized controlled trials, systematic reviews, meta-analyses, and prospective cohort studies. Preclinical studies were considered when human data were unavailable or when they provided mechanistic evidence that helped to interpret clinical findings.

Microbiome and organ function: fundamental concepts

Microbial composition and clinically relevant metabolic functions

The gastrointestinal tract, and the colon in particular, harbors a dense and metabolically active microbial community [20]. In healthy adults, *Firmicutes* and *Bacteroidetes* form the dominant bacterial populations, although their relative levels vary between individuals [21]. When explaining host-microbiome interactions, characterizing microbial functions is often more informative than measuring bacterial abundance.

Dietary fiber is metabolized by the gut microbiota into short-chain fatty acids, the principal products being acetate, propionate, and butyrate [22]. SCFAs provide an energy source for the intestinal epithelium, inhibit histone deacetylases, and activate immune signaling pathways through the G protein-coupled receptors GPR41 and GPR43 [22]. A further function of intestinal microorganisms is the conversion of primary bile acids into secondary bile acids, which activate farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) signaling [23]. They also contribute to xenobiotic metabolism and vitamin synthesis and generate a range of compounds from amino acids, including indole derivatives and precursors of uremic toxins [24]. These functions offer plausible mechanisms through which intestinal microbial activity can influence hepatic and renal physiology [25].

Clinical consequences of microbial disruption

Changes in the composition and function of the gut microbiota have been reported in cirrhosis, non-alcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease (NAFLD/MASLD), chronic kidney disease, and other metabolic disorders [4, 5, 26, 27]. These changes include reduced species diversity, depletion of short-chain fatty acid-producing bacteria, shifts in the metabolites produced, and loss of intestinal barrier integrity. The depletion of the butyrate producers *Faecalibacterium prausnitzii* and *Roseburia* is of particular importance [28]. Butyrate supports colonocyte metabolism and also helps to maintain epithelial barrier function [16, 29, 30]. In advanced CKD, fecal butyrate concentrations have been reported to be markedly lower than in healthy controls [31] and to correlate with levels of inflammatory markers [32]. In patients with cirrhosis, the combination of low fecal butyrate and high deoxycholic acid concentrations has been associated with mortality [33].

Although these associations indicate a link between altered microbial metabolism and advanced organ disease, they do not establish cause and effect. Dietary changes, medication use, reduced renal function, and portal hypertension can each alter the intestinal ecosystem. Dysbiosis may consequently contribute to chronic organ disease, but it may equally be a consequence of it [34].

The gut-liver interface: bile acids, FXR signaling, and hepatic disease

The portal circulation delivers gut-derived nutrients, microbial products, and metabolites directly to the liver [8, 9]. Among the pathways connecting the gut microbiota with hepatic metabolism, FXR-mediated bile acid signaling is one of the most prominent [11, 35].

FXR participates in the regulation of hepatic lipid and bile acid metabolism through signaling pathways involving the small heterodimer partner (SHP), sterol regulatory element-binding protein 1c (SREBP-1c), fibroblast growth factor 19 (FGF19), and cytochrome P450 7A1 (CYP7A1) [36]. Because gut bacteria modify the bile acid pool, dysbiosis may disturb the balance between FXR agonists and antagonists and thereby affect hepatic metabolic regulation [37]. Secondary bile acids also link microbial bile acid metabolism to glucagon-like peptide-1 (GLP-1) release and glucose homeostasis through TGR5-mediated signaling [38].

The bile acid-microbiome-FXR axis provides a

biological connection between microbial activity and metabolic liver disease [39]. Although therapies targeting bile acid receptors have been investigated in non-alcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (NASH/MASH), the clinical effects of FXR-targeted drugs should not be interpreted as evidence that correcting dysbiosis alone can reverse liver-related pathology [40]. This axis is better regarded as a metabolic network in which both microbial and host components may serve as therapeutic targets.

The gut-kidney interface: uremic toxins and the bidirectional effects of CKD

As the principal organ of excretion, the kidney is extensively exposed to a variety of metabolites produced by intestinal microorganisms. IS, PCS, and TMAO are the most widely studied of these [41, 42]. As renal function declines, and where conventional hemodialysis proves inadequate, the concentrations of protein-bound metabolites rise [43].

Experimental studies suggest that IS and PCS may contribute to renal injury [44]. IS has been reported to act on the aryl hydrocarbon receptor (AhR), nuclear factor kappa B (NF-κB), and transforming growth factor beta (TGF-β) signaling pathways, whereas PCS has been linked to oxidative stress and p38 mitogen-activated protein kinase (MAPK)-mediated cellular injury [14, 45]. In observational studies, high levels of these solutes have been associated with CKD progression, cardiovascular events, and mortality [14, 46, 47]. These findings do not prove causality, however, because circulating toxin levels are also influenced by residual renal function.

The uremia, dietary changes, and medication use that accompany CKD can affect the composition of the gut microbiota. For example, as bacterial ureases metabolize urea in the intestinal lumen, proteolytic organisms may come to predominate over SCFA-producing commensals within the microbial community [16]. The gut-kidney interaction thus becomes bidirectional: CKD can alter the gut microbiota, while microbial metabolites can contribute to the inflammatory processes associated with CKD progression.

The integrated gut-liver-kidney axis and its clinical relevance

The interactions between the gut, liver, and kidney have given rise to the concept of a gut-liver-kidney axis [6]. Hepatorenal syndrome is an important clinical example in which portal hypertension, bacterial translocation from the gut, systemic inflammation, circulatory dysfunction, and deteriorating renal function occur together [48]. This complex syndrome, however, cannot be explained by microbiome changes alone.

In a randomized, placebo-controlled proof-of-concept study, three months of supplementation with pasteurized *Akkermansia muciniphila* in overweight or obese adults with insulin resistance (n = 32) was well tolerated, and favorable changes in insulin sensitivity, insulinemia, and total cholesterol were reported relative to placebo. Because the study was designed to assess safety and feasibility, it does not permit conclusions about clinical endpoints [49]. Moreover, this finding does not mean that microbiome-based treatment strategies specific to hepatic or renal patients have been developed.

Commonly used drugs such as proton pump inhibitors and antibiotics can alter the composition of the gut microbiota [50]. For microbiome findings in hepatic and renal populations to be interpreted reliably, medication exposure must therefore be taken into account as a potential confounder.

Microbiome interactions in liver diseases

Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed NAFLD, is one of the most common chronic liver diseases worldwide [51]. Differences in gut microbiota composition have been reported in patients with MASLD [52]. Specific taxonomic patterns, however, vary with population, diet, disease stage, and analytical methods, and findings are thus not consistent across studies.

Metagenomic studies indicate that microbial patterns may change with disease stage. Increased abundance of *Escherichia coli* and decreased abundance of commensals such as *Faecalibacterium prausnitzii* and *Eubacterium rectale* have been reported in advanced disease [53, 54]. In one study, fecal microbial features combined with clinical variables identified advanced fibrosis with a high area under the receiver operating characteristic curve (AUROC) [55]. Although this finding suggests that microbial analysis has diagnostic potential, such classifiers must be validated in prospective, independent studies before they can be used for clinical staging.

Intestinal dysbiosis has been linked to MASLD progression through several mechanisms. Increased intestinal permeability may enhance the passage of bacterial products such as LPS into the portal circulation, where they can activate Kupffer cells and Toll-like receptor 4 (TLR4)-mediated inflammatory pathways [9, 56]. Changes in endogenous ethanol production, bile acid metabolism, and short-chain fatty acid levels are also among the proposed mechanisms [52]. Although these mechanisms are biologically plausible, the contribution of each to disease progression is not yet clear.

Diet is a major determinant of the relationship between metabolic disease and the gut microbiome. Fiber-rich dietary patterns improve established metabolic risk factors and may also modify microbial metabolism and short-chain fatty acid production [57]. The microbiome may mediate some of the metabolic effects of dietary interventions; however, current evidence does not show that microbiome changes are the principal mechanism underlying the beneficial effects of diet on MASLD.

Alcohol-related liver disease and cirrhosis

In alcohol-related liver disease, the intestinal barrier is disrupted and the microbial composition changes [58]. Chronic ethanol use impairs the integrity of epithelial junctions, increasing intestinal permeability and the passage of microbial products into the portal circulation [59]. Patients with alcohol-related cirrhosis show enrichment of oral-origin taxa such as *Veillonella* and *Streptococcus*, and the degree of this "oraliza-

tion" correlates with disease severity [26].

Interventional studies provide preliminary evidence that modifying the microbiome may influence clinical outcomes. In the randomized trial by Pande *et al*. [60], patients with severe alcohol-associated hepatitis were assigned to fecal microbiota transplantation or prednisolone. Among participants who completed the study, 90-day survival was 75% in the FMT group and 56.6% in the prednisolone group ($p = 0.044$). Although these findings support further research, the study design and the need for independent replication currently limit the acceptance of FMT as an established treatment for severe alcohol-associated hepatitis.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is one of the clearest examples of the interaction between intestinal microbial metabolism and the clinical complications of cirrhosis. Reduced hepatic ammonia clearance combined with continued intestinal ammonia production contributes to the development of hyperammonemia [61]. Commonly used treatments such as lactulose and rifaximin can modify the intestinal environment, but their clinical benefit cannot be explained solely by changes in microbiota composition [61].

FMT has also been examined for the treatment of recurrent HE. In the THEMATIC trial, FMT added to standard therapy was reported to reduce the recurrence rate during follow-up and to provide evidence of engraftment of donor microorganisms in the gut [62]. An increase in *Lachnospiraceae* was associated with a sustained response [62]. These findings support further research into microbiome-based therapies for HE. Current evidence is insufficient, however, to recommend FMT as routine treatment or to define the optimal donor, preparation, and dose.

Viral hepatitis and the gut microbiome

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have been associated with changes in the composition and metabolism of the gut microbiota [63, 64]. In chronic HBV infection, depletion of beneficial microorganisms and enrichment of *Enterobacteriaceae* and *Veillonellaceae* have been linked to fibrosis and immune dysregulation [63, 65]. Changes in gut microbiota composition have also been reported during nucleoside and nucleotide analogue therapy [66].

After HCV treatment with direct-acting antivirals, microbial diversity may increase, particularly in patients without advanced liver disease [64, 67]. This finding suggests that at least part of the dysbiosis observed in viral hepatitis may be related to the degree of hepatic dysfunction and may change as the disease resolves.

Whether dysbiosis that persists after viral suppression contributes independently to residual fibrosis progression or to other forms of clinical progression has not yet been clarified. At present, therefore, microbiome assessment in viral hepatitis should be regarded as a research tool rather than as a component of standard antiviral monitoring.

Autoimmune hepatitis: microbial signatures and immune dysregulation

In patients with autoimmune hepatitis (AIH), depletion of SCFA-producing bacterial species and enrichment of certain taxa, including *Veillonella*, have been reported [68]. A microbial panel comprising several species distinguished AIH patients from healthy controls with an AUROC of 0.83 [68].

These findings point to a strong relationship between the gut microbiota and the immune system in AIH. Impaired intestinal barrier function, microbial translocation, and an imbalance in T helper 17 (Th17)/regulatory T cell (Treg) differentiation are among the proposed mechanisms [29, 69, 70]. Experimental studies also suggest that specific commensal microorganisms may influence hepatic inflammation [69].

Current evidence is insufficient to determine whether dysbiosis is a trigger of AIH pathogenesis or develops secondary to inflammation and hepatic dysfunction [71]. The role of microbiome-based therapies in AIH should therefore remain a research question.

Primary biliary cholangitis

In primary biliary cholangitis (PBC), the gut microbial composition is markedly altered, with reduced microbial diversity, depletion of *Ruminococcus bromii*, and enrichment of *Haemophilus* and *Veillonella* [72, 73]. The correlation of these changes with biochemical disease stage suggests that gut microbiome alteration in PBC may be more than an incidental finding and may provide meaningful evidence of disease-related complications. Microbial changes associated with ursodeoxycholic acid (UDCA) therapy have also been reported [72]. Although these findings point to a possible interaction between treatment, bile acid metabolism, and intestinal microbial ecology, they do not show that the therapeutic effect of UDCA is mediated through the microbiome. Metabolomic findings relating to bile acids and fatty acids support a biological interaction between the gut and the biliary system, but prospective studies are needed to confirm these relationships mechanistically [73].

Primary sclerosing cholangitis, hepatocellular carcinoma, and unifying themes

Primary sclerosing cholangitis (PSC) frequently coexists with inflammatory bowel disease [74]. Reduced microbial diversity and shifts in the proportions of bile acid-metabolizing or pro-inflammatory microorganisms have been reported in PSC [11, 75]. Because chronic inflammation and microbial products may contribute to tumor development, microbial and bacterial metabolite-related pathways are also being investigated in hepatocellular carcinoma (HCC) [10].

In HCC patients receiving immune checkpoint inhibitors, differences in pretreatment fecal microbial composition have been shown to be associated with treatment response [76]. These findings raise the possibility of developing microbiome-derived predictive biomarkers. The association does not prove, however, that altering the microbiome will improve the efficacy of immunotherapy. Microbial profiles must be validated prospectively before they can guide treatment selection.

Table 1 (Ref. [34, 63, 65, 68, 70, 73, 77–94]) summarizes

Table 1. Patterns of dysbiosis in liver and kidney diseases.

Disease	Depleted Taxa	Enriched Taxa	Key Metabolic Consequences
NAFLD/MASLD	*Faecalibacterium*, *Coprococcus*, and *Ruminococcus* [77]	*E. coli* (enriched in advanced disease; some strains ethanol-producing) [34]	Impaired FXR signaling, increased endogenous ethanol, LPS translocation [78]
Alcohol-related liver disease	Butyrate-producing *Clostridiales* [79]	*Veillonella*, *Streptococcus* (oral-origin taxa) [80]	Tight junction disruption and endotoxemia [81]
Hepatic encephalopathy	*Lachnospiraceae*, *Ruminococcaceae*, and other butyrate producers [82]	*Enterobacteriaceae*, *Streptococcaceae* [82]	Hyperammonemia, systemic inflammation [83]
Chronic HBV	Decreased *Bifidobacteriaceae*/*Enterobacteriaceae* ratio (ratio-level change; taxon-level depletion not established) [84]	*Veillonellaceae* [85]; *Enterobacteriaceae* [65]	Peripheral immune modulation, fibrosis progression [63]
Autoimmune hepatitis	*Lachnospira* and *Ruminococcaceae* [68]	*Veillonella* [68]	Th17/Treg imbalance, immune activation [70]
PBC	*Ruminococcaceae*, *Faecalibacterium* [86]	*Haemophilus*, *Veillonella* [73]	Altered bile acid metabolism, immune-mediated bile-duct injury [86]
PSC	Reduced overall diversity [87]	*Veillonella*, *Streptococcus*, and *Enterococcus* [88]	Biliary inflammation; microbiome-related immune effects remain under investigation [88]
CKD (stages 3–5)	*Faecalibacterium*, *Roseburia*, *Prevotella* [89]	*Enterobacteriaceae*, *Clostridium* [90]	IS, PCS, and TMAO accumulation; intestinal barrier dysfunction [91]
Post-kidney transplant	Butyrate-producing commensals [92]	*Proteobacteria* [92]	Tacrolimus metabolism; dysbiosis associated with rejection [93, 94]

NAFLD, non-alcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HBV, hepatitis B virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; CKD, chronic kidney disease; IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine N-oxide; LPS, lipopolysaccharide; FXR, farnesoid X receptor; Th17, T helper 17 cells; Treg, regulatory T cells; E. coli, Escherichia coli.

the principal patterns of dysbiosis reported in liver and kidney diseases. Similar changes in the intestinal barrier and in microbial metabolism are also seen in patients with MASLD [95]. Although these findings support continued research, their clinical significance varies by disease. Microbiome measurements are not yet used in routine hepatological assessment.

Microbiome interactions in kidney diseases

Chronic kidney disease and gut dysbiosis

The global prevalence of chronic kidney disease is estimated at approximately 12–15% [96]. Studies have shown that the composition of the gut microbiota differs according to the stage of CKD [27]. In cohorts of CKD patients, decreased abundance of short-chain fatty acid-producing bacteria such as *Faecalibacterium prausnitzii* and *Roseburia* has been reported, together with increased abundance of proteolytic or urease-containing families such as *Enterobacteriaceae* and *Clostridiaceae* [16]. This microbial shift is consistent with increased amino acid fermentation and greater production of uremic toxin precursors. The causal nature of this relationship, however, has not yet been clarified. Declining renal function, dietary restrictions, medication use, and uremia-related changes in the intestinal environment can all affect microbiota composition.

Uremic toxins of microbial origin

Among the uremic toxins produced in the gut (Table 2, Ref. [97–99]), indoxyl sulfate and p-cresyl sulfate are the most extensively studied [100]. Gut bacteria metabolize tryptophan and tyrosine to form the precursors of these toxins, respectively [101]. A decline in glomerular filtration rate is associated with rising circulating levels of IS and PCS [14, 46]. Hepatic oxidation of the compounds generated by microbial metabolism of dietary choline and L-carnitine produces trimethylamine N-oxide, which has been linked to cardiovascular disease [46, 47]. Because IS and PCS are bound to plasma proteins, their removal by conventional hemodialysis is limited [14]. High uremic toxin levels have been associated with CKD progression and mortality [44], but residual renal function must be considered as an important factor when these associations are evaluated [102].

Mechanisms of uremic toxin-mediated injury

Experimental models examined in several studies reveal possible mechanisms of the cellular injury that uremic toxins may cause. These pathways are thought to participate in

Table 2. Major gut-derived uremic toxins: sources, pathways, and clinical impact.

Uremic Toxins	Precursor/Source	Metabolic Pathway	Target Organ Injury	Clinical Correlations
Indoxyl sulfate (IS)	Tryptophan	Bacterial tryptophanase → indole → hepatic sulfation	AhR activation in tubular/endothelial cells; NF-κB, TGF-β signaling; oxidative stress	CKD progression, cardiovascular events, all-cause mortality [97]
p-Cresyl sulfate (PCS)	Tyrosine	Bacterial fermentation → p-cresol → hepatic sulfation	ROS generation, leukocyte activation, podocyte injury	CKD progression, cardiovascular mortality [98]
TMAO	Choline, L-carnitine	Bacterial TMA lyase → TMA → hepatic FMO3 oxidation	Renal fibrosis, endothelial dysfunction, foam cell formation	Atherosclerosis, renal fibrosis, cardiovascular events in CKD [99]

IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine N-oxide; AhR, aryl hydrocarbon receptor; NF-κB, nuclear factor kappa B; TGF-β, transforming growth factor beta; ROS, reactive oxygen species; TMA, trimethylamine; FMO3, flavin-containing monooxygenase 3; CKD, chronic kidney disease.

inflammation and fibrosis. Nevertheless, direct extrapolation of mechanisms observed in experimental models to human CKD should be approached with care. The interaction can be viewed as bidirectional within the framework of the reciprocal relationships of the kidney-gut axis: declining renal function increases toxin retention and alters the intestinal environment, while gut-derived metabolites may act on pathways associated with disease progression [14, 15].

Intestinal barrier dysfunction in CKD

Intestinal barrier dysfunction in CKD is the result of several mechanisms operating simultaneously. Uremia may impair the function of tight junction proteins, fluid overload may cause mucosal edema, and bacterial urease may disrupt epithelial integrity by converting luminal urea to ammonia [103]. Translocation of microbial products across the compromised barrier has been associated with systemic inflammation and cardiovascular risk [99]. Dialysis-related hemodynamic changes may add to this process [104]. It remains difficult, however, to determine the clinical contribution of each mechanism independently of the severity of the kidney disease itself.

Microbiome alterations after kidney transplantation

Kidney transplantation can alter the composition of the gut microbiota through factors such as perioperative antibiotic use and long-term immunosuppression [105]. Increased abundance of *Proteobacteria* and decreased abundance of butyrate-producing bacteria have been reported in transplant recipients, and these changes have been observed to persist for more than a year after transplantation [92]. Early findings indicate that specific microbial species after transplantation may be associated with altered tacrolimus metabolism and with graft outcomes. Prospective interventional studies are needed, however, to establish any causal relationships [106].

Microbiome and immunological interactions

Gut microbiome and immune homeostasis

Commensal bacteria interact continuously with pattern recognition receptors on epithelial cells and mucosal immune cells, in particular Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors [107]. The microbial signals transmitted through these interactions induce the differentiation of regulatory T cells, calibrate the Th17/Treg axis, and regulate mucosal immunoglobulin A (IgA) secretion, thereby helping to maintain the immune homeostasis on which both the liver and the kidney depend [30].

Immunological consequences in liver diseases

In liver disease, increased intestinal permeability may raise exposure to pathogen-associated toxins reaching the portal circulation [108]. LPS and other microbial toxins activate Kupffer cells and hepatic stellate cells through pattern recognition pathways, including TLR signaling, and thereby contribute to inflammation and fibrogenesis [109]. Short-chain fatty acids, in contrast, may influence histone deacetylase activity and the differentiation of regulatory T cells [20]. Current data support a biological interaction between intestinal microbial activity and hepatic immunity, but the impact of this interaction in individual liver diseases has not yet been clarified.

Immunological consequences in kidney diseases

CKD-associated systemic inflammation is influenced by translocated microbial products and by retained uremic solutes that activate inflammatory pathways in renal and circulating immune cells [110]. This has been linked experimentally to oxidative stress in renal tissue [99]. IgA nephropathy offers a distinct example of a possible gut-kidney immune connection: abnormal mucosal immune responses have been implicated in the production of galactose-deficient IgA1 [111] and in the formation of nephritogenic immune complexes [112]. These observations do not establish a single microbiome-driven mechanism across renal diseases, but they identify pathways that warrant disease-specific study [113].

The gut-liver-kidney immune axis

Hepatorenal syndrome is a clinical condition that illustrates the interaction of intestinal, hepatic, circulatory, and renal

processes. Portal hypertension and impaired intestinal barrier function may increase bacterial translocation [114]; the ensuing systemic inflammation may then interact with circulatory dysfunction and renal vasoconstriction [115]. Preclinical studies have reported that acetate and butyrate supplementation may reduce renal ischemia-reperfusion injury through effects on histone deacetylase activity in tubular and immune cells [116]. Although these findings provide insight into possible mechanisms, they are insufficient to support the use of short-chain fatty acids as treatment for hepatorenal syndrome or other combined liver-kidney disorders.

Microbiome modulation and therapeutic approaches

The demonstration of a relationship between intestinal dysbiosis and liver and kidney diseases has increased interest in microbiome-based therapeutic approaches. These range from dietary components and microbial preparations to fecal microbiota transplantation, and they also include experimental methods aimed at modifying specific microbial functions (Table 3, Ref. [60, 62, 117–119]). Whereas probiotics, prebiotics, synbiotics, and FMT have been evaluated in clinical trials, engineered live biotherapeutic products (LBPs), bacteriophages, and postbiotics remain at an experimental stage in the context of liver and kidney diseases [120, 121].

Improvements in microbial composition or inflammatory markers do not always correspond to clinically meaningful outcomes. Differences in disease stage, nutritional status, medication use, and the interventions themselves make comparisons between studies difficult. Microbiome-based therapies should accordingly not be treated as a single therapeutic category but evaluated separately according to the disease and the treatment response under study.

Probiotics, prebiotics, and synbiotics: evidence from meta-analyses

Probiotics, prebiotics, and synbiotics are among the most frequently investigated microbiome-targeted interventions in liver and kidney disease [122].

A meta-analysis published in 2024 reported that probiotic, prebiotic, or synbiotic supplementation had favorable effects in reducing liver enzymes, lipid profiles, and inflammatory cytokines in patients with NAFLD [123]. Differences between formulations indicate that these interventions should not be regarded as equivalent. Comparing treatments that share

Table 3. Comparison of microbiome-targeted therapeutic approaches in liver and kidney diseases.

Therapeutic Approach	Mechanism of Action	Strongest Evidence	Key Limitations
Probiotics	Introduction of defined beneficial strains	NAFLD: improved ALT and fibrosis markers (meta-analysis, 37 RCTs) [117]	Strain-specific effects; limited uremic toxin reduction in CKD alone
Prebiotics	Fermentable substrates promoting SCFA-producing commensals	CKD: meta-analysis shows reduction in PCS and IS [118]	Gastrointestinal tolerance; variable individual responses
Synbiotics	Combined probiotic + prebiotic for substrate-driven effects	NAFLD: formulation-dependent improvements in TNF-α, GGT [119] (meta-analysis, 34 RCTs); CKD: modest uremic toxin reduction	Heterogeneous formulations; lack of standardization; inconsistent results across trials
FMT	Whole-ecosystem microbial restoration	HE: reduced recurrence (THEMATIC trial) [62]; alcoholic hepatitis: improved 90-day survival [60]	Infection risk in immunocompromised; regulatory barriers; donor variability
Rifaximin	Gut-acting antibiotic that modifies microbial function	HE: established prophylaxis for recurrent episodes	Minor effects on microbial diversity; resistance concerns with prolonged use
Engineered LBPs	Genetically modified bacteria degrading specific substrates	PKU: phenylalanine reduction (phase 2 trial, SYNB1934)	Early-stage; no hepatic/renal trials completed yet
Bacteriophage therapy	Selective lysis of pathogenic species	Alcoholic hepatitis: reduced injury in cytolysin+ *E. faecalis* model; NAFLD: phage against *K. pneumoniae*	Requires rapid pathogen ID; phage resistance; personalized selection
Postbiotics	Bioactive microbial metabolites without live organisms	Pasteurized *A. muciniphila*: improved insulin sensitivity (RCT)	Limited clinical data; optimal formulations undefined

FMT, fecal microbiota transplantation; HE, hepatic encephalopathy; LBP, live biotherapeutic product; PKU, phenylketonuria; RCT, randomized controlled trial; SCFA, short-chain fatty acid; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; TNF-α, tumor necrosis factor alpha; IS, indoxyl sulfate; PCS, p-cresyl sulfate; NAFLD, non-alcoholic fatty liver disease; CKD, chronic kidney disease; E. faecalis, Enterococcus faecalis; K. pneumoniae, Klebsiella pneumoniae.

common mechanisms and similar clinical endpoints within the same analytical framework may help to assess their relative effects, but it does not mean that the interventions are interchangeable.

Although these findings are promising, they should be interpreted with caution in clinical practice. Because between-study heterogeneity exceeded 60% for most outcomes and the strains, doses, and treatment durations used varied markedly, it is difficult to conclude that the reported effects are consistent and generalizable [124]. In addition, the reported benefits are based mainly on treatment responses in surrogate endpoints. The current evidence is therefore insufficient to support the routine use of any particular formulation as standard treatment.

In CKD, one of the principal therapeutic goals is to reduce the levels of gut-derived uremic toxins. In a meta-analysis of seven trials with a total of 331 patients, prebiotics ranked highest for lowering PCS levels and probiotics ranked highest for lowering IS levels [118]. Most of the individual effects, however, did not reach statistical significance, and the limited number of participants reduced confidence in the ranking of the interventions.

Small randomized trials of synbiotics containing *Lactobacillus* and fiber have reported changes in PCS, IS, or inflammatory markers in predialysis and hemodialysis patients [118, 125]. These studies, however, were short in duration, enrolled small samples, and produced inconsistent results. A reduction in uremic toxin levels does not show that supplementation slows CKD progression or improves survival [126]. Longer trials with standardized preparations and clinically meaningful outcomes are needed to evaluate these effects.

Fecal microbiota transplantation: efficacy and emerging safety data

Unlike the transfer of single strains, FMT transplants a complex microbial community containing a large number of microorganisms. Among liver diseases, recurrent hepatic encephalopathy is one of the indications for which the clinical evidence for this approach is most advanced [19].

In the THEMATIC trial, 60 patients with cirrhosis and recurrent HE were randomized to receive FMT capsules or placebo. Patients treated with FMT experienced fewer recurrent HE episodes during 24 weeks of follow-up, and greater intestinal engraftment of *Lachnospiraceae* members was associated with durability of response [62]. Although the findings are clinically meaningful, the single-center design and limited sample size reduce their generalizability.

Pande and colleagues compared FMT with prednisolone in patients with severe alcohol-associated hepatitis. Among the 112 participants who completed the trial, 90-day survival was 75% in the FMT group and 56.6% in the prednisolone group (p = 0.044) [60]. Although the difference in survival was significant, the absence of blinding and of a placebo control group complicates interpretation of the findings. The results need to be confirmed in larger, multicenter trials before FMT can be accepted as an effective treatment for this indication.

Evidence in kidney disease is not yet adequate and rests largely on experimental models and small exploratory studies [112, 127]. Findings obtained in liver disease thus cannot be extrapolated directly to CKD.

The frequency of conditions such as impaired intestinal barrier function and immunosuppression in cirrhosis makes safety assessment particularly important in potential candidates. Transmission of extended-spectrum beta-lactamase-producing *Escherichia coli* (*E. coli*) via donor stool has caused invasive infections and has made stricter donor screening criteria necessary [128]. A systematic review reported that FMT can cause adverse events, most of which consisted of mild gastrointestinal symptoms [129].

Rigorous donor screening and patient-level assessment of infection risk are prerequisites for the safe use of FMT [130]. Particularly in patients with hepatic and renal disease, the inadequacy of long-term safety data and surveillance protocols shows that short-term adverse event data alone are not sufficient to demonstrate safety [131]. The persistence of donor organisms in the recipient and the potential transfer of antimicrobial resistance determinants should be treated not merely as theoretical concerns but as fundamental safety questions that must be answered through long-term follow-up. Safety is therefore not a secondary criterion added after efficacy assessment; it is a basic condition that determines the benefit-risk balance of FMT and which patient groups can be enrolled in trials. Future studies should include protocols that monitor these risks systematically.

Antibiotics and the microbiome

Antibiotics illustrate the difficulty of distinguishing deliberate microbiome modulation from unintended microbial disruption. Rifaximin is used as a mainstay of therapy for the prevention of recurrent HE and appears to affect microbial metabolic activity without producing major changes in overall microbiota structure [61, 132]. Its clinical benefit shows that modifying microbial function can be clinically relevant even when no major taxonomic changes are observed.

This view should not be generalized to systemic broad-spectrum antibiotics. Repeated antibiotic exposure can reduce microbial diversity, increase the risk of *Clostridioides difficile* infection, and promote antimicrobial resistance [133]. This problem is relevant to CKD patients, who often receive repeated courses of antimicrobial therapy for urinary tract or dialysis access infections [134, 135]. Whether antibiotic-associated microbiome disruption independently worsens renal outcomes in humans requires prospective evaluation.

Engineered live biotherapeutic products

Engineered LBPs represent a different therapeutic approach: rather than changing the overall structure of the microbiome, genetically modified organisms are designed to perform predefined metabolic tasks [136]. Clinical evidence for this approach is so far limited to fields outside hepatology and nephrology.

SYNB1934, an *E. coli* Nissle 1917 strain engineered to express phenylalanine ammonia lyase, reduced postprandial phenylalanine exposure by 43% in a phase 2 trial in patients with phenylketonuria [137]. This finding suggests that engineered intestinal bacteria can modulate clinically meaningful metabolic pathways.

Potential applications in liver and kidney disease remain conceptual. Strategies that could be investigated include strains designed to reduce indole or trimethylamine production in CKD or to modify bile acid metabolism in liver disease [138, 139]. Although some clinical studies evaluating the efficacy of engineered live biotherapeutic products in hepatic or renal indications have been completed, therapeutic efficacy has not yet been demonstrated [140]. LBPs should consequently be regarded as experimental therapies rather than as treatment options that will be available in the near term.

Bacteriophage therapy: precision targeting of pathogenic species

Bacteriophages can selectively target specific bacterial strains while largely preserving the overall structure of the microbial community [141]. This specificity makes bacteriophages a promising approach in disorders in which a particular microorganism or microbial product has been linked to disease severity.

In the cohort of 79 patients with alcohol-associated hepatitis studied by Duan *et al*. [142], cytolysin-producing *Enterococcus faecalis* (*E. faecalis*) was detected in 31.6% of patients (25/79); 180-day mortality was 89% in cytolysin-positive and 3.8% in cytolysin-negative patients. This association rests on a single cohort and its external validation is limited. In a prospective cohort conducted in Denmark, cytolysin positivity was detected in only 10.7% of patients (3/28), and 180-day mortality in the cytolysin-positive and cytolysin-negative groups was 1/3 and 9/25, respectively (p = 1.0) [143]. With only three positive patients, this study was not powered to exclude a prognostic difference. The available data therefore show that prevalence varies between populations, but they neither confirm nor exclude the prognostic association. Bacteriophages targeting cytolytic *E. faecalis* strains reduced hepatic injury and inflammation in an experimental model of alcohol-associated liver disease [142, 144]. In experimental models, targeting high-alcohol-producing *Klebsiella pneumoniae* strains with bacteriophages has also been shown to improve hepatic steatosis [93].

Although these studies provide evidence that disease-associated bacterial species can be targeted therapeutically, they have not yet demonstrated the therapeutic efficacy of this approach in patients. No randomized human trial has evaluated the efficacy of bacteriophage therapy in hepatic or renal indications [145]. Translation into clinical practice will require reliable identification of the target pathogenic strain, assessment of phage resistance, standardized manufacturing, and appropriate regulatory standards. Bacteriophage therapy is therefore, at this stage, a preclinical precision-microbiome strategy.

Postbiotics: potential without the administration of live microorganisms

Postbiotics aim to reproduce beneficial microbial functions without the need to administer live microorganisms. The fact that live microbial therapies raise safety concerns in certain populations, including patients receiving immunosuppressive treatment, makes this approach potentially important. A theoretical safety advantage, however, should not be regarded as evidence of clinical superiority.

In a randomized study of overweight and obese individuals, supplementation with pasteurized *Akkermansia muciniphila* was reported to improve insulin sensitivity and several metabolic parameters [49]. Other approaches include SCFAs, bile acid derivatives, and microbial tryptophan metabolites intended to reproduce functions associated with a healthy intestinal microbiome [4, 146].

Results specific to hepatic and renal disease remain limited [147]. Because no postbiotic product has established efficacy in these indications, the optimal compound, dose, route of administration, and target population remain uncertain. Although postbiotics thus constitute a promising area of research where the administration of live microorganisms is undesirable, their potential role in hepatology and nephrology has not yet been established by the available clinical evidence.

Future directions and clinical applications

Next-generation analytical approaches

The value of microbiome analysis will depend less on identifying bacterial differences than on its power to detect microbial functions associated with disease characteristics or treatment response. Shotgun metagenomics and metatranscriptomics characterize microbial species and functions in greater detail than 16S rRNA analysis, while metabolomics can identify circulating or intestinal metabolites associated with microbial activity [4, 148]. Using these approaches together may therefore provide a more comprehensive and informative assessment than examining microbial composition alone.

Several studies support this potential. A fecal metagenomic classifier based on 37 species distinguished the presence of advanced fibrosis in individuals with NAFLD with an AUROC of 0.94 [53, 54]. The diagnostic discrimination of microbial analysis has been demonstrated in cirrhosis cohorts from different geographic regions [54]. In patients with hepatocellular carcinoma, differences in the abundance of *Lachnospiraceae* and *Ruminococcaceae* have been reported to be associated with the response to immune checkpoint inhibitors [149].

Although these findings are promising, diagnostic discrimination demonstrated in a single population should not be regarded as evidence of clinical benefit. Before microbiome-based analyses can be used for fibrosis assessment or treatment decisions, the additional value they provide over validated clinical scores and imaging methods must be confirmed in independent prospective cohorts. Because diet, medication use, and individual characteristics can substantially influence microbial structure, it is also important to test whether the findings remain consistent across different geographic populations.

In the short term, multi-omics approaches are expected to contribute more to the elucidation of disease mechanisms than to diagnostic applications. Examining the relationships between microbial genes and metabolites such as IS, PCS, TMAO, SCFAs, and bile acid derivatives may help to identify the microbial functions that act on disease progression. It may also make it possible to investigate whether the observed

effects reflect potentially pathogenic functions or changes that accompany disease without demonstrating direct causality.

Toward personalized microbiome medicine

The fundamental difficulty in microbiome-based therapy is inter-individual variation. Patients with the same clinical diagnosis differ markedly in baseline microbial composition, diet, medication exposure, intestinal barrier integrity, host metabolism, and immunity [4]. These inter-individual differences may partly explain why apparently similar microbiome therapies have produced inconsistent results in clinical trials [150].

This heterogeneity has increased interest in using microbial and metabolic analyses to identify individuals who are most likely to respond to treatment. In liver disease, microbiome-based analyses that could be used for fibrosis stratification have been investigated [53, 54]. In CKD, measurement of the microbial pathways that generate IS and PCS may provide information beyond circulating toxin concentrations [151]. These approaches, however, are still at the research stage.

Which types of analysis are needed for clinically usable personalization has not yet been clarified. Taxonomic abundance measurements alone are not expected to be sufficient. Future stratification models may benefit from integrating data on microbial functions with metabolomic findings and conventional clinical variables. Whether host genetic data would add predictive value to such models remains uncertain.

Inferences about therapeutic efficacy call for even greater caution. Experimental findings indicate that specific microbial pathways can be targeted by engineered bacteria or bacteriophages. Differences in SCFA production or uremic toxin metabolism are also thought to influence responses to dietary or microbial therapies. Although these observations generate hypotheses for prospective trials, directing patients to specific microbiome-based therapies on the basis of their individual microbial profiles is not yet recommended.

Developing a clinically useful and prudent microbiome strategy requires more than demonstrating an association between microbial features and disease. A proposed biomarker must be reproducible, predict clinically meaningful outcomes, and provide information beyond existing markers [152]. It must also be shown that an intervention selected on the basis of the biomarker can improve clinical outcomes [152]. None of the approaches discussed in this section yet meets all of these criteria.

Challenges for clinical translation

The gap between the evidence obtained in studies and routine clinical practice remains a problem. One of the principal reasons for this gap is the difficulty of selecting suitable patients. In current trials, patients are enrolled according to conventional diagnostic categories rather than validated microbiome-based phenotypes [153]. There are also no consensus criteria for determining which patients with liver disease or CKD would benefit most from microbiome-directed therapies.

Safety is another important limitation, especially for interventions that involve the transfer of live microorganisms or complex microbial communities. This concern is particularly relevant in patients with decompensated cirrhosis and in transplant recipients, in whom intestinal barrier disruption or immunosuppression may increase the risk of donor-derived infection. Experience with FMT has demonstrated the critical importance of donor screening in reducing the risk of transmitting infectious pathogens and antimicrobial-resistant microorganisms [128]. Appropriate long-term surveillance strategies for populations with liver and kidney disease, however, have not yet been defined [131].

A third, methodological, challenge is the difficulty of reproducing study results. Differences in specimen collection and storage conditions, DNA extraction and sequencing platforms, the choice of 16S variable regions, reference databases, and bioinformatic analysis methods can cause biologically similar samples to be characterized as different microbial profiles [154]. Diet, geographic location, age, medication use, and comorbidities [131] introduce further sources of variation. This is a major limitation particularly when microbial analyses developed in single-center studies are proposed as biomarkers for broader populations.

The clinical evaluation of microbiome-based therapies also presents several difficulties. Probiotic and synbiotic products differ in strain, dose, and substrate, whereas FMT differs in donor, preparation method, route of administration, and the site of microbial engraftment [155]. This diversity makes it difficult to determine whether inconsistent trial results arise from the therapeutic approach itself or from differences between the individual interventions [156].

Questions concerning standardization remain unresolved. FMT, engineered LBPs, and bacteriophage-based therapies [157] differ from one another in their composition and in the requirements of their manufacturing processes [156]. A single standard is accordingly not expected to cover all microbiome therapeutics.

For these reasons, more detailed sequencing alone is not sufficient to bring microbiome-based approaches into routine clinical practice [158]. Future studies should use standardized methods, include adequate numbers of participants, and evaluate clinically meaningful outcomes [159]. Biomarkers and therapeutic approaches must also be validated in prospective studies. The fundamental question to be answered is not whether dysbiosis occurs in liver and kidney diseases, but whether measuring or modifying it improves the patient's clinical course relative to current treatment.

Limitations

This review has several limitations. As a narrative review, it did not follow a predefined systematic review protocol, and study selection may therefore be open to bias. The literature search was conducted in the PubMed, Scopus, and Web of Science databases, and randomized trials, systematic reviews, meta-analyses, and prospective studies were prioritized. Some relevant publications may nevertheless have been missed.

The results summarized here carry important limitations with regard to direct comparison between studies and the generalizability of the findings. Differences in patient populations, disease stages, microbiome sampling and analytical methods, and outcome definitions make it difficult to evaluate the ob-

served effects robustly. In addition, a substantial proportion of the pathophysiological relationships rests on cross-sectional human studies or experimental models; although these findings offer biologically acceptable explanations, they do not by themselves establish causality or the success of clinical interventions. Changes in microbial diversity or metabolite concentrations should thus not be interpreted as evidence of clinical benefit unless improvement in patient-relevant outcomes has been demonstrated.

Microbiome research has rapidly reached a broad research community; the evidence presented here therefore reflects only the literature within the stated search period and may need to be updated as new study findings emerge. Although technological advances improve the analysis and characterization of the microbiome, they do not in themselves provide evidence of clinical validity or of improvement in patient outcomes. The current results should consequently be interpreted carefully, taking into account the early stage of clinical development and the need for independent validation.

Conclusion

The evidence accumulated over the past decade suggests that there is a meaningful relationship between the intestinal microbiome and hepatic and renal pathologies, and that this relationship may operate through shared biological pathways. Disruption of the intestinal barrier and microbial translocation, together with changes in bile acid and short-chain fatty acid metabolism [160] and the accumulation of gut-derived metabolites, offer consistent explanations of how dysbiosis may be linked to inflammation and organ dysfunction [13, 161]. These shared pathways support viewing the gut-liver and gut-kidney axes as intersecting biological systems rather than as separate processes. This consistency alone, however, does not prove causality or the benefit of clinical interventions. The clinical importance of this framework therefore needs to be confirmed in studies that examine patient outcomes.

The level of evidence differs markedly between the explanation of biological mechanisms and the evaluation of therapeutic applications. Microbiome-based therapies have produced promising results in defined clinical settings, and hepatic encephalopathy is one of the areas in which the clinical evidence is strongest [162, 163]. By contrast, the evidence in metabolic liver disease and CKD is more limited and inconsistent [13, 18, 164], and engineered LBPs, bacteriophages, and postbiotics remain largely experimental [165]. Favorable results obtained in a particular disease or with a particular intervention should thus not be interpreted as evidence of the general clinical efficacy of microbiome-based approaches. Likewise, changes in microbial composition or in certain biomarkers should not be regarded as clinical benefit unless improvement in patient-relevant outcomes has been demonstrated.

Future research should establish which microbiome findings are reproducible across different populations and whether they provide information beyond established clinical markers. Whether interventions selected on the basis of these findings improve patient-relevant outcomes should then be assessed with standardized sampling methods, adequately powered multicenter trials, and longer follow-up [166, 167]. Clearer and more consistent reporting of diet, medication exposure, and disease stage is also required [166].

The microbiome offers a useful framework for studying the interactions between the gut, liver, kidney, and immune system [168]. Its place in clinical practice, however, has not yet been clarified; the current evidence supports continued research in this field rather than its broad integration into hepatology and nephrology practice [166, 168].

Availability of data and materials

Not applicable. This is a review article and no original data were generated.

Author contributions

MYS—conceived the review, performed the literature search, drafted the manuscript, critically revised the content, and approved the final version for submission.

Ethics approval and consent to participate

Not applicable. This is a review article and does not involve human or animal subjects.

Acknowledgment

Not applicable.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Declaration of generative Artificial Intelligence (AI) use

AI-assisted tools were used for language editing and reference formatting during manuscript preparation. All scientific content, data interpretation, and conclusions are the sole responsibility of the author, who reviewed and verified the entire text. The author takes full responsibility for the accuracy of the final manuscript.

References

1. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. Journal of Hepatology. 2023; 79: 516–537.
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020; 395: 709–733.
3. Cheung A, Ahmed A. Nonalcoholic fatty liver disease and chronic kidney disease: a review of links and risks. Clinical and Experimental Gastroenterology. 2021; 14: 457–465.

4. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nature Medicine. 2018; 24: 392–400.
5. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022; 71: 1020–1032.
6. Fei DL, Liu Y, Liu J, Yu Z, Dong JL. Gut microbiota and the "gut-liver-kidney axis" theory: from mechanisms to therapeutics. Frontiers in Microbiology. 2025; 16: 1554458.
7. Integrative HMP (iHMP) Research Network Consortium. The integrative human microbiome project. Nature. 2019; 569: 641–648.
8. Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, *et al*. The gut-liver axis and the intersection with the microbiome. Nature Reviews Gastroenterology & Hepatology. 2018; 15: 397–411. Erratum in: Nature Reviews Gastroenterology & Hepatology. 2018; 15: 785.
9. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. Journal of Hepatology. 2020; 72: 558–577.
10. Hsu CL, Schnabl B. The gut-liver axis and gut microbiota in health and liver disease. Nature Reviews Microbiology. 2023; 21: 719–733.
11. Pabst O, Hornef MW, Schaap FG, Cerovic V, Clavel T, Bruns T. Gut-liver axis: barriers and functional circuits. Nature Reviews Gastroenterology & Hepatology. 2023; 20: 447–461.
12. Panwar S, Sharma S, Tripathi P. Role of barrier integrity and dysfunctions in maintaining the healthy gut and their health outcomes. Frontiers in Physiology. 2021; 12: 715611.
13. Yang T, Richards EM, Pepine CJ, Raizada MK. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nature Reviews Nephrology. 2018; 14: 442–456.
14. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. Journal of the American Society of Nephrology. 2014; 25: 1897–1907.
15. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, *et al*. Chronic kidney disease alters intestinal microbial flora. Kidney International. 2013; 83: 308–315.
16. Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL, Vaziri ND. Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. American Journal of Nephrology. 2014; 39: 230–237.
17. Şumlu E, Terzioğlu MA. New therapeutic approaches targeting the gut microbiota in chronic kidney disease. 2023. Available at: https://hdl.handle.net/20.500.12498/6436 (Accessed: 28 October 2026).
18. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D. Gut microbiome in chronic kidney disease: challenges and opportunities. Translational Research. 2017; 179: 24–37.
19. Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, *et al*. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology. 2017; 66: 1727–1738.
20. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nature Reviews Immunology. 2016; 16: 341–352.
21. Tanca A, Abbondio M, Palomba A, Fraumene C, Manghina V, Cucca F, *et al*. Potential and active functions in the gut microbiota of a healthy human cohort. Microbiome. 2017; 5: 79.
22. Zhang D, Jian YP, Zhang YN, Li Y, Gu LT, Sun HH, *et al*. Short-chain fatty acids in diseases. Cell Communication and Signaling. 2023; 21: 212.
23. Wu J, Wang K, Wang X, Pang Y, Jiang C. The role of the gut microbiome and its metabolites in metabolic diseases. Protein & Cell. 2021; 12: 360–373.
24. Xu Y, Bi WD, Shi YX, Liang XR, Wang HY, Lai XL, *et al*. Derivation and elimination of uremic toxins from kidney-gut axis. Frontiers in Physiology. 2023; 14: 1123182.
25. Zhang Y, Sun C, Wang Y, Zhang H, Fan Y, Zhao H, *et al*. Targeting gut-liver-kidney axis: microbiota-derived metabolites and therapeutic implications. Cell Communication and Signaling. 2026; 24: 107.
26. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, *et al*. Altered profile of human gut microbiome is associated with cirrhosis and its complications. Journal of Hepatology. 2014; 60: 940–947.
27. Zhao J, Ning X, Liu B, Dong R, Bai M, Sun S. Specific alterations in gut microbiota in patients with chronic kidney disease: an updated systematic review. Renal Failure. 2021; 43: 102–112.
28. Ning L, Zhou YL, Sun H, Zhang Y, Shen C, Wang Z, *et al*. Microbiome and metabolome features in inflammatory bowel disease via multi-omics integration analyses across cohorts. Nature Communications. 2023; 14: 7135.
29. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. Nature Reviews Immunology. 2017; 17: 219–232.
30. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Research. 2020; 30: 492–506.
31. Wang B, Luan J, Zhao W, Yu J, Li A, Li X, *et al*. Comprehensive multiomics analysis of the signatures of gastric mucosal bacteria and plasma metabolites across different stomach microhabitats in the development of gastric cancer. Cellular Oncology. 2025; 48: 139–159.
32. Wang S, Lv D, Jiang S, Jiang J, Liang M, Hou F, *et al*. Quantitative reduction in short-chain fatty acids, especially butyrate, contributes to the progression of chronic kidney disease. Clinical Science. 2019; 133: 1857–1870.
33. Odenwald MA, Ramaswamy R, Lin H, Lehmann C, Moran A, Mullowney MW, *et al*. Fecal butyrate and deoxycholic acid concentrations correlate with mortality in patients with liver disease. Gastro Hep Advances. 2025; 4: 100695.
34. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology. 2021; 19: 55–71.
35. Milosevic I, Vujovic A, Barac A, Djelic M, Korac M, Radovanovic Spurnic A, *et al*. Gut-liver axis, gut microbiota, and its modulation in the management of liver diseases: a review of the literature. International Journal of Molecular Sciences. 2019; 20: 395.
36. Schmitt J, Kong B, Stieger B, Tschopp O, Schultze SM, Rau M, *et al*. Protective effects of farnesoid X receptor (FXR) on hepatic lipid accumulation are mediated by hepatic FXR and independent of intestinal FGF15 signal. Liver International. 2015; 35: 1133–1144.
37. Huang F, Zheng X, Ma X, Jiang R, Zhou W, Zhou S, *et al*. Theabrownin from Pu-erh tea attenuates hypercholesterolemia via modulation of gut microbiota and bile acid metabolism. Nature Communications. 2019; 10: 4971.
38. Perino A, Demagny H, Velazquez-Villegas L, Schoonjans K. Molecular physiology of bile acid signaling in health, disease, and aging. Physiological Reviews. 2021; 101: 683–731.
39. Li T, Chiang JY. Bile acid signaling in metabolic disease and drug therapy. Pharmacological Reviews. 2014; 66: 948–983.
40. Albhaisi SAM, Bajaj JS. The influence of the microbiome on NAFLD and NASH. Clinical Liver Disease. 2021; 17: 15–18.
41. Evenepoel P, Poesen R, Meijers B. The gut-kidney axis. Pediatric Nephrology. 2017; 32: 2005–2014.
42. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. Journal of the American Society of Nephrology. 2014; 25: 657–670.
43. Deltombe O, Van Biesen W, Glorieux G, Massy Z, Dhondt A, Eloot S. Exploring protein binding of uremic toxins in patients with different stages of chronic kidney disease and during hemodialysis. Toxins. 2015; 7: 3933–3946.
44. Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins. 2021; 13: 142.
45. Wang X, Yang S, Li S, Zhao L, Hao Y, Qin J, *et al*. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. Gut. 2020; 69: 2131–2142.
46. Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, *et al*. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circulation Research. 2015; 116: 448–455.
47. Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circulation Research. 2020; 127: 553–570.
48. Song Y, Yang X, Yu C. Understanding and treating hepatorenal syndrome: insights from recent research. Seminars in Liver Disease. 2025; 45: 328–347.
49. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, *et al*. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nature Medicine. 2019; 25: 1096–1103.

50. Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DPY, Fu J, *et al*. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes. 2017; 8: 351–358.
51. Ren R, Liang X, Wei X. Metabolic dysfunction-associated steatotic liver disease: pathogenesis and novel treatment options. Molecular Biomedicine. 2026; 7: 80.
52. Zhang J, Tong X, Lin W, Issa R, Wang L, Zhang B, *et al*. Bidirectional crosstalk of the gut-liver axis in metabolic dysfunction-associated steatotic liver disease. Chinese Medical Journal. 2026; 139: 1876–1878.
53. Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, *et al*. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metabolism. 2017; 25: 1054–1062.e5. Erratum in: Cell Metabolism. 2019; 30: 607.
54. Oh TG, Kim SM, Caussy C, Fu T, Guo J, Bassirian S, *et al*. A universal gut-microbiome-derived signature predicts cirrhosis. Cell Metabolism. 2020; 32: 878–888.e6. Erratum in: Cell Metabolism. 2020; 32: 901.
55. Caussy C, Tripathi A, Humphrey G, Bassirian S, Singh S, Faulkner C, *et al*. A gut microbiome signature for cirrhosis due to nonalcoholic fatty liver disease. Nature Communications. 2019; 10: 1406.
56. Seki E, Schnabl B. Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut. The Journal of Physiology. 2012; 590: 447–458.
57. Hamamah S, Iatcu OC, Covasa M. Dietary influences on gut microbiota and their role in metabolic dysfunction-associated steatotic liver disease (MASLD). Nutrients. 2024; 17: 143.
58. Stärkel P, Schnabl B. Bidirectional communication between liver and gut during alcoholic liver disease. Seminars in Liver Disease. 2016; 36: 331–339.
59. Szabo G. Gut-liver axis in alcoholic liver disease. Gastroenterology. 2015; 148: 30–36.
60. Pande A, Sharma S, Khillan V, Rastogi A, Arora V, Shasthry SM, *et al*. Fecal microbiota transplantation compared with prednisolone in severe alcoholic hepatitis patients: a randomized trial. Hepatology International. 2023; 17: 249–261.
61. Campion D, Giovo I, Ponzo P, Saracco GM, Balzola F, Alessandria C. Dietary approach and gut microbiota modulation for chronic hepatic encephalopathy in cirrhosis. World Journal of Hepatology. 2019; 11: 489–512.
62. Bajaj JS, Fagan A, Gavis EA, Sterling RK, Gallagher ML, Lee H, *et al*. Microbiota transplant for hepatic encephalopathy in cirrhosis: the THEMATIC trial. Journal of Hepatology. 2025; 83: 81–91.
63. Shen Y, Wu SD, Chen Y, Li XY, Zhu Q, Nakayama K, *et al*. Alterations in gut microbiome and metabolomics in chronic hepatitis B infection-associated liver disease and their impact on peripheral immune response. Gut Microbes. 2023; 15: 2155018.
64. Hsu YC, Chen CC, Lee WH, Chang CY, Lee FJ, Tseng CH, *et al*. Compositions of gut microbiota before and shortly after hepatitis C viral eradication by direct antiviral agents. Scientific Reports. 2022; 12: 5481.
65. Nasta P, Di Gregorio M, Zaia M, Carosi G. Gut microbiota alterations associated with viral activity in chronic hepatitis B. Archives of Case Reports. 2026; 10: 21–29.
66. Lu YX, He CZ, Wang YX, Ai ZS, Liang P, Yang CQ. Effect of entecavir on the intestinal microflora in patients with chronic hepatitis B: a controlled cross-sectional and longitudinal real-world study. Infectious Diseases and Therapy. 2021; 10: 241–252.
67. Chuaypen N, Jinato T, Avihingsanon A, Nookaew I, Tanaka Y, Tangkijvanich P. Long-term benefit of DAAs on gut dysbiosis and microbial translocation in HCV-infected patients with and without HIV coinfection. Scientific Reports. 2023; 13: 14413.
68. Lou J, Jiang Y, Rao B, Li A, Ding S, Yan H, *et al*. Fecal microbiomes distinguish patients with autoimmune hepatitis from healthy individuals. Frontiers in Cellular and Infection Microbiology. 2020; 10: 342.
69. Sun C, Zhu D, Zhu Q, He Z, Lou Y, Chen D. The significance of gut microbiota in the etiology of autoimmune hepatitis: a narrative review. Frontiers in Cellular and Infection Microbiology. 2024; 14: 1337223.
70. Cheng Z, Yang L, Chu H. The gut microbiota: a novel player in autoimmune hepatitis. Frontiers in Cellular and Infection Microbiology. 2022; 12: 947382.
71. Zhang L, Yang L, Chu H. Targeting gut microbiota for the treatment of primary biliary cholangitis: from bench to bedside. Journal of Clinical and Translational Hepatology. 2023; 11: 958–966.
72. Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, *et al*. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut. 2018; 67: 534–541.
73. Lv LX, Fang DQ, Shi D, Chen DY, Yan R, Zhu YX, *et al*. Alterations and correlations of the gut microbiome, metabolism and immunity in patients with primary biliary cirrhosis. Environmental Microbiology. 2016; 18: 2272–2286.
74. Lazaridis KN, LaRusso NF. Primary sclerosing cholangitis. The New England Journal of Medicine. 2016; 375: 1161–1170.
75. Allegretti JR, Kassam Z, Carrellas M, Mullish BH, Marchesi JR, Pechlivanis A, *et al*. Fecal microbiota transplantation in patients with primary sclerosing cholangitis: a pilot clinical trial. The American Journal of Gastroenterology. 2019; 114: 1071–1079.
76. Lee PC, Wu CJ, Hung YW, Lee CJ, Chi CT, Lee IC, *et al*. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. Journal for ImmunoTherapy of Cancer. 2022; 10: e004779.
77. Li F, Ye J, Shao C, Zhong B. Compositional alterations of gut microbiota in nonalcoholic fatty liver disease patients: a systematic review and meta-analysis. Lipids in Health and Disease. 2021; 20: 22.
78. Chen J, Vitetta L. Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. International Journal of Molecular Sciences. 2020; 21: 5214.
79. Wolstenholme JT, Duong NK, Brocato ER, Bajaj JS. Gut-liver-brain axis and alcohol use disorder: treatment potential of fecal microbiota transplantation. Alcohol Research: Current Reviews. 2024; 44: 01.
80. Dubinkina VB, Tyakht AV, Odintsova VY, Yarygin KS, Kovarsky BA, Pavlenko AV, *et al*. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. Microbiome. 2017; 5: 141.
81. Rao R. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. Hepatology. 2009; 50: 638–644.
82. Bajaj JS. The role of microbiota in hepatic encephalopathy. Gut Microbes. 2014; 5: 397–403.
83. Zhu R, Liu L, Zhang G, Dong J, Ren Z, Li Z. The pathogenesis of gut microbiota in hepatic encephalopathy by the gut-liver-brain axis. Bioscience Reports. 2023; 43: BSR20222524.
84. Wang J, Wang Y, Zhang X, Liu J, Zhang Q, Zhao Y, *et al*. Gut microbial dysbiosis is associated with altered hepatic functions and serum metabolites in chronic hepatitis B patients. Frontiers in Microbiology. 2017; 8: 2222.
85. Li SQ, Shen Y, Zhang J, Weng CZ, Wu SD, Jiang W. Immune modulation of gut microbiota and its metabolites in chronic hepatitis B. Frontiers in Microbiology. 2023; 14: 1285556.
86. Zhou YJ, Ying GX, Dong SL, Xiang B, Jin QF. Gut microbial profile of treatment-naive patients with primary biliary cholangitis. Frontiers in Immunology. 2023; 14: 1126117.
87. Hov JR, Karlsen TH. The microbiome in primary sclerosing cholangitis: current evidence and potential concepts. Seminars in Liver Disease. 2017; 37: 314–331.
88. Little R, Wine E, Kamath BM, Griffiths AM, Ricciuto A. Gut microbiome in primary sclerosing cholangitis: a review. World Journal of Gastroenterology. 2020; 26: 2768–2780.
89. Zhang Y, Zhong W, Liu W, Wang X, Lin G, Lin J, *et al*. Uncovering specific taxonomic and functional alteration of gut microbiota in chronic kidney disease through 16S rRNA data. Frontiers in Cellular and Infection Microbiology. 2024; 14: 1363276.
90. Xu KY, Xia GH, Lu JQ, Chen MX, Zhen X, Wang S, *et al*. Impaired renal function and dysbiosis of gut microbiota contribute to increased trimethylamine-N-oxide in chronic kidney disease patients. Scientific Reports. 2017; 7: 1445.
91. Lau WL, Savoj J, Nakata MB, Vaziri ND. Altered microbiome in chronic kidney disease: systemic effects of gut-derived uremic toxins. Clinical Science. 2018; 132: 509–522.
92. Swarte JC, Douwes RM, Hu S, Vich Vila A, Eisenga MF, van Londen M, *et al*. Characteristics and dysbiosis of the gut microbiome in renal transplant recipients. Journal of Clinical Medicine. 2020; 9: 386.
93. Gan L, Feng Y, Du B, Fu H, Tian Z, Xue G, *et al*. Bacteriophage targeting

microbiota alleviates non-alcoholic fatty liver disease induced by high alcohol-producing Klebsiella pneumoniae. Nature Communications. 2023; 14: 3215.
94. Degraeve AL, Haufroid V, Loriot A, Gatto L, Andries V, Vereecke L, *et al*. Gut microbiome modulates tacrolimus pharmacokinetics through the transcriptional regulation of ABCB1. Microbiome. 2023; 11: 138.
95. Bai J, Zhang L, He L, Zhou Y. Altered mitochondrial function: a clue therapeutic strategies between metabolic dysfunction-associated steatotic liver disease and chronic kidney disease? Frontiers in Nutrition. 2025; 12: 1613640.
96. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, *et al*. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLOS ONE. 2016; 11: e0158765.
97. Lano G, Burtey S, Sallée M. Indoxyl sulfate, a uremic endotheliotoxin. Toxins. 2020; 12: 229.
98. Gryp T, Vanholder R, Vaneechoutte M, Glorieux G. p-cresyl sulfate. Toxins. 2017; 9: 52.
99. Rukavina Mikusic NL, Kouyoumdzian NM, Choi MR. Gut microbiota and chronic kidney disease: evidences and mechanisms that mediate a new communication in the gastrointestinal-renal axis. Pflügers Archiv: European Journal of Physiology. 2020; 472: 303–320.
100. Hardjo M, Wakamatsu T, Watanabe K, Yamazaki S, Yamamoto S. Comprehensive bibliometric analysis of uremic toxin research. Toxins. 2025; 17: 537.
101. Snelson M, Kellow NJ, Coughlan MT. Modulation of the gut microbiota by resistant starch as a treatment of chronic kidney diseases: evidence of efficacy and mechanistic insights. Advances in Nutrition. 2019; 10: 303–320.
102. Eloot S, Van Biesen W, Glorieux G, Neirynck N, Dhondt A, Vanholder R. Does the adequacy parameter Kt/V(urea) reflect uremic toxin concentrations in hemodialysis patients? PLOS ONE. 2013; 8: e76838.
103. Vaziri ND, Yuan J, Nazertehrani S, Ni Z, Liu S. Chronic kidney disease causes disruption of gastric and small intestinal epithelial tight junction. American Journal of Nephrology. 2013; 38: 99–103.
104. Meijers B, Jouret F, Evenepoel P. Linking gut microbiota to cardiovascular disease and hypertension: lessons from chronic kidney disease. Pharmacological Research. 2018; 133: 101–107.
105. Ahmad S, Bromberg JS. Current status of the microbiome in renal transplantation. Current Opinion in Nephrology and Hypertension. 2016; 25: 570–576.
106. Lee JR, Muthukumar T, Dadhania D, Taur Y, Jenq RR, Toussaint NC, *et al*. Gut microbiota and tacrolimus dosing in kidney transplantation. PLOS ONE. 2015; 10: e0122399.
107. Hill DA, Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. Annual Review of Immunology. 2010; 28: 623–667.
108. Alam N, Jia L, Cheng A, Ren H, Fu Y, Ding X, *et al*. Global research trends on gut microbiota and metabolic dysfunction-associated steatohepatitis: insights from bibliometric and scientometric analysis. Frontiers in Pharmacology. 2024; 15: 1390483.
109. Zheng Z, Wang B. The gut-liver axis in health and disease: the role of gut microbiota-derived signals in liver injury and regeneration. Frontiers in Immunology. 2021; 12: 775526.
110. Lau WL, Kalantar-Zadeh K, Vaziri ND. The gut as a source of inflammation in chronic kidney disease. Nephron. 2015; 130: 92–98.
111. Gesualdo L, Di Leo V, Coppo R. The mucosal immune system and IgA nephropathy. Seminars in Immunopathology. 2021; 43: 657–668.
112. Alobaidi S. The gut-kidney axis in chronic kidney disease: mechanisms, microbial metabolites, and microbiome-targeted therapeutics. Frontiers in Medicine. 2025; 12: 1675458.
113. Magliocca G, Mone P, Di Iorio BR, Heidland A, Marzocco S. Short-chain fatty acids in chronic kidney disease: focus on inflammation and oxidative stress regulation. International Journal of Molecular Sciences. 2022; 23: 5354.
114. Quigley EMM. Bacterial translocation in acute and chronic portal hypertension. Hepatology. 1994; 20: 264–266.
115. Chen YY, Chen DQ, Chen L, Liu JR, Vaziri ND, Guo Y, *et al*. Microbiome-metabolome reveals the contribution of gut-kidney axis on kidney disease. Journal of Translational Medicine. 2019; 17: 5.
116. Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJ, de Almeida DC, *et al*. Gut bacteria products prevent AKI induced by ischemia-reperfusion. Journal of the American Society of Nephrology. 2015; 26: 1877–1888.
117. Song Y, Liu S, Zhang L, Zhao W, Qin Y, Liu M. The effect of gut microbiome-targeted therapies in nonalcoholic fatty liver disease: a systematic review and network meta-analysis. Frontiers in Nutrition. 2025; 11: 1470185.
118. Cedillo-Flores R, Cuevas-Budhart MA, Cavero-Redondo I, Kappes M, Ávila-Díaz M, Paniagua R. Impact of gut microbiome modulation on uremic toxin reduction in chronic kidney disease: a systematic review and network meta-analysis. Nutrients. 2025; 17: 1247.
119. Hadi A, Mohammadi H, Miraghajani M, Ghaedi E. Efficacy of synbiotic supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials: synbiotic supplementation and NAFLD. Critical Reviews in Food Science and Nutrition. 2019; 59: 2494–2505.
120. Rutter JW, Dekker L, Owen KA, Barnes CP. Microbiome engineering: engineered live biotherapeutic products for treating human disease. Frontiers in Bioengineering and Biotechnology. 2022; 10: 1000873.
121. Kim DY, Lee SY, Lee JY, Whon TW, Lee JY, Jeon CO, *et al*. Gut microbiome therapy: fecal microbiota transplantation *vs* live biotherapeutic products. Gut Microbes. 2024; 16: 2412376.
122. Krumbeck JA, Walter J, Hutkins RW. Synbiotics for improved human health: recent developments, challenges, and opportunities. Annual Review of Food Science and Technology. 2018; 9: 451–479.
123. Pan Y, Yang Y, Wu J, Zhou H, Yang C. Efficacy of probiotics, prebiotics, and synbiotics on liver enzymes, lipid profiles, and inflammation in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. BMC Gastroenterology. 2024; 24: 283.
124. Rong L, Ch'ng D, Jia P, Tsoi KKF, Wong SH, Sung JJY. Use of probiotics, prebiotics, and synbiotics in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. 2023; 38: 1682–1694.
125. Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, *et al*. Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. Clinical Journal of the American Society of Nephrology. 2016; 11: 223–231.
126. He M, Wei W, Zhang Y, Xiang Z, Peng D, Kasimumali A, *et al*. Gut microbial metabolites SCFAs and chronic kidney disease. Journal of Translational Medicine. 2024; 22: 172.
127. Barba C, Soulage CO, Caggiano G, Glorieux G, Fouque D, Koppe L. Effects of fecal microbiota transplantation on composition in mice with CKD. Toxins. 2020; 12: 741.
128. U.S. Food and Drug Administration. Fecal microbiota for transplantation: safety communication—risk of serious adverse reactions due to transmission of multi-drug resistant organisms. 2019. Available at: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due (Accessed: 28 October 2026).
129. Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. Alimentary Pharmacology & Therapeutics. 2021; 53: 33–42.
130. Wang JW, Kuo CH, Kuo FC, Wang YK, Hsu WH, Yu FJ, *et al*. Fecal microbiota transplantation: review and update. Journal of the Formosan Medical Association. 2019; 118: S23–S31.
131. Yadegar A, Bar-Yoseph H, Monaghan TM, Pakpour S, Severino A, Kuijper EJ, *et al*. Fecal microbiota transplantation: current challenges and future landscapes. Clinical Microbiology Reviews. 2024; 37: e0006022.
132. Bajaj JS. Alcohol, liver disease and the gut microbiota. Nature Reviews Gastroenterology & Hepatology. 2019; 16: 235–246.
133. Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. Frontiers in Cellular and Infection Microbiology. 2020; 10: 572912.
134. Hui K, Nalder M, Buising K, Pefanis A, Ooi KY, Pedagogos E, *et al*. Patterns of use and appropriateness of antibiotics prescribed to patients receiving haemodialysis: an observational study. BMC Nephrology. 2017; 18: 156.
135. Ramezani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R, Raj

DS. Role of the gut microbiome in uremia: a potential therapeutic target. American Journal of Kidney Diseases. 2016; 67: 483–498.
136. Nazir A, Hussain FHN, Raza A. Advancing microbiota therapeutics: the role of synthetic biology in engineering microbial communities for precision medicine. Frontiers in Bioengineering and Biotechnology. 2024; 12: 1511149.
137. Vockley J, Sondheimer N, Puurunen M, Diaz GA, Ginevic I, Grange DK, *et al*. Efficacy and safety of a synthetic biotic for treatment of phenylketonuria: a phase 2 clinical trial. Nature Metabolism. 2023; 5: 1685–1690.
138. Lubkowicz D, Hava DL, Lewis K, Isabella VM. Rational engineering of *Escherichia coli* Nissle 1917 as live biotherapeutic to degrade uremic toxin precursors. ACS Synthetic Biology. 2024; 13: 1077–1084.
139. Fleishman JS, Kumar S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. Signal Transduction and Targeted Therapy. 2024; 9: 97.
140. Aggarwal N, Kitano S, Puah GRY, Kittelmann S, Hwang IY, Chang MW. Microbiome and human health: current understanding, engineering, and enabling technologies. Chemical Reviews. 2023; 123: 31–72.
141. Principi N, Silvestri E, Esposito S. Advantages and limitations of bacteriophages for the treatment of bacterial infections. Frontiers in Pharmacology. 2019; 10: 513.
142. Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, *et al*. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature. 2019; 575: 505–511.
143. Cold F, Heintz JE, Ghathian KSA, Stenbøg PA, Hansen LH, Carstens AB, *et al*. Low incidence of cytolysin-positive *E. faecalis* and no correlation to survival in Danish patients with alcohol-associated hepatitis: a prospective cohort study. Gut Microbes Reports. 2025; 2: 2549729.
144. Crunkhorn S. Phages fight alcoholic hepatitis. Nature Reviews Drug Discovery. 2020; 19: 20.
145. Fujiki J, Schnabl B. Phage therapy: targeting intestinal bacterial microbiota for the treatment of liver diseases. JHEP Reports. 2023; 5: 100909.
146. Cani PD, Depommier C, Derrien M, Everard A, de Vos WM. Akkermansia muciniphila: paradigm for next-generation beneficial microorganisms. Nature Reviews Gastroenterology & Hepatology. 2022; 19: 625–637. Erratum in: Nature Reviews Gastroenterology & Hepatology. 2022; 19: 682.
147. Chen X, Yuan C, He J, Li W, Liao C. Current research status and trends in the bioactivity of postbiotics. Frontiers in Food Science and Technology. 2025; 5: 1692683.
148. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, *et al*.; for "Precision Medicine and Pharmacometabolomics Task Group"-Metabolomics Society Initiative. Metabolomics enables precision medicine: "a white paper, community perspective". Metabolomics. 2016; 12: 149.
149. Mao J, Wang D, Long J, Yang X, Lin J, Song Y, *et al*. Gut microbiome is associated with the clinical response to anti-PD-1 based immunotherapy in hepatobiliary cancers. Journal for ImmunoTherapy of Cancer. 2021; 9: e003334.
150. Healey GR, Murphy R, Brough L, Butts CA, Coad J. Interindividual variability in gut microbiota and host response to dietary interventions. Nutrition Reviews. 2017; 75: 1059–1080.
151. Wu IW, Lin CY, Chang LC, Lee CC, Chiu CY, Hsu HJ, *et al*. Gut microbiota as diagnostic tools for mirroring disease progression and circulating nephrotoxin levels in chronic kidney disease: discovery and validation study. International Journal of Biological Sciences. 2020; 16: 420–434.
152. Lord SJ, St John A, Bossuyt PM, Sandberg S, Monaghan PJ, O'Kane M, *et al*.; Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine. Setting clinical performance specifications to develop and evaluate biomarkers for clinical use. Annals of Clinical Biochemistry. 2019; 56: 527–535.
153. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nature Reviews Gastroenterology & Hepatology. 2019; 16: 605–616. Erratum in: Nature Reviews Gastroenterology & Hepatology. 2019; 16: 642.
154. Schmidt TSB, Raes J, Bork P. The human gut microbiome: from association to modulation. Cell. 2018; 172: 1198–1215.
155. Young VB. Treatment with fecal microbiota transplantation: the need for complete methodological reporting for clinical trials. Annals of Internal Medicine. 2017; 167: 61–62.
156. Cordaillat-Simmons M, Rouanet A, Pot B. Live biotherapeutic products: the importance of a defined regulatory framework. Experimental & Molecular Medicine. 2020; 52: 1397–1406.
157. Hoffmann DE, Javitt GH, Kelly CR, Keller JJ, Baunwall SMD, Hvas CL. Fecal microbiota transplantation: a tale of two regulatory pathways. Gut Microbes. 2025; 17: 2493901.
158. Porcari S, Ng SC, Zitvogel L, Sokol H, Weersma RK, Elinav E, *et al*. The microbiome for clinicians. Cell. 2025; 188: 2836–2844.
159. Cano RJ, García Menéndez G. Why clinical trials of microbiome-targeted interventions often fail to support health claims: a commentary on probiotics and translational design. Microorganisms. 2026; 14: 470.
160. Anand S, Mande SS. Host-microbiome interactions: gut-liver axis and its connection with other organs. npj Biofilms and Microbiomes. 2022; 8: 89.
161. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, *et al*. Microbiota in health and diseases. Signal Transduction and Targeted Therapy. 2022; 7: 135.
162. Gao J, Nie R, Chang H, Yang W, Ren Q. A meta-analysis of microbiome therapies for hepatic encephalopathy. European Journal of Gastroenterology & Hepatology. 2023; 35: 927–937.
163. Hassouneh R, Bajaj JS. Gut microbiota modulation and fecal transplantation: an overview on innovative strategies for hepatic encephalopathy treatment. Journal of Clinical Medicine. 2021; 10: 330.
164. Bahitham W, Banoun Y, Aljahdali M, Almuaiqly G, Bahshwan SM, Aljahdali L, *et al*. "Trust your gut": exploring the connection between gut microbiome dysbiosis and the advancement of Metabolic Associated Steatosis Liver Disease (MASLD)/Metabolic Associated Steatohepatitis (MASH): a systematic review of animal and human studies. Frontiers in Nutrition. 2025; 12: 1637071.
165. Yadav M, Chauhan NS. Microbiome therapeutics: exploring the present scenario and challenges. Gastroenterology Report. 2022; 10: goab046.
166. Dey P, Choubey S. An urgent need for longitudinal microbiome profiling coupled with machine learning interventions. Frontiers in Microbiology. 2024; 15: 1487841.
167. Zhang WY, Zhang YL, Yu QQ, Zhou JT, Miao H, Liu LM, *et al*. Gut microbial-derived metabolites: key players in kidney disease and renal fibrosis. International Journal of Biological Sciences. 2026; 22: 5421–5443.
168. Allaband C, McDonald D, Vázquez-Baeza Y, Minich JJ, Tripathi A, Brenner DA, *et al*. Microbiome 101: studying, analyzing, and interpreting gut microbiome data for clinicians. Clinical Gastroenterology and Hepatology. 2019; 17: 218–230.