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REVIEW

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Impact of gut microbiota on metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma: pathways, diagnostic opportunities and therapeutic advances

Ayana R. Kumar[1,2], Bhagyalakshmi Nair[1,2], Adithya Jayaprakash Kamath[1,3], Lekshmi R. Nath[1*], Daniela Calina[4*] and Javad Sharifi-Rad[5,6,7*]

Abstract

Metabolic dysfunction-associated steatohepatitis (MASH) and progression to hepatocellular carcinoma (HCC) exhibits distinct molecular and immune characteristics. These traits are influenced by multiple factors, including the gut microbiome, which interacts with the liver through the "gut–liver axis". This bidirectional relationship between the gut and its microbiota and the liver plays a key role in driving various liver diseases, with microbial metabolites and immune responses being central to these processes. Our review consolidates the latest research on how gut microbiota contributes to MASH development and its progression to HCC, emphasizing new diagnostic and therapeutic possibilities. We performed a comprehensive literature review across PubMed/MedLine, Scopus, and Web of Science from January 2000 to August 2024, focusing on both preclinical and clinical studies that investigate the gut microbiota's roles in MASH and HCC. This includes research on pathogenesis, as well as diagnostic and therapeutic advancements related to the gut microbiota. This evidence emphasizes the critical role of the gut microbiome in the pathogenesis of MASH and HCC, highlighting the need for further clinical studies and trials. This is to refine diagnostic techniques and develop targeted therapies that exploit the microbiome's capabilities, aiming to enhance patient care in liver diseases.

Keywords Gut microbiota, Metabolic dysfunction-associated steatohepatitis/non-alcoholic steatohepatitis, Hepatocellular carcinoma, Immune modulation

*Correspondence:
Lekshmi R. Nath
lekshmirnath@aims.amrita.edu
Daniela Calina
calinadaniela@gmail.com
Javad Sharifi-Rad
javad.sharifirad@gmail.com
Full list of author information is available at the end of the article

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Introduction

The human gut consists of an abundant and diverse microbial population and the bacterial density in the colon has been estimated to be 10^{11}–10^{12} per ml [1]. The molecular techniques involving metabolomic, lipidomic, metatranscriptomic and metagenomic deciphered the impact of gut microbial populations in different organs [2]. The alterations in the microbial composition in the gut lead to the development of various diseases including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), type-2 diabetes, atopy, autoimmune diseases (ulcerative colitis, lupus, psoriasis, multiple sclerosis, and Crohn's disease), hepatic steatosis and several types of carcinomas (oral cancer, gastric cancer, colorectal cancer, lung cancer, cervical cancer, gall bladder cancer, hepatocellular carcinoma, etc.) [3–8]. Gut microbiota consists of several microorganisms belonging to the category of bacteria, viruses and yeast. The most prominent bacterial phyla in the composition of gut microbiota are *Firmicutes* and *Bacteroidetes* [9, 10]. Other microbes including *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* are also present. The *Firmicutes* phylum mainly possesses 200 different genera, for example, *Lactobacillus, Clostridium, Bacillus, Ruminococcus and Enterococcus*. *Clostridium* genera are most prominent in (around 95%) the *Firmicutes* phyla. *Bacteroidetes* are composed of prime genera such as *Bacteroides* and *Prevotella* [11, 12]. The clinical study revealed that the presence of bacteria named *Ruminococcus obeum* and *Alistipes* was reduced while *Dorea*, *Lactobacillus*, and *Megasphaera* were enriched in NAFLD patients compared to healthy individuals [1, 13, 14]. Compared to fatty liver patients, NASH patients possess higher levels of *Firmicutes* but lower levels of *Bacteroidetes* at the phylum level [15]. Studies demonstrated that the patients with cirrhosis showed higher levels of *Enterobacteriaceae* and *Streptococcus* and low levels in *Akkermansia*. In HCC patients, the presence of *Bacteroides* and *Ruminococcaceae* was elevated, while *Bifidobacterium* was reduced. Bacteria such as *Akkermansia* and *Bifidobacterium* were inversely correlated with calprotectin concentration (cellular inflammatory markers). The fecal microbial diversity is evident in cirrhosis to early HCC, and the presence of phylum *Actinobacteria* was high in the early stage of HCC. Similarly, *Gemmiger and Parabacteroides* were higher in early HCC than in cirrhosis. On the other hand, butyrate-producing genera declined and lipopolysaccharide-producing genera were enriched in early HCC than healthy individuals [16, 17]. The abnormal increase of *Bacteroidetes/Firmicutes* ratio in NASH patients may increase the occurrence of HCC [18]. Evidence suggests that the changes in the composition and diversity of gut microbiome may lead to the development and progression of different liver diseases. Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), refers to a range of liver conditions characterized by the accumulation of excess fat in the liver (≥ 5% hepatic steatosis). This spectrum of disease begins with steatotic liver disease (SLD), which represents the early stage of liver fat accumulation [19]. As the condition progresses, it may develop into metabolic MASH, formerly known as non-alcoholic steatohepatitis (NASH), which involves liver inflammation and damage, potentially with or without fibrosis. In more advanced stages, MASLD can lead to cirrhosis, liver failure, and even liver cancer [20]. Epidemiological evidence shows that NAFLD, along with its more severe form, non-alcoholic steatohepatitis (NASH), is increasingly recognized as a major contributor to hepatocellular carcinoma (HCC). Dysbiosis in the gut microbiome can disrupt homeostasis, exacerbating liver cell injury by triggering various immune-mediated responses.Several genomic factors interrupt the gut–liver axis and increase microbial exposure to the liver [21]. Evidences indicate that microbial metabolites such as secondary bile acids, trimethylamine, short-chain fatty acids, etc., are responsible for the onset and progression of liver diseases [22]. Improper microbial production and the entry of microbial products into the liver via the portal vein can cause hepatic inflammation and lead to the development of NAFLD to NASH progression [23]. The gut microbiota influences NASH to HCC progression, via modulating different factors, such as gut epithelial permeability, hepatic Toll-like receptor (TLR) endogenous alcohol production, choline metabolism, bile acid metabolism, and release of inflammatory cytokines [24–30]. The present review elaborates on the importance of gut microbiota-mediated influences in MASH and HCC. Also, it highlights the diagnostic and therapeutic importance of gut microbiota in MASH and HCC (Fig. 1) (Table 1).

Methodology

This review was conducted by searching electronic databases to identify studies that report on the role of gut microbiota in the development of metabolic dysfunction-associated steatohepatitis /non-alcoholic steatohepatitis (MASH/NASH) and its progression to hepatocellular carcinoma (HCC). The databases included PubMed/MedLine, Scopus, and Web of Science. The search was conducted from January 2000 to August 2024 to encompass recent developments in the field (Fig. 2). The search strategy employed both Medical Subject Headings (MeSH) and free-text terms to ensure comprehensive coverage of the literature. The MeSH terms used were: "Gut Microbiota" [MeSH];

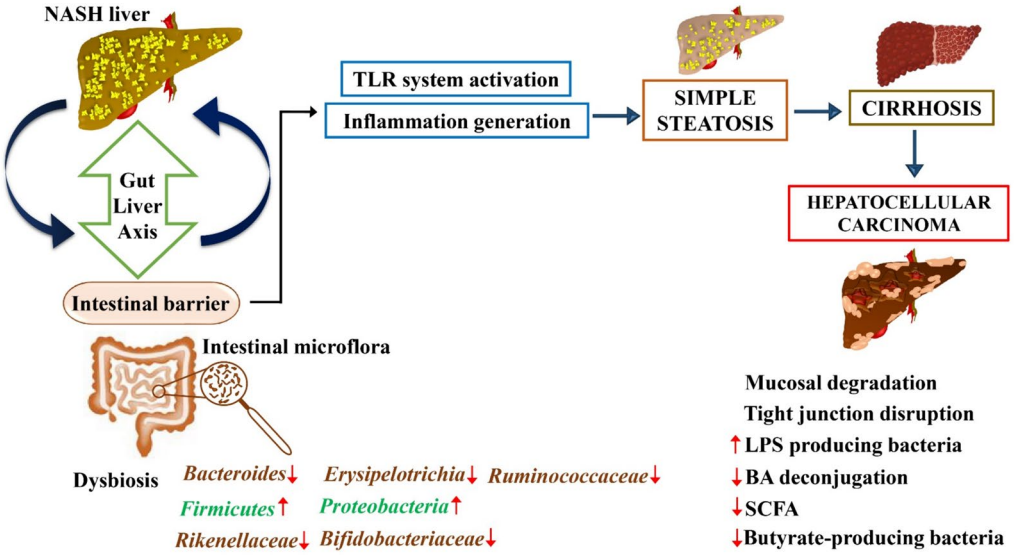

Fig. 1 Progression of liver disease from MASH to hepatocellular carcinoma via gut–liver axis dysregulation. The figure illustrates the pathological progression from MASH to HCC through disruptions in the gut–liver axis. The MASH liver exhibits alterations in the intestinal barrier and gut microbiota, leading to dysbiosis characterized by fluctuations in key bacterial populations. The dysregulated gut microbiota affects the intestinal barrier's integrity, fostering mucosal degradation and tight junction disruption. This breakdown facilitates the systemic infiltration of lipopolysaccharides (LPS) and other bacterial metabolites into the liver through the portal circulation. Increased TLR (Toll-like receptor) activation in the liver induces inflammation, progressing from simple steatosis to cirrhosis and ultimately culminating in hepatocellular carcinoma. Key changes in microbial populations include increased Firmicutes and Proteobacteria, with a decrease in Bacteroides, Erysipelotrichia, Ruminococcaceae, Rikenellaceae, and Bifidobacteriaceae. The figure also notes a decrease in bile acid (BA) deconjugation, short-chain fatty acids (SCFA), and butyrate-producing bacteria, which are critical to maintaining hepatic and intestinal health. Symbols: ↑increase, ↓decrease

Table 1 Expression of different microbiome in MASH-induced HCC

Sl. No	Gut microbiome	Status in MASH	Status in HCC
1	Bacteroides	Bacteroides ↑ [104]	Bacteroides ↑ [105]
2	Enterococcus	Enterococcus ↑ [104]	Enterococcus ↑ [105]
3	Ruminococcaceae	Ruminococcaceae ↑ [104]	Ruminococcaceae ↑ [105]
4	Bifidobacterium	Bifidobacterium ↓ [104]	Bifidobacterium ↓ [105]
5	Oscillospira	Oscillospira ↓ [104]	Oscillospira ↑ [105]
6	Lachnospiraceae	Lachnospiraceae↑ [104]	Lachnospiraceae↑ [105]

"Hepatocellular Carcinoma" [MeSH]; " Metabolic dysfunction-associated fatty liver disease/Non-alcoholic Fatty Liver Disease" [MeSH]; " Metabolic dysfunction-associated steatohepatitis/Non-alcoholic Steatohepatitis" [MeSH]; "Microbiome" [MeSH]; These terms were combined with additional keywords and phrases relevant to the study topic, such as "intestinal microbiome", "liver cancer", "MASH/NASH", "immune modulation", and "therapeutic implications". Boolean operators (AND, OR) were used to combine these terms effectively.

Inclusion criteria:

- Studies published in English.
- Studies that directly investigated the impact of gut microbiota on the pathogenesis, progression, or treatment of MASH/NASH and HCC.
- Both preclinical and clinical studies.
- Reviews, meta-analyses, randomized controlled trials, cohort studies, and case–control studies.

Exclusion criteria:

- Studies published before the year 2000.
- Studies not in English.

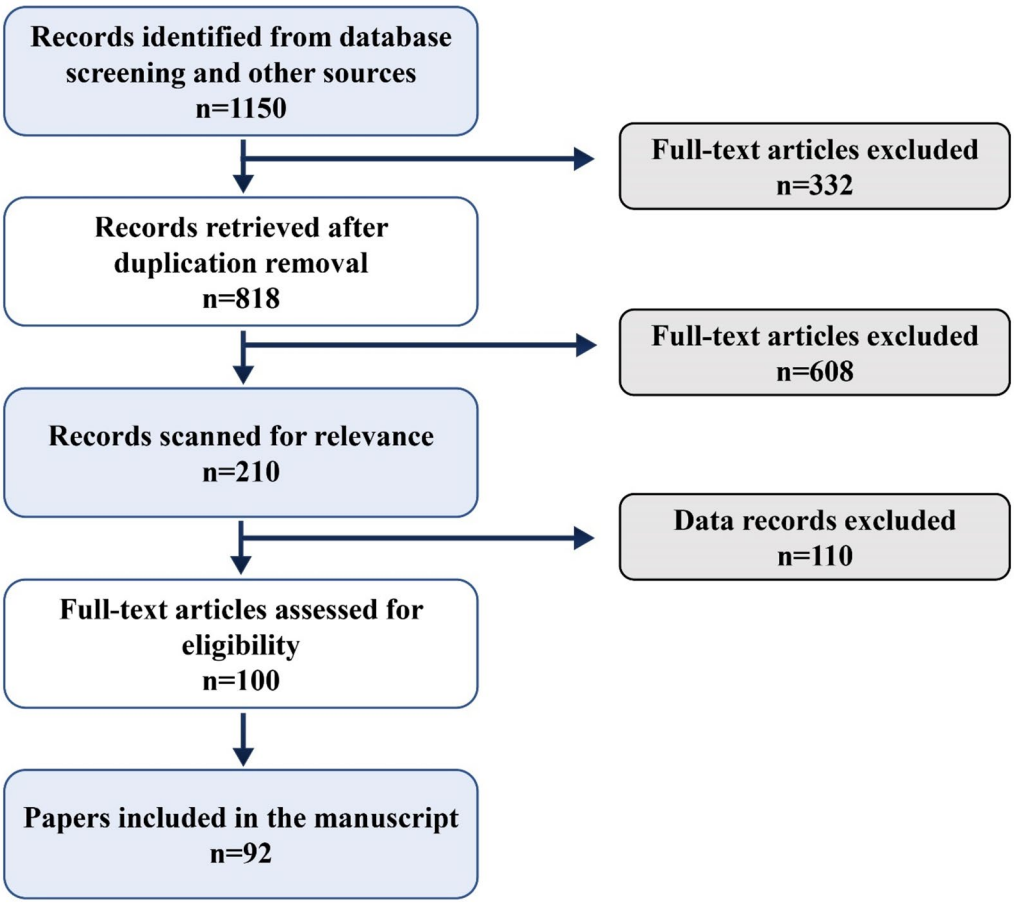

Fig. 2 Flow diagram of the study selection

- Studies focusing on alcoholic liver disease or other forms of liver disease not directly related to MASH/NASH or HCC.
- Commentaries, editorials, and expert opinions without original data or systematic analysis.
- Studies with incomplete data or unclear methodologies.

The most representative data are summarized in tables and figures.

Immune modulatory role of gut microbiota in MAFLD/MASH to HCC progression

Numerous preclinical and clinical studies have established that abnormal expression of gut microbiota and its metabolites are closely associated with liver diseases such as MAFLD, MASH (formerly known as NAFLD and NASH), Cirrhosis and HCC [31, 32]. The alternations in the gut microflora can facilitate the synthesis of free fatty acids (FFA) in the intestine and increase the permeability of FFA across the intestinal area which may lead to the development of NAFLD [33, 34]. The studies indicated that the high-fat diet could increase the number of alcohol-producing bacteria such as *Escherichia* genus members of the *Proteobacteria* phylum in the gut, which may produce acetate and acetaldehyde via the oxidation of ethanol and facilitate the synthesis of fatty acids and contributes to the development of NAFLD [35]. Recent studies suggest that the gut microflora is altered due to genetic predisposition and improper diet which may affect the lipid and hepatic carbohydrate metabolism and also influence the activities of anti-inflammatory and pro-inflammatory agents in the liver and may lead to the development of NAFLD and its progression to NASH [32]. The consumption of obesogenic foods such as a high-fat diet may disrupt the Gram-negative bacteria that are present in the intestinal tract and increase the level of lipopolysaccharides (LPS), which can act as a key regulator for producing inflammatory responses in the liver tissue and produce liver injury via activating TLR4 signaling and cause the development of NAFLD and its progression [34]. Moreover, the high-fat diet can also modulate

the enzyme produced by the gut microbiome, it may act as a catalyst for the conversion of choline into toxic metabolites, known as dimethylamine and trimethylamine. These metabolites can be converted into trimethylamine oxide (TMAO) in the liver, which produces inflammation in the hepatocytes and the progression of NAFLD into NASH [36]. The clinical studies indicated that the overgrowth of bacteria in the small intestine due to high-fat diet and genetic factors in NAFLD patients may increase the risk for the development of NASH [37–39]. Small intestinal bacterial overgrowth (SIBO) prominently affects the progression of NASH in NAFLD patients. Wigg et al. [41] carried out a comparative study to evaluate the presence of SIBO in NASH patients as well as in healthy controls [40]. The report indicated that 50% of NASH patients were observed with SIBO whereas SIBO was limited up to 22% in healthy controls. They evaluated the mean levels of tumor necrosis factor TNF-α in NASH patients and healthy people and it was found to be 14.2 and 7.5 pg/ml, respectively. The amount of intestinal bacteria was quantified via glucose hydrogen breath test and quantitative jejunal aspirate culture (the removal and culture of a sample of intestinal fluid) and the outcome indicated that low-grade SIBO around ≥ 103 CFU/ml in NASH patients compared with that of controls. These data established that patients with NASH have the highest prevalence of SIBO [41]. Shanab et al. [43] reported that an increased level of SIBO in NASH patients increases the hepatic release of interleukin-8 (IL-8) and increases the expression of Toll-like receptors-4 (TLR-4) which facilitates the development and progression of NASH [42]. The imbalance in toll-like receptor (TLR) also contributes to the progression of NAFLD to NASH. Abnormal bacterial DNA, LPS and other endogenous substances can activate the innate immune system via TLR 4 and TLR 9 which will facilitate the production of kuffer cells and interleukin-1β (IL-1β). IL-1β can uphold the accumulation of lipids and also increase the cell death of hepatocytes followed by inflammation and steatosis [43]. Moreover, microbial pathogen-associated molecular patterns can activate different inflammasome such as NLRP1 (NALP1), NLRP3 (NALP3, cryporin), NLRC4 (IPAF), AIM2 and NLRP6 can facilitate the progression of NAFLD and contribute to the initiation of steatosis [44]. The evidence suggests that TLR 4 and microbacteria-derived LPS are the key factors that lead to the progression of cirrhosis [45]. Gut dysbiosis may cause systemic inflammation and immunodeficiency by impairing the functions of immune cells such as T cells, B cells, macrophages, etc., and cause the development of cirrhosis-associated immune dysfunction (CAID). CAID can promote the translocation of bacterial products into the bloodstream and facilitate the intensity of inflammation in the body [46]. Moreover, gut dysbiosis can disrupt the bacterial flora and facilitate the LPS/TLR4-mediated signaling. It can also initiate the cirrhotic to cancer progression via increased secretion of chemokines from HSCs and chemotaxis of Kupffer cells which stimulate the profibrogenic cytokine TGF-b [47]. The cirrhosis to HCC progression is driven by different inflammatory pathways, initiated via the crosstalk between the intestinal bacteria, immune system, and liver. The inflammatory process mainly encompasses the interplay between the macrophages, Kupffer cells, and PAMPs in the liver cells. These Kupffer cells, macrophages, and PAMPs can elicit the NF-κB pathway through binding with nucleotide-binding oligomerization domain-like receptors (NOD-like receptors) and TLRs, particularly TLR-4 and TLR-9 [48]. The gut microbiota-mediated TLR-4 signaling pathway participates in the pro-inflammatory response in the liver and promotes HCC development [49]. The inflammatory chain reactions may elicit excess cytokine release and inflammation in the liver in turn causing dysbiosis of the microbiota. This increases Kupffer cells mediated secretion of inflammatory cytokines, such as *tumor necrosis factor*-α (TNF-α), interleukin-8 (IL-8), and IL-1β. Excessive cytokines may elicit lipid accumulation and apoptosis in hepatocytes and can cause steatosis and inflammation. Increased levels of pro-inflammatory cytokines due to the abnormal regulation of gut microbiota were observed in almost all NAFLD and NASH patients, which promote the development and progression of NASH through TLR-triggered pathways [50, 51]. Thus, gut microbiota-mediated cytokines play a key role in the initiation and progression of NAFLD to NASH to HCC [52–54]. Dysbiosis induced by cirrhosis, coupled with increased intestinal permeability, may trigger the release of pathogen-associated molecular patterns (PAMPs) and metabolites mediated by the gut microbiome, leading to enhanced inflammation, damage, and fat production in the liver [55]. Research indicates that PAMPs initiate the release of cytokines and chemokines such as IL8, IL-17, and IL1β through TLR activation, intensifying immune cell presence in the liver [56, 57]. Continuous production of these cytokines can lead to DNA damage and oxidative stress, thereby initiating and advancing hepatocellular carcinoma (HCC) [57, 58]. Furthermore, metabolites produced by the microbiota, including bile acids, short-chain fatty acids, PAMPs, lipoteichoic acid (LTA), and branched-chain amino acids, are known to activate hepatic stellate cells (HSCs) via the senescence-associated secretory phenotype (SASP), promoting hepatocyte proliferation and increasing susceptibility to HCC [59]. Clinical and preclinical studies demonstrated that bile acid (BA) metabolism also plays a significant role in

NASH to HCC progression. [60, 61]. Increased levels of bile acids in the liver can prompt inflammation, hepatocyte DNA damage, and apoptosis; hence tumorigenesis will occur in the liver [62]. Furthermore, dysbiosis in NASH will increase the abundance of Gram-positive microorganisms in the microflora, thus stimulating HCC through an increase in the synthesis of secondary BA including deoxycholic acid (DCA), which restricts the activation of liver sinusoidal endothelial cell (LSEC) and facilitates the suppression of chemokine ligand 6 (CXCL6), natural killer T cell recruitment (NK), and produce tumorigenesis [63, 64]. Additionally, secondary bile acids directly initiate the development of HCC from NASH via stimulating mTOR signaling [65]. Guerra Ruiz et al. [64] demonstrated that the serum levels of lipopolysaccharides (LBP) were significantly increased in NASH patients compared with healthy patients with simple steatosis. The augmented serum LBPlevel was connected with abnormal expression of tumor necrosis factor (TNF-α) in the liver tissue. The increased level of TNF-α plays a key role in the development of HCC [66, 67]. Obesity is another risk factor that influences the changes in the composition of the microbiota and its metabolites such as LPS or PAMPs [68]. The injured hepatocytes can produce damage-associated molecular patterns (DAMPs) which prompt the inflammatory molecules via TLR and activation of target immune cells and arouse the transition from NAFLD–NASH–HCC [69]. Current evidence indicates that gut microbiome can also have an impact on antitumor responses, which may provide a novel perspective on refining the effectiveness of cancer immunotherapy [70]. Emerging evidence established that the abnormal characterization of gut microbiota can elicit immunosuppression by inducing M2 (pro-tumor)-like tumor-associated macrophage (TAM). Dysbacteriosis associated with IL-25-persuaded activation of M2 macrophages can augment HCC progression by secreting C-X-C motif chemokine ligand 10 (CXCL10) and augment epithelial–mesenchymal transition pathway (EMT) [71]. Studies revealed that gut microbiota can produce oncogenesis and cancer progression in myeloid-derived suppressor cells (MDSC) dependent manner [72]. Abnormal gut microbiome-mediated dysbiosis can disturb homeostasis, consequently prompting immune-mediated hepatocyte injury which further prompts the HCC progression. Metabolomics and metagenomic studies related to gut** microbiota discovered that the gut microbiota causes T cell-mediated immune suppression via increasing the level of regulatory T cells (T reg) and reducing the level of CD8 + T cells including cytotoxic T cells [73]. Moreover, Kang, Y et al., 2021 demonstrated that the gut microbiota can increase the generation of prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) enzymes which inhibits the antitumor immune responses through Prostaglandin E2 receptor 4 (EP4 receptor), hence facilitate HCC progression [29]. The expression of different proteins such as CD68 (Cluster of Differentiation 68) is considered a marker of macrophages and TLR (TLR-2, TLR-4, TLR-5 and TLR-9) plays a negative role in the activation of the innate immune system. Studies demonstrated that CD68 is a tumor-associated macrophage and it leads to the development of NAFLD and NASH-HCC progression [31]. It also indicates that a leaky gut can result in the overproduction of gut microbiota-derived metabolites, potentially impacting the hepatic immune system and increasing the risk of HCC [74] (Fig. 3).

Table 2 summarizes the roles of microbial and immune factors in the progression from MASH to HCC.

Immunotherapeutic significance of modulating gut microbiota in MASH and HCC

NASH-induced dysbiosis in the gut microbiota leads to an increase in intestinal permeability, thereby increasing exposure to bacterial metabolites in the liver and causing severe inflammation, contributing to HCC [76]. Modulating gut microbiota-mediated bile acids (BAs) metabolism, toll-like receptor (TLR) activity, regulating farnesoid X receptor (FXR)/Takeda G protein-coupled receptor 5 (TGR5) activation, choline metabolism, and targeting inflammatory cytokines are considered novel therapeutic options against NASH and NASH-associated HCC [18]. Therapeutic targeting of the gut microbiota against NASH and HCC is highly attractive; meanwhile, these treatment modalities show a low risk of adverse effects and a high safety profile, including fecal microbiota transplantation (FMT), probiotics, prebiotics, synbiotics (combination of prebiotics and probiotics), antibiotics, and immunotherapies [29]. The predominant mechanisms behind the gut microbiota-targeted therapies are as follows: controlling the T helper 17 (Th17) cell proliferation which may raise the secretion of interleukin-17 (IL-17); decreasing the level of metastasis through reduction of the overexpression of vascular endothelial growth factor (VEGF) limiting the angiogenesis lymphangiogenesis, and inflammations [77]. Additionally, alterations in regulating gut microbiota may stimulate the synthesis of short-chain fatty acids (SCFAs) and eventually restrict the progression of NASH to HCC. Modulations in the composition of gut microbiota may upsurge the production of propionate that may help the patients to recover from HCC through cyclic adenosine 3′,5′-monophosphate (cAMP) level-dependent pathway and the stimulation of G protein-coupled receptors 43 (GPR43) [78]. Moreover, regulation of gut microbiota may accomplish an anti-HCC effect by increasing the level of hepatic CXCR6 + NKT cells and

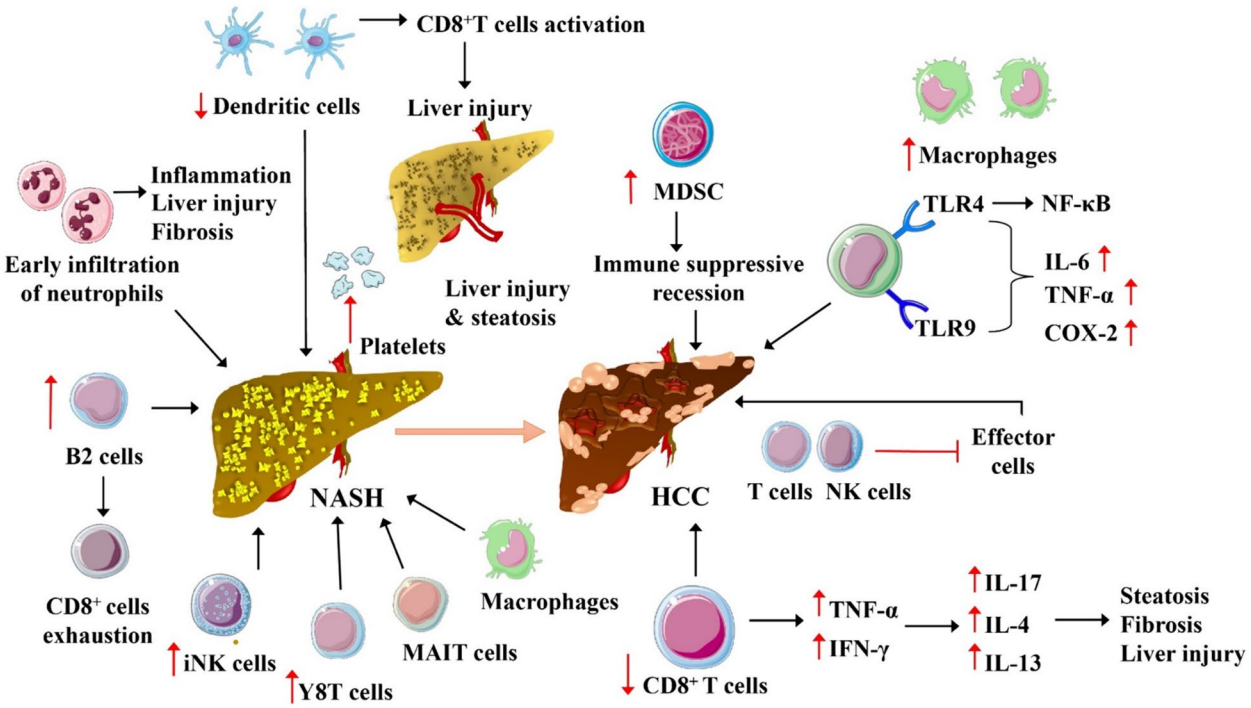

Fig. 3 Potential mechanisms for gut microbiota-associated immune modulation in MASH–HCC progression. This figure illustrates the complex immune interactions and cellular transformations involved in the progression from MASH to HCC. Key features include the early infiltration of neutrophils leading to inflammation, liver injury, and fibrosis, and the role of B2 cells and CD8 + T cells in modulating the immune response. Activation of CD8 + T cells contributes to further liver injury and steatosis, while the presence of myeloid-derived suppressor cells (MDSC) indicates an immune suppressive state facilitating cancer progression. The diagram also highlights the activation of macrophages through toll-like receptors (TLR4 and TLR9) leading to an increase in inflammatory cytokines (IL-6, TNF-α) and COX-2, which are important in the development of HCC. Additionally, the impact of various cytokines such as TNF-α, IFN-γ, IL-17, IL-4, and IL-13 on the hepatic environment, promoting steatosis, fibrosis, and liver injury, is depicted. Abbreviations and symbols: B2 cells: a type of B cell involved in immune response; CD8 + T cells: cytotoxic T cells which are a part of the immune system that kills cancer cells, virus-infected cells, and other damaged cells; COX-2: cyclooxygenase-2, an enzyme that plays a crucial role in inflammation; HCC: hepatocellular carcinoma; IFN-γ: interferon gamma, a cytokine critical for innate and adaptive immunity; IL-4: interleukin 4, a cytokine involved in the regulation of immune responses; IL-6: interleukin 6, a cytokine involved in inflammation and maturation of B cells; IL-13: interleukin 13, involved in inflammatory responses; IL-17: interleukin 17, a pro-inflammatory cytokine; iNK cells: invariant natural killer T cells, a component of the immune system that recognizes lipid antigens; MAIT cells: mucosal-associated invariant T cells, involved in the mucosal immunity; MDSC: myeloid-derived suppressor cells, regulate immune responses in cancer; NASH: non-alcoholic steatohepatitis

elevating the level of interferon-gamma (IFN-γ). Simultaneously, CXCR6 + NKT cell accumulation was controlled through the expression of CXCL16 in the liver sinusoidal endothelial cells, which was connected with microbiome-triggered primary-to-secondary bile acid conversion [79].

Probiotics are primarily utilized to correct microbial imbalances [65]. Clinical applications of probiotic bacteria have demonstrated effectiveness in decelerating the progression of NASH and reducing the spread of HCC cells by diminishing the activation of inflammation mediated by toll-like receptors (TLRs). Pathogen-associated molecular patterns (PAMPs) contribute to the development of NASH and HCC by activating inflammatory responses through TLRs. Using microbial agents, particularly probiotic bacteria, has proven to mitigate liver metastasis by curtailing the excessive inflammatory responses triggered by TLRs [80]. In experiments, rats with liver cirrhosis treated with *Lactiplantibacillus plantarum* exhibited reduced TLR4 expression and minimal liver damage. Additionally, sterilizing the gut and deactivating the TLR4 receptor significantly slowed HCC progression by 80–90%, suggesting their potential as a preventative measure against HCC [81]. Research by Li et al. in 2016, confirmed that a combination of probiotics could limit NASH and its progression to HCC by lowering the levels of pro-inflammatory cytokines like IL-17 in mouse models. It also indicated that probiotics could reduce liver fat and aspartate aminotransferase (AST) levels in NASH patients [82], [NCT00870012, NCT01791959]. Probiotics triggered the growth of gut microbiota composition towards specific beneficial bacteria including *Prevotella* and *Oscillibacter*. *Prevotella*

Table 2 Impact of gut microbiota and immune factors on MAFLD/MASH to HCC progression

Microbial and immune factors	Impact on MAFLD/MASH	Impact on HCC progression	Evidence	References
Small intestinal bacterial overgrowth (SIBO)	Associated with 50% of NASH patients Linked to higher levels of TNF-α	↑ Hepatic inflammation and cytokine production ↑ IL-8, ↑ TLR-4	Clinical study	[41, 42] [43]
TLR-4-mediated pathway	Augments hepatic inflammation by enhancing secretion of pro-inflammatory cytokines (↑) ↑ level of LPS Increase the expression of CD68 (tumor-associated macrophage)	Directly linked to the development of HCC via sustained inflammatory responses (↑) NAFLD and NASH-HCC progression	Preclinical study Germ-free animal model	[31, 48, 49]
Pathogen-associated molecular patterns (PAMPs)	↑Iintestinal permeability allow microbial metabolites to promote liver inflammation (↑)	↑ IL-8, ↑ IL-17, ↑ IL-1β ↑chemokines release, exacerbating liver injury and initiating HCC (↑)	Germ-free animal model Clinical study	[55, 56] [56]
Bile acid metabolism	Dysregulated metabolism contributes to liver inflammation (↑)	Altered metabolism leads to increased secondary bile acids, promoting HCC via mTOR signaling and inflammation (↑)	Clinical study	[58–60]
Prostaglandin E2 (PGE2) and COX-2 enzymes	Not directly mentioned in NAFLD/NASH context	Suppress antitumor immune responses, facilitating HCC progression (↑)	Preclinical study	[30]
DAMPs and cytokine production	Activates inflammatory pathways through TLR stimulation (↑)	↑ Chronic cytokine release ↑DNA damage ↑Oxidative stress ↑HCC progression	Clinical study	[67]
Microbial dysbiosis	This leads to SIBO and imbalances in key bacterial populations, aggravating liver conditions (↑) Promote steatohepatitis via modulating Toll-like receptor 4 (TLR4) and TLR9	Increases the risk of HCC by altering liver immune responses and metabolic functions (↑) HCC was developed due to hepatic inflammation	Clinical study germ-free animal model	[75]

↑: indicates an increase in activity; ↓: indicates a decrease in activity. COX-2: cyclooxygenase-2; DAMPs: damage-associated molecular patterns; HCC: hepatocellular carcinoma; IL-1β: interleukin-1 beta; IL-8: interleukin-8; IL-17: interleukin-17; mTOR: mechanistic target of rapamycin; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PAMPs: pathogen-associated molecular patterns; PGE2: prostaglandin E2; SIBO: small intestinal bacterial overgrowth; TLR-4: toll-like receptor 4; TNF-α: tumor necrosis factor-alpha

and *Oscillibacter* elicit anti-inflammatory metabolites, which afterward diminished the T helper 17 cells (Th17) polarization and increase the differentiation of regulatory T cells ((Treg)/Type 1 regulatory T (Tr1)) cells in the gut and produce anti-inflammatory responses in the cancer cells. Besides, probiotics can control the abnormal growth of segmented filamentous bacteria (SFB), which are the foremost bacteria to increase the level of Th17 in the body. Thus, the administration of probiotics intensely decreases the level of SFB which leads to reduce the production of pro-inflammatory cytokines such as IL-17. The IL-17A formed from Th17 could favor angiogenesis, thus reduction of Th17 and IL-17 level may reduce HCC progression. Different clinical and preclinical studies have shown that probiotics are effective against NASH and HCC [83]. Furthermore, *Helicobacter* sp. was found in the surroundings of NASH cells and its translocation might be possible to elicit HCC. To this end, the intestinal microbial profile might be prominently exhibit the beneficial rates in HCC patients experiencing treatment with immunotherapy such as immune checkpoint inhibitors (ICIs), indicating that the gut micro flora targeted immunotherapy could be beneficial for liver cancer [84]. A double-blind, randomized, placebo-controlled trial of probiotics in patients with Child–Pugh A-B cirrhosis was conducted to evaluate the predictive role and risk of the microbiome in HCC development. In this particular study, they evaluate the role of probiotics towards the presence of endotoxins (LPS) and different cytokines (IL-6 and TNF-α) in the tumor microenvironment (TME) and also evaluate the expression of TLR4 in mononuclear cells (NCT03853928) [85].

Prebiotics are non-absorbent oligosaccharide substances that accelerate the growth of bacteria. It can also reduce the growth of harmful bacteria and maintain the balance of gut microbiota. They mainly initiate the production of SCFAs and regulate the immune responses in the liver cells. Hence, prebiotics alter the gut microbiota to reduce the progression of NASH as well as NASH-associated HCC [86]. Dietary polyphenols are significant prebiotics used in this modern era due to their great therapeutic value. They mainly include flavonoids including lignins, and phenolic acids found in tea, vegetables, nuts, fruits and wine. One of the significant prebiotic

polyphenols is ellagic acid which is an antioxidant having anti-cancer properties. The ellagic acid is metabolized by micro-flora present in the colon producing urolithins that are abundantly present in certain nuts and berries [87]. Urolithins can suppress the COX-2-associated inflammation in liver cells [88]. Another polyphenol such as resveratrol which is naturally found in grapes can also reduce or prevent NASH [89, 90] and HCC progression by destroying the metastatic invasion and tumor cell migration in liver cancer [91, 92]. Resveratrol acts as an immunomodulatory agent by either stimulating the immune cells situated in the tumor microenvironment (TME) or by sensitizing tumor cells toward the cytotoxic signaling of immune cells [93]. Quercetin is another dietary flavonoid that works as a prebiotic through the suppression of activated nuclear factor kappa B (NF-kB) in hepatocytes [94, 95]. A prospective cohort study demonstrated that increasing the consumption of tree nuts such as almonds, hazelnuts, pistachios, macadamias, cashews and pecans was related to a reduced risk of NASH and HCC [96–98]. The combinatorial effects of pectins and fructo-oligosaccharide (FOS) with raspberry polyphenols on microbial fermentation and modulation of inflammation and lipid metabolism in the liver was evaluated and thus suggests, FOS and pectins improved the action of the raspberry polyphenolic extract against NASH and HCC [99, 100]. Moreover, a study on hepatocytes demonstrated that polyphenols extracted from raspberries also control immunometabolic signals connected with the development of obesity [90, 101]. Supplementation with prebiotics will also help the activation of AMPK [102, 103]. *Astragalus* polysaccharides, grifolan, lentinan, and krestin (PSK) display anti-cancer properties by regulating the activity of the immune system and eliciting direct actions against cancer cells [104]. Clinical studies revealed that Omega 3 fatty acid and EPA (eicosapentaenoic acid) are active against HCC [NCT04682665]. Some of the clinical trials also established the effectiveness of synbiotic and prebiotics against NASH [NCT02530138, NCT01791959, NCT03184376 and NCT03897218].

Antibiotics can be also used to reduce or remove the altered gut microbial content; this can help restrict the inflammatory signals from leaky guts. Different preclinical evidences suggest that different antibiotics such as vancomycin, metronidazole, ampicillin, and neomycin significantly decrease HCC proliferation [105]. Antibiotic cocktails (ABX, including vancomycin, primaxin, and neomycin) produce anti-HCC effect. These antibiotics can increase the hepatic CXCR6 + NKT cells and also enhance the level of INF-γ and inhibit cancer cell growth [105]. A phase 2, interventional study was also evaluate the safety and efficacy of solithromycin against NASH without cirrhosis [NCT02510599]. A randomized interventional clinical trial established the effect of rifaximin on the lipopolysaccharides (LPS) and related cytokine levels in NAFLD and NASH [NCT02009592]. The prolonged antibiotics belonging to β-lactams, tetracyclines, fluoroquinolones, sulfonamides, and aminoglycosides impacts human gut flora. They can modify the diversity of bacterial flora and composition leading to the occurrence of various metabolic alterations in the body that contribute to the onset and progression of NAFLD [106]. Deregulated metabolism in the body especially in the metabolism of SCFA may lead to obesity, metabolic syndrome, and diabetes. Moreover, studies indicated that the continuous use of antibiotics can cause the depletion in gut bacterial diversity and may increase the susceptibility to infections [107]. The continuous use of antibiotics may increase the level of the antibiotic-resistant gene in the microbiome. These pools of resistant genes can initiate antibiotic resistance [108]. In this scenario, the major challenge is to facilitate the growth of beneficial microorganisms, meanwhile reducing the proportion of microorganisms that are responsible for dysbiosis to promote the patient's health. Thus, the development of novel antibiotics can be personalized for a patient based on intestinal and biochemical individuality. The use of selective antibiotics will minimize the negative impact of antibiotics on human health due to changes in the gut microbiome [109]. Fecal microbiota transplantation (FMT) is a medical procedure for the transfer of a small sample of stool (faces) from a healthy person to a diseased person [110]. The healthy stool sample comprises trillions of beneficial microbiomes that can ameliorate the health of the diseased person. Studies suggest that FMT can restore the healthy bacteria in the lower intestine, which will also help to terminate the growth of *Clostridium difficile* from the intestinal area [111, 112]. As mentioned earlier a healthy intestinal tract possesses a large number of healthy bacteria, but in certain conditions, the use of antibiotics may restrict the growth of good bacteria, and it may promote the development of unhealthy bacteria in the colon. FMT is usually preferred to treat *Clostridioides difficile* infection (CDI) and also in patients who suffer from IBD [114, 115]. Based on clinical trial of FMT is extended to irritable bowel syndrome, hepatic encephalopathy, diabetes mellitus, refractory diarrhea, fatty liver disease, metabolic syndrome, neurological disease (parkinsonism), and neuropsychiatric disease (autism spectrum disorder) [115, 116]. FMT procedure can be achieved via using different techniques such as colonoscopy, enema, nasogastric (NG) tube and oral capsules (VOWST, SER-109) [117, 118]. Currently, the U.S. Food and Drug Administration (FDA) approves FMT only for the treatment of recurrent CDI that is not responsive to standard antibiotic therapy. Two different

FMT therapies have been approved by the FDA REBYOTA (fecal microbiota, live—JSLM) and VOWST [119]. Studies revealed that FMT elicits around 80–90% in preventing CDI from recurring after antibiotics. Nevertheless, there are several short-term and long-term adverse effects are also associated with FMT [120]. Thus, rigorous donor screening and testing should be mandated to minimize the risk of FMT.

Table 3 outlines the impact of gut microbiota modulation on immune responses in MASH and HCC, detailing therapeutic strategies and their outcomes.

Limitations and challenges

Despite the comprehensive analysis of the role of gut microbiota in the development of non-alcoholic steatohepatitis (NASH) and its progression to hepatocellular carcinoma (HCC) presented in this manuscript, several limitations and challenges remain that need to be addressed:

i. The majority of studies discussed are preclinical, involving animal models or in vitro systems. These studies provide valuable insights, but may not fully replicate the complex interactions and environmental factors influencing human gut microbiota and liver disease progression. Thus, translating these findings into clinical practice requires much attention, as human studies are more variable and complex.
ii. The gut microbiome is extraordinarily complex, with a vast number of microbial species that have not been fully characterized. This complexity makes it challenging to determine causal relationships between specific microbial changes and disease states. The functional roles of many species within the microbiome and their interactions with host metabolism and immunity are still poorly understood.
iii. There is significant variability in microbiota composition among different populations due to factors such as diet, genetics, lifestyle, and antibiotic

Table 3 Immunotherapeutic effect of gut microbiota modulation in MASH and HCC

Category	Agent	Mechanism of Action	Outcome and Benefits	References
Prebiotics	*Kappaphycus striatum*	Carrageenan polysaccharide with different molecular weights	Immunostimulating activities and antitumor effect via increasing NK cell activity	[72]
	Ganoderma lucidum	Elicits immune regulation, decreases blood sugar and lipid levels	Upsurge anti-inflammatory and anti-hypoxia effects; scavenges free radicals	[121]
	Antrodia cinnamomea	Stimulates immune modulatory action via TLR5 and NLRP3	↑Immune response, potentially beneficial against cancer	[122]
	Hirsutella sinensis	↑Cytotoxic T cells ↓Regulatory T cell production in the TME	↑Anti-cancer effects by stimulating T cell activity and inhibiting immune inhibitors	[123]
	Polyphenols	↑immune cells in the TME	↑ immune cells to potentially counteract cancerous growth	[124]
	Lactobacillus acidophilus, Lactobacillus reuteri + Inulin	↑Secretion of Th1 mediated T cells	Augments cytokine secretion (e.g., IFN-γ), ↓angiogenesis, ↑cytotoxicity and antigen presentation	[125]
Probiotics	*Lactobacillus rhamnosus*	Modulates gut microbiota; ↓endotoxemia	↓TNF-α expression, ↓inflammation and liver damage	[126]
	Streptococcus thermophilus	↑Gut homeostasis ↓Intestinal and hepatic inflammation	Helps restrict progression of cirrhosis to HCC	[127]
	Lactiplantibacillus plantarum	↓TLR4 expression, gut sterilization and TLR4 receptor inactivation	Abridges the progression of HCC by 80% to 90%	[56]
Antibiotics	Vancomycin	Inhibits fermentable fiber-induced liver cancer by downregulating TLR	Potentially reduces liver cancer progression	[29, 128]
	Metronidazole	↓Butyrate-producing bacteria	↓Occurrence of HCC by impacting bacterial profiles linked to cancer progression	[129]
	Ampicillin	Interferes with TLR protein	↓HCC progression	[130]
	Neomycin	↓IL-6, ↓TNF-α,↓Ki67	↓Inflammatory and proliferative markers associated with HCC	[130]
Fecal microbiota transplantation	REBYOTA and VOWST	The spore suspension is produced by treating fecal matter with ethanol to kill live organisms that are not spores	Helps to destroy *Clostridioides difficile* from the digestive tract	[113]

HCC: hepatocellular carcinoma; IL-6: interleukin 6; Ki67: a proliferation marker; NASH: non-alcoholic steatohepatitis; NK cells: natural killer cells; NLRP3: NLR family pyrin domain containing 3; TME: tumor microenvironment; TLR: toll-like receptor; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor. Symbols: ↓decrease; ↑increase

use. This variability can affect the reproducibility and applicability of findings across different demographic and geographic groups.

iv. Current methodologies for analyzing the gut microbiome, such as 16S rRNA sequencing and metagenomic sequencing, have limitations in resolution, and accuracy and may not capture the full spectrum of microbial diversity or the functional potential of the microbiome. Additionally, these methods are susceptible to contamination and other technical issues that can affect data quality and interpretation.

v. Modulating the gut microbiota presents a promising therapeutic avenue, but developing effective microbiota-based therapies is challenging. Issues include ensuring the stability and survival of probiotic strains, the unpredictability of prebiotic effects on the existing gut flora, and the potential for adverse effects from broad-spectrum antibiotics.

vi. The regulatory pathway for microbiota-targeted therapies is not fully established, which may pose challenges in clinical trial design, approval, and market access. Safety concerns also remain, particularly regarding the long-term impacts of altering the gut microbiome on immune function and susceptibility to other diseases.

vii. The interactions between gut microbiota-modulating therapies and existing treatments for NASH and HCC are not well understood. These interactions could affect the efficacy and safety profiles of treatments.

viii. The cost of developing microbiota-targeted therapies and the technological demands of such treatments may limit their accessibility, especially in low-resource settings where NASH and HCC are increasingly prevalent.

These limitations underscore the need for further research to better understand the gut microbiome's role in liver diseases and to develop safe, effective, and accessible therapies. Future studies should aim to incorporate larger, more diverse human cohorts, utilize advanced technologies for microbiome analysis, and explore the mechanistic pathways connecting the gut microbiome to liver disease outcomes.

Conclusions

Unhealthy gut microbiota and its metabolites lead to the generation of improper immune signaling in the liver leading to the initiation and progression of different kinds of liver diseases such as MAFLD, MASH, and especially HCC progression. Probiotics, prebiotics, and synbiotics may exemplify advanced, safe, and affordable treatment strategies against these diseases. However, preclinical and well-designed human trials prove that the modifications in the gut microbiota elicit immune modulations in the TME along with anti-tumor response. Understanding the pivotal role of the gut microbiota in the cancer progression may empower the discovery of more effective diagnostic and prevention modalities against HCC. Thus, the treatment of MASH and HCC via targeting the gut microbiota will be an effective research direction in the future for treating MASH-induced HCC. Gene sequencing and machine learning-based data analysis help to identify a key biomarker for the detection of liver illnesses, particularly in MASH-associated HCC. In these circumstances, more numbers of laboratory-based mechanistic evaluations and detailed clinical trials are needed to estimate the composition of gut microflora and this will help to select appropriate useful bacterial strains for the treatment of cancer. Hence, more evidence is needed to translate the existing knowledge relating to the functional aspects of the gut microbiome into diagnostic, prognostic, and therapeutic strategies in patients suffering with HCC. However, evidence suggests that modulation of gut microbiota paves way to a promising therapeutic strategy for the treatment and prevention of MASH and MASH-associated HCC.

Abbreviation lists

ABX	Antibiotic cocktails
AMPK	AMP-activated protein kinase
AST	Aspartate aminotransferase
BA	Bile acid
BAs	Bile acids
COX-2	Cyclooxygenase-2
cAMP	Cyclic adenosine monophosphate
CXCL16	Chemokine (C-X-C motif) ligand 16
CXCR6	C-X-C chemokine receptor type 6
DCA	Deoxycholic acid
DAMPs	Damage-associated molecular patterns
EPA	Eicosapentaenoic acid
FMT	Fecal microbiota transplantation
FXR	Farnesoid X receptor
GPR43	G protein-coupled receptor 43
HCC	Hepatocellular carcinoma
HSCs	Hepatic stellate cells
ICIs	Immune checkpoint inhibitors
IFN-γ	Interferon gamma
IL-1β	Interleukin-1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-17	Interleukin 17
LPS	Lipopolysaccharides
LSEC	Liver sinusoidal endothelial cell
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MDSC	Myeloid-derived suppressor cells
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NF-κB	Nuclear factor kappa B
NK	Natural killer
NKT	Natural killer T
NLRP3	NLR family pyrin domain containing 3

PAMPs	Pathogen-associated molecular patterns
PGE2	Prostaglandin E2
PSK	Polysaccharide krestin
RCTs	Randomized controlled trials
SASP	Senescence-associated secretory phenotype
SCFAs	Short-chain fatty acids
SFB	Segmented filamentous bacteria
SIBO	Small intestinal bacterial overgrowth
TGR5	Takeda G protein-coupled receptor 5
Th17	T helper 17
TLR	Toll-like receptor
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-alpha
Treg	Regulatory T cells
Tr1	Type 1 regulatory T
VEGF	Vascular endothelial growth factor

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Author details
[1]Department of Pharmacognosy, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Ponekkara P. O., Kochi, Kerala 682041, India. [2]Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Science Campus, Ponekkara P. O., Kochi, Kerala 682041, India. [3]Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health. Science Campus, Ponekkara P. O., Kochi, Kerala 682041, India. [4]Department of Clinical Pharmacy, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania. [5]Universidad Espíritu Santo, Samborondón, 092301, Ecuador. [6]Centro de Estudios Tecnológicos y Universitarios del Golfo, Veracruz, Mexico. [7]Department of Medicine, College of Medicine, Korea University, Seoul 02841, Republic of Korea.

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