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1 **Gut Dysbiosis Signature Associated with Hepatitis B Virus-Related Diseases: An**  
2 **Insightful Review Using AI-Powered Research Tools**

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18 **ABSTRACT**

19 **Background:** Hepatitis B virus (HBV) has threatened public health, mainly resulting in liver  
20 fibrosis, cirrhosis, and even damage due to hepatic carcinoma. Growing evidence has  
21 supported the role of gut microbiota in different stages of liver disease. However, the  
22 mechanisms of hepatic injury from gut microbiota dysbiosis are not fully understood.  
23 Moreover, no consensus has been reached on the microbial signatures across different disease  
24 stages. This review aims to find an agreement on a signature microbiota profile in HBV-  
25 infected patients at different disease stages compared to healthy controls. These profiles may  
26 enable the identification of new diagnostic and therapeutic tools for HBV based on  
27 microbiome-targeting approaches. **Methods:** Different literature databases and artificial  
28 intelligence (AI)-powered research tools have been investigated. Qualitative analysis of the  
29 studies was performed considering consistent dysregulated taxa in at least two studies as  
30 reproducible differential results. **Results:** Among 334 screened articles, 86 eligible articles  
31 were identified. Interestingly, AI tools helped us identify six studies not detected by the  
32 traditional search. 25 eligible human case-control microbiome studies, *three* mycobome  
33 studies, and 17 microbiota-targeted therapeutic studies were finally included and  
34 summarized. Most studies reported HBV-associated dysbiosis in different subgroups at the  
35 phyla and genus levels, while few studies referred to the species level. The results of studies  
36 were contradictory in some cases. However, we could infer reproducible results of a signature  
37 microbiota profile in HBV-associated infections characterized by an increase in  
38 *p\_Pseudomonadota*, *c\_Bacilli*, *g\_Prevotella*, *g\_Streptococcus*, *g\_Veillonella* and a decrease  
39 in *c\_Clostridia*, *f\_Lachnospiraceae*, and *g\_Roseburria*. A high abundance of *Saccharomyces*  
40 *cerevisiae* and *Candida tropicalis* was a constant finding. **Conclusions:** Study findings  
41 indicate a signature microbial composition in HBV-associated infection despite the  
42 challenging microbiota composition detected in different disease subgroups. These taxa

43 showed diagnostic power between health and most disease stages, implicating the potential of  
44 the gut microbial as non-invasive biomarkers for diagnosing pan-HBV-induced liver disease.

45 **KEYWORDS**

46 Hepatitis B virus infection, Gut Dysbiosis, Fecal Microbiota, Mycobiota, Systematic Review,  
47 Artificial Intelligence

## 48 INTRODUCTION

49 About 296 million individuals are chronically infected with hepatitis B virus (HBV)  
50 worldwide, with 1.5 million new infections yearly [1]. Despite the World Health  
51 Organization's objective of eliminating viral hepatitis as a public health hazard by 2030,  
52 annual global HBV mortality is expected to rise by 39% from 2015 to 2030 if current trends  
53 continue [2]. Different disease stages are diagnosed by hepatitis B-e antigen (HBeAg), HBV  
54 DNA levels, alanine aminotransferase (ALT) values, and liver inflammation. Balancing the  
55 pathogenic ability and immunity defense, some patients could be carriers or experience  
56 chronic hepatitis B (CHB), characterized by elevated ALT levels and moderate/severe liver  
57 diseases [3]. Although the CHB disease course has been described in the literature, the  
58 pathophysiology of HBV disease progression is not entirely understood [4,5]. Many studies  
59 highlighted the role of different factors, such as HBV viral load, HBV mutations, and host  
60 immunity, in the disease progression [6–8]. CHB infection tends to be asymptomatic;  
61 however, tissue repair against inflammation makes CHB patients at high risk of manifesting  
62 fibrosis, cirrhosis as well as fatal complications, such as portal hypertension, spontaneous  
63 bacterial peritonitis (SBP) [9], hepatic encephalopathy (HE) [10], and hepatocellular  
64 carcinoma (HCC) [11].

65 'Gut-Liver-Axis' describes the bidirectional interconnecting relationship between the  
66 gut and liver where bile, nutrients, and other metabolites are exchanged [12]. Typically, the  
67 gut hosts a myriad of microbiota, such as bacteria [13], fungal species [14], and  
68 bacteriophages [15], described as a superorganism [16], that play different complex  
69 immunological and nutritional roles in both the gastrointestinal tract and the liver [17,18].  
70 Predominant strains in the adult intestine belong to the major phyla of *Bacteroidota* (formerly  
71 *Bacteroidetes*), *Bacillota* (formerly *Firmicutes*), and *Proteobacteria* (formerly  
72 *Pseudomonadota*) containing gram-negative bacteria and gram-positive *Clostridia* [19]. A

73 growing body of literature suggests a connection between gut microbiota dysbiosis and CHB  
74 [20–22], in addition to significant differences in gut microbial composition between CHB or  
75 HBV-related liver cirrhosis (LC) and healthy controls have been widely reported [23,24].  
76 However, no agreement has been reached on distinctive microbial signatures across different  
77 disease stages.

78         Advancements in therapeutic options, including interferon and antiviral treatment  
79 (AVT), can only suppress HBV DNA replication or reduce cirrhosis and HCC complications  
80 but cannot cure CHB [25,26]. Therefore, further development of new treatment methods is  
81 critical for the global eradication of HBV. Additionally, emerging data reveals that directed  
82 treatment of dysbiosis may have potential therapeutic value in liver disease and CHB  
83 management [27,28]. Therefore, we addressed the cutting edge of the latest microbiota-  
84 targeted therapies in CHB patients with highlights on the future research directions of clinical  
85 trials.

86         Herein, the objectives of the current review will mainly summarize and discuss: (1)  
87 Gut microbiota alteration in different stages of HBV; (2) A distinctive microbiome signature  
88 in HBV-infected patients at various stages of the disease. These profiles might make it  
89 possible to find novel HBV diagnostic and treatment options: (3) Gut microbiota-related  
90 mechanisms of liver fibrosis, and (4) Gut microbiota-targeted treatment for HBV infection  
91 and associated complications.

92

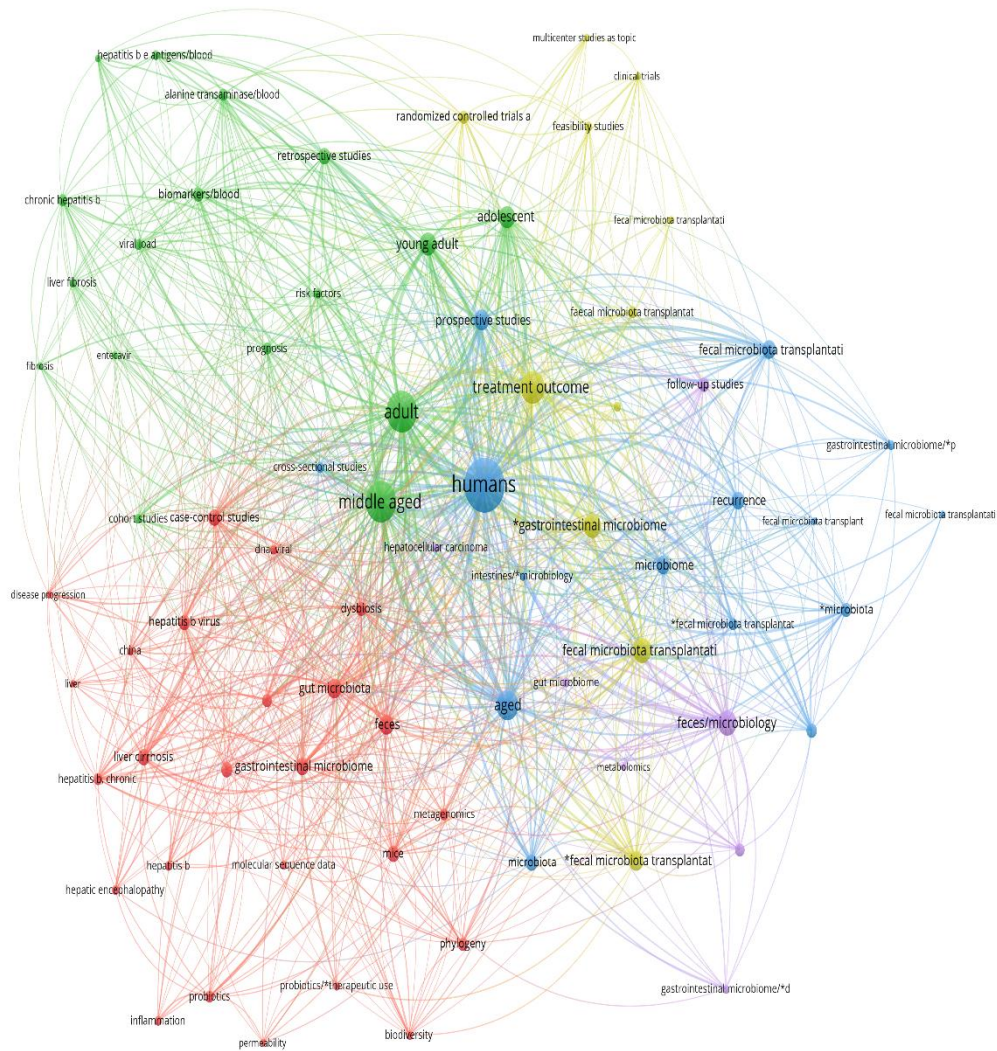
## 93 **1. DATA COLLECTION**

### 94 **1.1 Methods of Bibliographic strategy and selection criteria**

95 A systematic literature search was conducted for case-control studies on CHB and  
96 microbiota. In a comprehensive search, PubMed, Google Scholar, Wiley Library, and Web of  
97 Science (WOS), as well as artificial intelligence (AI)-powered research tools such as

98 Semantic Scholar and Scite, were investigated. Additionally, cross-referencing of all selected  
99 articles was reviewed. The search keywords and their synonyms were identified by MeSH  
100 database. The search was applied from 2000 and included only the articles written in English.  
101 We used Publish or Perish [29] and Zotero [30] software to retrieve and analyze citations.  
102 In order to include all relevant literature and decrease the chances of missing relevant trials,  
103 we generated a broad screening approach with the query using the keywords in the following  
104 syntax ("metagenom\* OR microbio\* OR fecal flora OR intestinal flora OR gut bacteria OR  
105 Human microbio\* OR dysbios\* OR disbios\* OR bacterial translocation OR disbacterios\*"  
106 AND "HBV" OR "chronic hepatitis B" OR hepatitis B AND virus AND infection AND  
107 Chronic OR hepatic cirrhosis OR liver fibrosis" OR "gut liver axis" OR pr?biotic\* OR "fecal  
108 microbiota transplantation" OR "Fecal transplantation"). As detailed in **Supplementary**  
109 **Table S1** [31], this syntax has been adjusted for every database.

110 A mapping of terms used in the titles/Abstracts of HBV-studied microbiome articles  
111 retrieved from different databases is illustrated in **Fig. 1**. This indicates that further  
112 explorations and more studies and other geographical locations into investigating dysbiosis in  
113 CHB patients are needed.



114

115 **Figure 1: Visualization of Term Mapping using VOS Viewer Software.**

116 The figure provides a visualization of the most common terms in the 334 retrieved articles of this review about  
 117 gut microbiota dysbiosis in HBV-related infection in several screened databases. The terms include all keywords

118 or MeSH terms used in the titles/Abstracts of 307 HBV-studied microbiome articles between 2000 and 2023.

119 The figure illustrates the mapping of terms using VOS Viewer software, showcasing the relationships and

120 connections between different terms. Terms in this network are connected by co-occurrence (based on the

121 documents' terms occurring together) to discover the best search keywords and define the popularity, age, and

122 impact of topics in the detected studies. The minimum number of occurrences of a keyword is *five*. Out of 1825

123 keywords, 110 met the threshold. For every 110 keywords, the total strength of the co-occurrence links with

124 other keywords was calculated. The keywords with the greatest total link strength were selected.



125 The color-coded nodes and edges represent clusters and associations, and terms – are located relative to each  
126 other so that the distance between two objects is an approximate measure of their similarity within the set,  
127 providing insights into the semantic landscape of the analyzed articles. The terms are grouped in colored  
128 clusters. Cluster 1 (**Red**; 25 items) as China, metagenomics, gut microbiota, hepatitis B, chronic, case-control  
129 studies; Cluster 2 (**Green**, 17 items) as adult, prognosis, fibrosis; Cluster 3 (**Blue**, 15 items) as fecal microbiota  
130 transplant, humans, microbiome, microbiota, prospective studies; Cluster 4 (**Yellow**, *eleven* items) as fecal  
131 microbiota transplants, clinical trials; Cluster 5 (**Purple**, *seven* items) as gut microbiome, metabolomics.

132 The Preferred Reporting Items for Systemic Reviews and Meta-Analysis Statement  
133 (PRISMA) guidelines were followed (**Fig. 2A**). The following inclusion criteria were  
134 considered: (1) Study design: peer-reviewed and published cross-sectional, case-control,  
135 cohort studies and interventional studies reporting the effects of HBV on human gut  
136 microbiota composition in adults, (2) Participants: case of patients diagnosed with HBV  
137 carriers, CHB and HBV-related complications such as LC, HCC, or liver transplantation  
138 (LT). Controls are population-based or hospital-based controls without related liver diseases.  
139 (3) Main outcome reported different taxa abundance as phylum, class, order, family, genus,  
140 and species of fecal microbiota or well-defined clinical outcome parameters associated with  
141 HBV-associated dysbiosis. (4) Publishing time cutoff is June 2023. The exclusion criteria  
142 included studies without a control group, cirrhosis studies not related to HBV infection, *in*  
143 *vitro* studies, studies without data on gut microbiome composition, studies reported in  
144 languages other than English, and gray literature

145

#### 146 **Study Selection and Data Extraction**

147 A total of 1888 articles were retrieved from PubMed, 1183 articles from Google Scholar, 588  
148 from Wiley Library, 1497 from WOS, 379 from Semantic Scholar, and 194 from Scite, for a  
149 total of 5729. The first selection based on titles and abstracts yielded 334 articles, of which 70  
150 duplicates were eliminated. After removing duplicate results, a list of 86 eligible publications

151 was generated, screening titles and abstracts. Each publication on this list was further  
152 reviewed independently to confirm adherence to the inclusion/exclusion criteria. Afterward,  
153 the full texts of relevant articles were retrieved and thoroughly inspected. Extracted data  
154 included study design, populations, sample size, study country, and gut microbiome analysis  
155 methodology. Extracted outcomes included HBV-related dysbiosis and assessment of hepatic  
156 markers, metabolites, immunological markers, and bile acids.

157

## 158 **1.2 Results of Bibliographic Search**

159 This systematic review yielded a total of 61 articles (**Fig. 2A**), including (25 eligible human  
160 case-control microbiome studies, *three* mycobiome studies, 17 microbiota-targeted  
161 therapeutic studies, *eight* mouse-model studies, and *nine* other studies (virome, probiotics  
162 studies)). AI tools such as Semantic Scholar shared the identification of 39.2% (22/56) of the  
163 studies found by manual citation searching with *six* studies that other databases haven't  
164 retrieved (**Fig. 2B**). Indicating that compared to traditional approaches, AI-powered research  
165 tools may be effective in decreasing the time required for literature search. However, we did  
166 not employ these AI tools or other AI-assisted technologies to replace our primary duty of  
167 data interpretation or scientific conclusion formulation. The included studies evaluated HBV-  
168 related dysbiosis in different patient subgroups. All the selected studies met the quality  
169 assessment requirements based on the modified STROBE checklist. A total of 24 papers were  
170 removed, with the reasons given in the **Supplementary Table. S2** [31].

171 Study characteristics are demonstrated in detail in the **Supplementary Table. S3** [31].

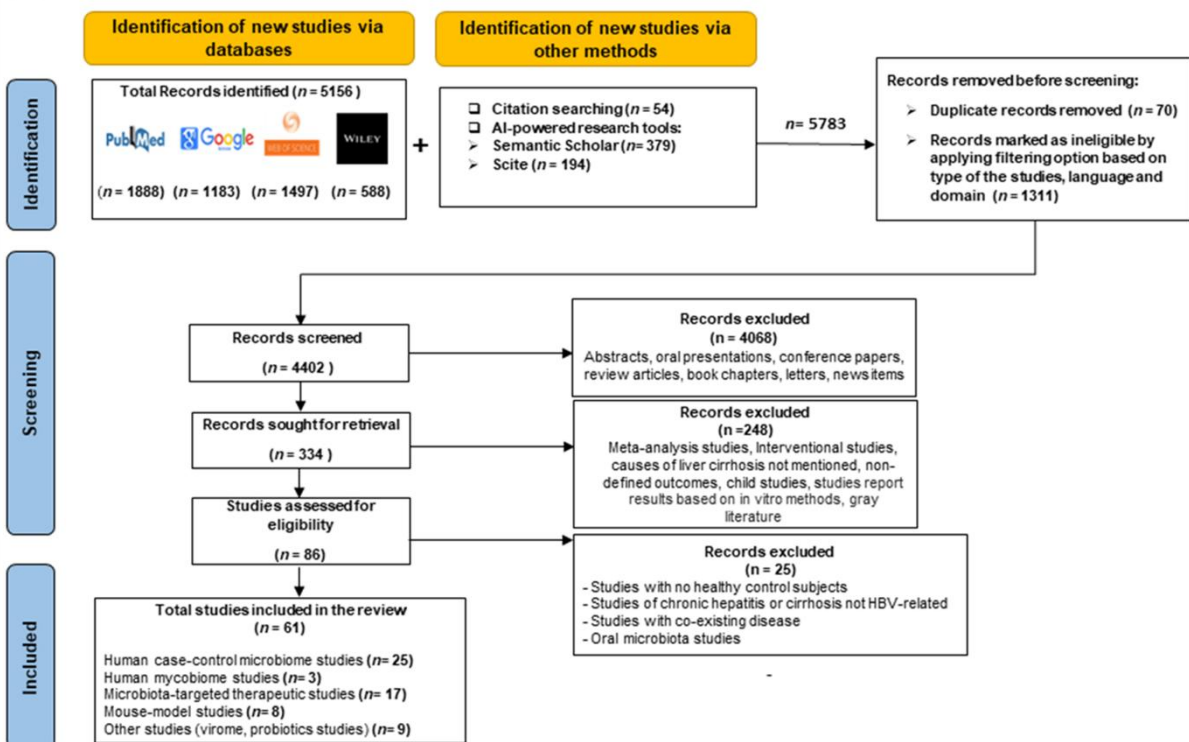
172 Different molecular methods were used to characterize gut microbiota, including denaturing  
173 gradient gel electrophoresis (DGGE), Quantitative PCR (qPCR), and sequencing of the 16s  
174 rRNA genes. All microbiota analyses were investigated in adults. All microbiome studies

175 were performed in Asia (22 studies were performed in China, *two* in South Korea, and *one* in  
 176 Taiwan).

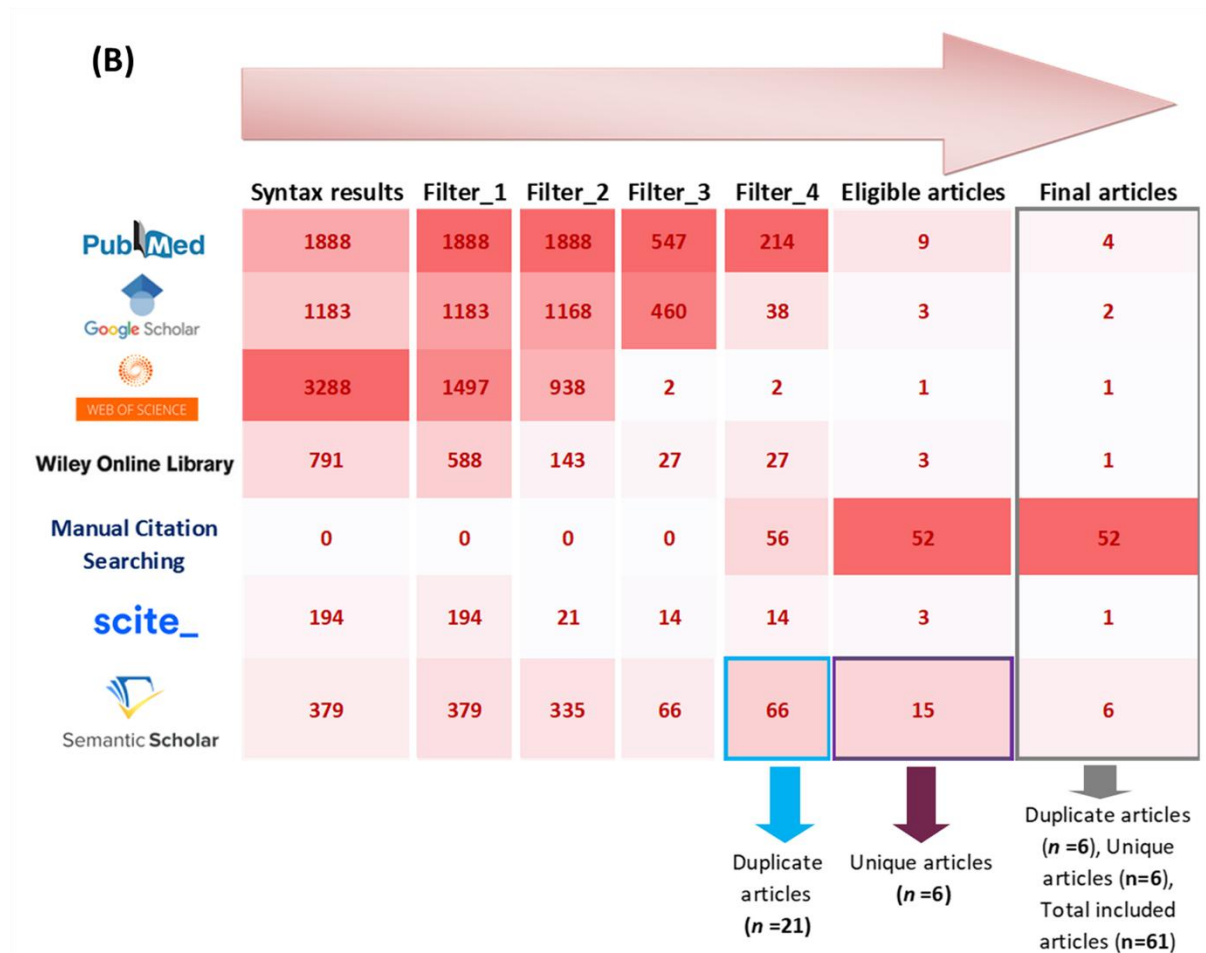
177 Regarding human microbiome studies, *seven* reported a correlation between gut dysbiosis and  
 178 hepatic markers, *three* reported changes in bile acids, *three* reported changes in  
 179 immunological markers, and *six* showed changes related to metabolic markers. Most studies  
 180 ( $n=23$ ) reported changes in microbiota profile to the genus level, while only seven reported  
 181 the species level. Different studies have reported either no change in beta microbial diversity  
 182 or difference between HBV-infected subgroups.

183

(A)



184



185

186 **Figure. 2 Data search and Collection process.** (A) A flowchart of how articles were identified and filtered to  
 187 be included in the systematic review based on the PRISMA statement. (B) A chart of the detailed number of  
 188 studies detected in all included databases applying different filters: Filter\_1 (language/ year/domain); Filter\_2  
 189 (exclusion of poster, review articles, book chapters, editorial material, letter abstract, early access); Filter\_3  
 190 (suitable title/abstract); Filter\_4 (inclusion full appropriate articles and applying manual citation searching).  
 191 Tools such as Semantic Scholar allowed the identification of 22 studies (the same studies found by manual  
 192 citation searching) with *six* studies that other databases haven't retrieved.

193

194 **2. GUT DYSBIOSIS CONTRIBUTES TO LIVER INJURY THROUGH GUT-LIVER**  
 195 **AXIS**

196 The individual's microbiota profile vastly differs between geographic regions [32]. In  
 197 addition to harboring other fungi and bacteria, the gut is also a binding site for the induction

198 of host immunity, affecting the gut mucosal barrier, lymphoid tissues, and regulatory T cells.  
199 Host immunity can be promoted when epithelial cells express pattern recognition receptors as  
200 toll-like receptors (TLR) specific to microbial particles like lipopolysaccharides (LPS) or  
201 peptidoglycans [33,34].

202 Usually, the intestinal microbiota and the liver coexist separately; however, the liver  
203 can be exposed to intestinal microbes during gut dysbiosis or liver cirrhosis [35]. Several  
204 studies have investigated the relationship between gut dysbiosis and cirrhosis of different  
205 aetiologies, such as cholangitis, metabolic liver disease, and alcoholic liver disease [36–39],  
206 with growing evidence suggesting that gut dysbiosis may accelerate simple steatosis to  
207 steatohepatitis [38]. So, the common mechanisms of gut dysbiosis-mediated liver injury  
208 could be endotoxemia, intestinal barrier dysfunction, and bile acid fluctuations [37]. Growing  
209 evidence suggests that gut dysbiosis and CHB infection may interact similarly to other liver  
210 diseases [40]. Therefore, this study summarizes the most recent available data about HBV-  
211 associated dysbiosis and the pathophysiology of related liver injury.

212

### 213 **3. CHARACTERISTICS OF HEPATITIS B PATIENTS WITH DYSBIOSIS**

214 Studies have shown that HBV-infected patients tend to have different gut microbiota profiles  
215 than healthy controls (**Supplementary Table. S3** [31]). Patients with HBV infection may  
216 experience different disease stages from HBV carriers, acute HBV infection to CHB without  
217 liver injury until HCC, depending on the host and viral variables [3]. In this part, HBV-  
218 related different stages of disease will be discussed concerning gut dysbiosis.

### 219 **3.1 Patients with no/mild liver injury (compensated patients)**

220 Patients in the compensated stage are often asymptomatic [41] or have treatable liver disease  
221 and, therefore, we considered a) HBV carriers, b) acute HBV infection, c) CHB or cirrhosis  
222 with Child-Turcotte-Pugh (CTP)- class A, are compensated patients with no/mild liver injury.

223

#### 224 **a) Hepatitis B virus (HBV) carriers**

225 After the infection, HBV may be spontaneously cleared or cause chronic disease in different  
226 individuals depending on factors such as age and immunity [42]. The same phenomenon has  
227 been observed in animal experiments, in which hepatitis B surface antigen (HBsAg) of  
228 immature mice remained positive [43]. A study by Lu et al. showed a decrease in the  
229 *Bifidobacteria/Enterobacteriaceae* (B/E) ratio in HBV carriers compared to controls [44].  
230 However, HBV carriers with normal ALT were somewhat similar to the control group but  
231 significantly different from those with high ALT, and the B/E ratio was not different between  
232 the groups [45]. They indicated that HBV carriers could have a similar microbiota profile as  
233 controls.

234 In addition, Chen et al. reported that HBV carriers had the highest observed species as  
235 controls but the lowest *Fusobacteria*, *BetaPseudomonadota*, and stable *Bacteroides*  
236 compared to controls [46]. Interestingly, Yang et al. suggested that HBV carriers might be the  
237 most suitable donors for fecal microbiota transplantation (FMT) for higher  $\alpha$  diversity and  
238 abundance of potentially beneficial *Lachnospira* genera [47]. Moreover, a recent study  
239 reported that gut microbiome in HBV carriers was dominated by taxa involved in fatty acid  
240 and lipid metabolism, such as *Eubacterium coprostanoligenes*, contributing to the  
241 cholesterol-lowering effects in HBV patients and *Alloprevotella* producing short-chain fatty  
242 acids (SCFAs) [48].

243       **b) Acute HBV infection**

244       Due to the difficulty of studying acute HBV infection in humans, animal studies have been  
245       used. By using a mouse model of both acute and CHB infection, Zhu et al. reported that  
246       *Bifidobacterium* and *Lactobacillus* peaked in both disease groups compared to controls at day  
247       14 and the ratio of *Firmicutes/Bacteroides* increased in the early stages of infection (Day 14)  
248       and decreased significantly over time (Day 49) [49]. A similar study on HBV-infected and  
249       ETV-treated mice also reported significant changes in genera, but found increases in  
250       *Butyricoccus* and decreases in *Clostridium* instead [40].

251

252       **c) Chronic hepatitis B (CHB): Non-end stage**

253       In humans, CHB is significantly correlated with changes to gut microbiota even with no/mild  
254       liver injury. CHB patients with CTP scores <9 (classes A and B) reported a significant  
255       increase in the *Veillonellaceae* family and a decrease in the *Alistipes*, *Asaccharobacter*,  
256       *Bacteroides*, *Butyricimonas*, *Parabacteroides*, and *Ruminococcus* genera [24]. Another study  
257       in CHB with fibrosis observed an increase in *Prevotella* and a decrease in the same genera as  
258       the previous study, responsible for bile acid metabolism, such as *Bacteroides*, *Clostridium*,  
259       *Lactobacillus*, *Ruminococcus* and *Bifidobacterium* [50]. These data demonstrate that  
260       compensated CHB infection with no/mild liver injury is associated with significant changes  
261       in the gut microbiota.

262       To further understand the gut microbiota dynamics in CHB, some studies investigated  
263       clinical indicators reflecting liver function and infection state. A recent study showed that  
264       *Lactobacillus*, *Clostridium*, and *Bifidobacterium* abundance was lower in patients with  
265       normal ALT than in controls [51]. In addition, *Bacteroides fragilis*, bile salt hydrolase (BSH)  
266       containing species, and the only member of archaeon harboring BSH activity,  
267       *Methanobrevibacter smithii*, was significantly lower in patients with normal ALT group [51].

268 Moreover, *Streptococcus*, *Veillonella*, and *Haemophilus* showed positive correlations with  
269 aromatic amino acids (such as phenylalanine and tyrosine), which are assumed to play roles  
270 in CHB progression [24]. In addition, *Dialister*, unclassified *Clostridiales* and  
271 *Ruminococcaceae* were positively associated with some hepatic inflammatory markers and  
272 enzymes [24].

273

### 274 **3.2 Patients with advanced stages of liver injury (decompensated patients)**

275 A growing number of studies have also revealed a correlation between the gut microbiota and  
276 advanced stages of HBV infection characterized by a) CHB-associated liver cirrhosis (CHB-  
277 LC), b) HCC, and c) HE. Liver cirrhosis is a dangerous premalignant condition with an  
278 increasing incidence of genetic aberrations and an elevated risk of HCC [52,53]. The  
279 diagnosis of decompensated cirrhosis is based on the presence of ascites, variceal bleeding or  
280 HE, and liver failure (LF) in the context of massive infiltration from a tumor [54].

281

#### 282 **a) Chronic hepatitis B-associated liver cirrhosis (CHB-LC): End-stage CHB**

283 Patients with CHB-LC showed lower diversity with the severity of the disease [46,47]. In a  
284 study by Deng et al., *Veillonellaceae* and *Lachnospiraceae* families were depleted, and  
285 *Megamonas* was enriched in patients with CHB-LC compared to controls [55]. Additionally,  
286 *Enterobacteriaceae* increased while *Bifidobacteria* and lactic acid bacteria (*Lactobacillus*,  
287 *Pediococcus*, *Leuconostoc*, and *Weissella*) showed a marked decrease in CHB-LC [44].  
288 Moreover, the B/E ratio can be used for tracing the progression of liver disease and was  
289 found to be decreased in CHB-LC [44].

290 According to the combined results of multiple studies, there is a well-acknowledged  
291 decrease in *Firmicutes* abundance and an increase in *Pseudomonadota* during the progression  
292 of CHB-LC [56]. However, a previous study reported a reduction in both *Bacteroidetes* and



293 *Firmicutes* from healthy to cirrhotics, while *Pseudomonadota* and *Actinobacteria* increased  
294 stepwise from healthy to cirrhotics [46]. *Bacteroides* were similar across all tested groups at  
295 the genus level, while *Haemophilus*, *Fusobacterium*, *Veillonella*, *Streptococcus*, and  
296 *Ruminococcus* increased in later disease stages. Additionally, two species were reported  
297 *Dialister succinatiphilus* and *Alistipes onderdonkii*, to be abundant in controls and decrease  
298 significantly with disease progression [46].

299 Additionally, dynamic alteration of gut microbiota is a valuable indicator to predict the  
300 prognosis of end-stage liver disease. *Enterococcus* was significantly higher, as mentioned in  
301 in the HBV-related LF (progression group), while abundant *Faecalibacterium* was associated  
302 with the regression group [57]. Moreover, a higher abundance of *E. coli* is consistent with an  
303 increasing level of LPS in the circulation of patients with end-stage liver disease [58–60].  
304 Interestingly, the microbiota profile of cirrhotics appeared to be more oriented toward  
305 methanethiol (CH<sub>3</sub>SH) production, whereas the control group resembled hydrogen sulfide  
306 (H<sub>2</sub>S) production. Serum methanethiol levels are linked to complications such as HE,  
307 implying a solid connection between dysbiosis and the severity of liver diseases [61].  
308 Furthermore, compared to compensated cirrhosis, the gut microbiota composition in the  
309 decompensation stage is characterized by an increase in the abundance of potentially  
310 pathogenic bacteria, particularly *Alcaligenaceae*, *Porphyromonadaceae*, *Veillonellaceae*, and  
311 *Enterobacteriaceae* [62].

312

### 313 **b) Hepatocellular carcinoma (HCC)**

314 Patients with HCC tend to present a distempered gut microbiota and abnormal metabolites  
315 [63]. Zheng et al. reported a depletion in butyrate-producing genera and an increase in LPS-  
316 producing genera; moreover, *Clostridioides* was positively related to the tumor size of HCC  
317 [22]. This finding was supported by another study that reported *Bacteroides*, *Lachnospiraceae*,

318 and *Clostridium XIVa* to be enriched in HCC patients, with a positive correlation with the  
319 tumor burden [64]. Additionally, *Parabacteroides* were significantly increased in the non-  
320 small group compared to the small HCC group [64]. By integrating the clinical characteristics  
321 and database analysis, serum bile acids as metabolites of the previous three genera could be  
322 essential mediators in promoting liver carcinogenesis.

323 Moreover, the abundance of *Prevotella* was much more significant in HBV-related HCC  
324 compared to non-HBV-HCC [63]. Interestingly, a recent study investigated gut microbiota  
325 profiles in HBV-related HCC patients with post-hepatectomy liver failure (PHLF) [65].  
326 *Bacteroides*, *Faecalibacterium*, and *Pantoea* abundances were higher post-operatively, while  
327 *Faecalibacterium* and *Subdoligranulum* were abundant pre-operative. However, the bacteria  
328 with significant postoperative differences showed no significant differences preoperatively,  
329 except for *Faecalibacterium* [65], which could be used as a potential marker of disease  
330 diagnosis and follow-up.

331

### 332 c) Hepatic encephalopathy (HE)

333 Hepatic encephalopathy (HE) is a fatal central nervous system complication caused by acute  
334 or chronic hepatitis or decompensated cirrhosis [66]; characterized by ammonia-related  
335 cerebral edema and consciousness disturbance [67].

336 Interestingly, research has shown a significant increase  
337 in *Veillonellaceae*, *Enterococcus*, *Megasphaera*, and *Burkholderia* in cirrhotic patients with  
338 HE. This taxonomic shift was associated with hyperammonaemia and systemic inflammation,  
339 contributing to worsening HE symptoms [68]. Other studies showed that cirrhosis-related  
340 cognitive dysfunction is associated with decreased abundance of autochthonous families and  
341 increased *Alcaligenaceae* and *Porphyromonadaceae* [69,70]. Even though the exact  
342 underlying mechanisms of HE in patients with cirrhosis remain unclear, the accumulation of

343 microbe-derived products such as ammonia, mercaptans, and benzodiazepine-like substances  
344 [62], as well as neurotransmitters produced by the microbiota, including serotonin dopamine  
345 [71] are believed to play a critical role. These substances can cross the blood-brain barrier  
346 and affect astrocyte function, likely to result in neurotransmission disorders [66]. Those  
347 findings suggest the impact of the network between the enteric and autonomic nervous  
348 systems on gut microbiota.

349

#### 350 **4. Intestinal microbiota signatures) in HBV-associated dysbiosis and related** 351 **pathophysiology**

352 It is essential to consider regional and geographical differences using gut microbiota profiles  
353 as diagnostic tools. The presence and accuracy of biomarkers found in one study may be  
354 completely different in another [32,72]. Therefore, we summarized the abundant taxa  
355 reported in various HBV-related diseases (**Fig. 3; Supplementary Table. S4** [31]) based on  
356 the qualitative analysis of the 25 human case-control microbiome studies included in this  
357 review (**Supplementary Table. S3** [31]). Notably, the mentioned abundance in each group  
358 was compared to the controls. Consistently dysregulated microbiota in at least two datasets  
359 were highlighted, denoting reproducible results, as depicted in **Fig. 3**. However, the CHB-LT  
360 group showed no reproducible results (**Supplementary Table. S4** [31]).

Abundant Taxa	HBV-Related Diseases				
	HBV-Carriers	CHB	CHB-LF	CHB-LC	CHB-HCC
<b>Phylum</b>					
<i>Bacteroidota</i> (formerly <i>Bacteroidetes</i> )	↓ (3)	↑ (4)	↓ (1)	↓ (5)	↑ (3)
<i>Bacillota</i> (formerly <i>Firmicutes</i> )	↓ (2)	↓ (4)	↑ (1)	↓ (7)	↓ (3)
<i>Pseudomonadota</i> (formerly <i>Proteobacteria</i> )	↑ (1)	↑ (4)	↑ (1)	↑ (7)	↑ (4)
<i>Actinomycetota</i> (formerly <i>Actinobacteria</i> )	↑ (1)	1:1	↑ (1)	↑ (4)	↑ (2)
<i>Fusobacteriota</i>	↑ (1)	↑ (1)	NA	↑ (2)	↑ (2)
<b>Class</b>					
<i>Clostridia</i>	neutral* (1)	↓ (2)	NA	↓ (3)	↓ (1)
<i>Bacteroidia</i>	NA	↑ (3)	NA	1:1	↑ (1)
<i>Gammaproteobacteria</i>	neutral* (1)	↑ (2)	NA	↑ (3)	NA
<i>Actinobacteria</i>	↑ (1)	1:1	NA	↑ (2)	↓ (1)
<i>Bacilli</i>	↑ (1)	1:1	NA	↑ (3)	↑ (2)
<b>Order</b>					
<i>Eubacteriales</i> (formerly <i>Clostridiales</i> )	↑ (1)	↓ (1)	NA	↓ (3)	1:1
<i>Bacteroidales</i>	NA	↑ (3)	NA	1:1	↑ (2)
<i>Enterobacteriales</i>	NA	↑ (1)	NA	↑ (2)	1:1
<i>Lactobacillales</i>	NA	neutral* (1)	NA	↑ (2)	↑ (2)
<b>Family</b>					
<i>Bifidobacteriaceae</i>	↓ (1)	↓ (2)	NA	↓ (2)	↓ (1)
<i>Enterobacteriaceae</i>	↓ (1)	1:1	NA	↑ (6)	↑ (2)
<i>Lachnospiraceae</i>	NA	1:1	NA	↓ (6)	↓ (2)
<i>Veillonellaceae</i>	NA	↑ (1)	NA	↑ (2)	NA
<i>Rikenellaceae</i>	NA	↑ (1)	NA	↓ (3)	1:1
<i>Ruminococcaceae</i>	NA	↓ (2)	NA	↓ (6)	↓ (2)
<i>Coriobacteriaceae</i>	NA	1:1	NA	↓ (2)	↓ (1)
<i>Clostridiaceae</i>	NA	↓ (1)	NA	↓ (4)	↓ (2)
<i>Bacteroidaceae</i>	NA	↑ (1)	NA	↓ (2)	1:1
<i>Streptococcaceae</i>	NA	neutral* (1)	NA	↑ (4)	↑ (2)
<i>Prevotellaceae</i>	NA	↑ (2)	NA	1:1	1:1
<b>Genus</b>					
<i>Clostridium</i>	1:1	↓ (2)	1:1	↓ (4)	↑ (1)
<i>Bifidobacterium</i>	neutral* (1)	↓ (3)	NA	↓ (3)	1:1
<i>Lactobacillus</i>	1:1	↓ (2)	↑ (2)	2:2	↑ (1)
<i>Veillonella</i>	1:1	↑ (3)	↑ (1)	↑ (4)	↑ (4)
<i>Megamonas</i>	↑ (1)	↑ (2)	↓ (1)	1:1	↓ (1)
<i>Desulfovibrio</i>	↑ (2)	↑ (1)	NA	↑ (1)	NA
<i>Prevotella</i>	↑ (1)	↑ (4)	↓ (2)	↓ (3)	↑ (2)
<i>Bacteroides</i>	↓ (1)	↑ (3)	↓ (1)	↓ (4)	↑ (2)
<i>Ruminococcus</i>	↑ (1)	↑ (2)	NA	3:3	↓ (2)
<i>Escherichia/Shigella</i>	↑ (1)	1:1	↑ (1)	↑ (2)	1:1
<i>Parabacteroides</i>	NA	↑ (1)	NA	1:1	↑ (2)
<i>Enterococcus</i>	↑ (1)	↑ (1)	↑ (3)	↑ (2)	1:1
<i>Faecalibacterium</i>	NA	↑ (2)	↑ (1)	1:1	↓ (2)
<i>Akkermansia</i>	↑ (1)	↑ (1)	NA	↑ (2)	NA
<i>Streptococcus</i>	↑ (1)	↑ (5)	↑ (2)	↑ (6)	↑ (3)
<i>Blautia</i>	↑ (1)	↑ (2)	↑ (1)	2:2	↑ (2)
<i>Roseburia</i>	↓ (1)	↓ (2)	↓ (1)	↓ (2)	↓ (1)
<i>Haemophilus</i>	NA	↑ (2)	NA	↑ (1)	NA
<i>Fusobacterium</i>	1:1	↑ (2)	↓ (1)	1:1	NA
<i>Sutterella</i>	↑ (1)	↑ (3)	NA	↑ (1)	NA
<i>Proteus</i>	NA	NA	NA	↑ (1)	↑ (2)
<i>Lachnospira</i>	↑ (1)	↓ (2)	↓ (1)	↓ (3)	↓ (3)
<i>Klebsiella</i>	↑ (1)	↑ (1)	↑ (2)	↑ (2)	↑ (1)
<b>Species</b>					
<i>Bacteroides eggerthi</i>	NA	↓ (1)	NA	↓ (2)	NA
<i>Escherichia coli</i>	NA	NA	NA	↑ (2)	NA

Reproducible results in at least 2 studies  
 Reproducible results in > 2 studies  
 Contradicting results (same number of studies ↑ vs. ↓)

361

362

Figure. 3 A chart summarizing consistently dysregulated gut microbiota taxa in at least two studies. Data was

363

collected from 25 human case-control studies involved in this review (Supplementary Table. S4). The results

364

represent the comparison of each group vs. the control group. Results in gray are non-reproducible.

365 \*: Neutral means no difference in abundance compared to the controls. Numbers between brackets denote the  
366 number of studies. ↑, increase in abundance reported; ↓, decrease in abundance reported

367 **HBV**: Hepatitis B virus; **CHB**: Chronic hepatitis B infection; **CHB-LF**: Chronic hepatitis B-associated liver  
368 failure; **CHB-LC**: Chronic hepatitis-associated liver cirrhosis; **CHB-HCC**: Chronic hepatitis B-associated  
369 hepatocellular carcinoma; **NA**: Not available.

370 Studies have shown that HBV-infected patients tend to have different abundance of  
371 gut microbiota profiles (**Fig. 3**). This section will cover the previously described gut  
372 microbiota with consistent dysregulated patterns (**Fig. 3**). In addition, the mechanisms by  
373 which microbiota-mediated liver injury occurs will be discussed.

374

### 375 *Pseudomonadota*

376 Many human studies have reported a consistent increase in *Pseudomonadota* abundance

377 [46,51,56,58]. *Pseudomonadota* is divided into *six* classes; among them is the

378 *Gammaproteobacteria* class, harboring human pathogens as *Escherichia* species [73].

379 Interestingly, those species were also highly abundant in HBV-related diseases [46,51,56,58].

380 *Pseudomonadota* was reported to cause hepatic injury via LPS-produced endotoxemia

381 [74]. Moreover, LPS increases blood-brain barrier permeability and stimulates tumor necrosis

382 factor (TNF), causing HE [75]. Interestingly, significantly abnormal LPS distributions were

383 observed in CHB patients with the highest levels at the peak of liver failure. Besides, LPS

384 changes were related to disease severity, implying that LPS causes secondary hepatic injury

385 [76].

386

### 387 **The *Bifidobacteria/Enterobacteriaceae* (B/E) ratio**

388 Several studies have used the shift in microbiota taxa to create unique heuristics that may

389 distinguish between distinct disease progression stages [44,46,56]. One is the

390 *Bifidobacteria/Enterobacteriaceae* (B/E) ratio, initially discussed in the HBV study by Lu et

391 al. 2011 [44]. The study reported low *Bifidobacteria* abundance in CHB patients and even  
392 lower in cirrhotic patients [44]. Moreover, *Enterobacteriaceae* family (mainly of Gram-  
393 negative bacteria with LPS [77]) was reported to be highly abundant in LC more than CHB  
394 [22,46,56,58]. However, other studies have found no difference in the B/E ratio between  
395 disease groups [24,45]. This suggests the B/E ratio is disturbed only in cirrhosis; however,  
396 those conclusions require further research on a larger population to be confirmed.

397

### 398 **The *Bacteroidetes/Firmicutes* (B/F) ratio**

399 The increased ratio of B/F was associated with inflammatory disorders in CHB-related  
400 complications [56,75,78]. Hence, many *Bacteroidetes* are Gram-negative bacteria that  
401 produce LPS, whereas *Firmicutes* are Gram-positive bacteria; an increased B/F ratio means a  
402 higher burden of LPS exposure [55]. As previously mentioned, evidence is emerging that  
403 CHB patients were often accompanied by metabolic endotoxemia, producing pro-  
404 inflammatory cytokines such as TNF- $\alpha$  and reactive oxygen species (ROS), promoting  
405 pathogenesis in liver diseases [79].

406

### 407 **Lactic acid-producing bacteria (LAB)**

408 Intestinal LAB bacteria include species belonging to genera such as *Lactobacillus*,  
409 *Leuconostoc*, *Pediococcus*, *Lactococcus*, *Streptococcus*, *Enterococcus*, *Bifidobacterium*, and  
410 *Weissella* [80]. Interestingly, one study has explicitly investigated the protective role of the  
411 total *Lactobacillus* species by quantitative PCR (qPCR) technique [81]. Wu et al. reported  
412 that *Lactobacillus* diversity was lowest in CHB-LC compared to the CHB-LT and control  
413 group. CHB-LC group showed an increase in *L. gasseri* and a decrease in *L. acidophilus* and  
414 *L. reuteri* [81]. Those *lactobacilli* may be involved in intestinal homeostasis. A previous  
415 study reported that *L. gasseri* and *L. acidophilus* produce gassericin A and acidocin B

416 bacteriocins with antibacterial activities [82]. Moreover, *L. reuteri* inhibited TNF- $\alpha$  induction  
417 by inducing various cytokines and may inhibit the actions of other *Lactobacillus* species,  
418 such as *L. rhamnosus* and *L. fermentum* [83].

419 Nevertheless, some studies reported increased abundance in the *Lactobacillales* order  
420 in CHB-LC [56,58] and the *Lactobacillaceae* family in CHB-HCC [46,84]. One study  
421 reported a marked decrease in *Lactobacillus* in CHB and CHB-LC [44]. Conversely,  
422 beneficial *Lactobacillus* was higher in patients with decompensated LC than those with  
423 compensated LC [85]. This finding suggests that *lactobacillus* in decompensated LC  
424 contradicted its probiotic function [75]. Therefore, further *Lactobacillus* investigation to the  
425 species level is recommended in HBV-related diseases.

426 Additionally, genera such as *Streptococcus* [45,46,55,85] and *Enterococcus*  
427 [22,46,56] showed high abundance in CHB, CHB-LC, and CHB-HCC. However,  
428 *Pediococcus*, *Leuconostoc*, *Weissella* [44], and *Bifidobacterium* [44,51,56,75] showed a  
429 marked decrease in CHB and CHB-LC.

430 Regarding *Bifidobacterium* species, one study reported marked alteration in CHB and  
431 CHB-LC groups by qPCR, shifting from beneficial to pathogenic species. The abundance of  
432 *B. catenulatum*/*B.pseudocatenulatum* group and *B. longum* was decreased, and *B. dentium*  
433 was increased in patient groups. However, no significant differences were detected for *B.*  
434 *bifidum* and *B. infantis* [86]. The protective role of *B. catenulatum* is to prevent bacteria  
435 translocation and decrease the release of local gut cytokine and endotoxins [87]. Clinical  
436 trials and animal experiments indicated *B. longum* effectively reduced serum ammonia levels  
437 in minimal HE [88]. Therefore, a supplement of probiotics for the above-mentioned species  
438 (except for *B. dentium*), may be helpful in patients with CHB-LC against liver damage.  
439 Indeed, *B. dentium* was considered to be an opportunistic pathogen reported to mainly

440 survive in the oral cavity [89]; however, it is still unknown whether any causal relation exists  
441 between a higher level of *B. dentium* in the intestine and liver injury,

442           Nevertheless, this contributory role is still an emerging issue. Therefore, the  
443 relationships between hepatic histopathological changes and the commonest beneficial gut  
444 microbiota, namely LAB, should be investigated further with more focus on the species level.

445

#### 446 **Sulfate-reducing bacteria (SRB)**

447 *The Desulfovibrio* genus is a dominant population of human intestinal SRB that widely exists  
448 in the anaerobic intestinal tract [90]. Different studies have shown that *Desulfovibrio*  
449 increases significantly in HBV carriers, CHB and CHB-LC [45,46], but there were  
450 differences at the species level. In addition to the direct influence of *Desulfovibrio*, its  
451 metabolites lead to the release of inflammatory cytokines, such as Interleukin-6 (IL-6), and  
452 Interleukin-8 (IL-8) [91]. Hydrogen sulfide (H<sub>2</sub>S), one of its primary metabolites, causes  
453 cytotoxicity [92], a proliferation of hepatic stellate cells (HSC), and the expression of hepatic  
454 fibrosis markers [93]. Interestingly, LC-derived *Desulfovibrio* showed a stronger H<sub>2</sub>S  
455 production ability and a higher antibiotic resistance compared to healthy-  
456 derived *Desulfovibrio* [94]. Hence, *Desulfovibrio* species could be used as a non-invasive  
457 biomarker in diagnosing and following CHB-LC, and therefore, they should be further  
458 investigated in larger study populations.

459           *Bilophila*, another SRB [95], showed increased abundance in the CHB-LF group of  
460 patients, associated with changes in hepatic biomarkers such as ALT and aspartate  
461 aminotransferase (AST) [57], while another study reported its decrease [96]. However, in a  
462 mouse model, *Bilophila* was increased in Entecavir (ETV)- treated HBV group [40].  
463 Therefore, further exploration of the relationship between SRB and the development of HBV-  
464 related complications is recommended.



465 **Bacteria associated with bile acids (BAs) metabolism**

466 Bile acids are produced in the liver and enter the small intestine to aid in the digestion of fats  
467 and fat-soluble vitamins [97]. Recent research has discovered a significant positive  
468 association between serum levels of primary BAs, and the advancement of liver fibrosis  
469 [50,61]. Moreover, several studies have indicated that CHB patients without liver cirrhosis  
470 showed a decreasing ratio of unconjugated/conjugated BAs [51]. Interestingly, genera that  
471 harbor bile salt hydrolase (BSH) enzymes used for BAs deconjugation, such as *Lactobacillus*,  
472 *Clostridium*, *Bifidobacterium*, *Enterobacteriaceae* were suppressed in CHB patients [51].  
473 Additionally, 7-alpha-hydroxysteroid dehydrogenase (hdhA) enzyme that is specifically  
474 responsible for secondary BA generation was impaired in CHB patients [98]. Notably, this  
475 enzyme is majorly found in *Clostridia*, *Ruminococcus* spp. [98]. *Bacteroides* also harbors  
476 hdhA enzyme, especially *B. fragilis* [99], which was significantly lower in CHB patients  
477 [51].

478

479 **Anti-inflammatory and butyrate-producing bacteria**

480 The anti-inflammatory short-chain fatty acids (SCFAs) activity and anti-carcinogenic  
481 potential roles of *Prevotella*, *Alloprevotella*, *Bacteroides*, *Ruminococcus*, *Faecalibacterium*,  
482 and *Phascolarctobacterium* have been reported [63]. CHB infection showed a progressive  
483 decline of *Phascolarctobacterium* [78] and *Bacteroides* [24,47,50,58] compared to healthy  
484 subjects; however, *Prevotella* [50,56,63,84] and *Alloprevotella* [48,63] were highly abundant  
485 in CHB-HCC. Additionally, several studies reported a decrease in *Faecalibacterium* in CHB  
486 [56,65,96,100,101], while others reported an increase in CHB-LC and HCC [57,63,75,100].  
487 Interestingly, *Faecalibacterium* were noted to be possible indicators of gut health [102];  
488 when *Faecalibacterium* levels were low, inflammatory processes were stimulated, resulting  
489 in the development of disease [103]. Furthermore, some studies reported an increased

490 abundance of *Ruminococcus* in CHB-LC and HCC [46,56], while others reported a decrease  
491 [78,84]. However, the precise taxonomic classification of *Ruminococcus* is misleading as it is  
492 continuously reclassified [104].

493 In this context, the mechanism of liver injury is the disruption of SCFAs production.  
494 The human microbiome degrades incomplete host digestion products and produces SCFAs  
495 products such as acetate, propionate, and butyrate. Butyrate has been identified as the primary  
496 energy source of enterocytes, and a lack of butyrate has been linked to decreased intestinal  
497 barrier integrity [97]. Moreover, butyrate is known as anticarcinogenic and anti-inflammatory  
498 and plays a role in oxidative stress [105].

499 *Anaerostipes*, producing SCFAs-genus, were also highly abundant in HBV carriers  
500 with normal than elevated ALT levels [45]. Moreover, *Anaerostipes* were more abundant in  
501 CHB [45,55] but declined in CHB-HCC patients [106]. Hence, the gut microbial composition  
502 varied according to HBV-induced serum ALT levels; these findings suggested a potential link  
503 between gut and liver inflammation [45].

504

#### 505 **Other CHB-associated taxa**

506 **Pro-inflammatory bacteria** such as *Enterococcus* [22,47,57] and *Escherichia Coli* [22,58]  
507 were reported to be highly abundant in CHB-LC. The liver injury could be explained through  
508 the activation of cytokines attracting inflammatory cells and enhancing myofibroblast  
509 formation [107]. Myofibroblasts, which produce collagen, are not found in healthy livers  
510 [108]; however, in response to toxic liver injury, myofibroblasts are primarily transformed  
511 from activated HSCs [109] and subsequently activated HSCs migrate and secrete  
512 extracellular matrix (ECM) to form a fibrous scar [110]. Moreover, several studies in CHB  
513 patients have postulated immunological links between gut dysbiosis and disease progression.  
514 [43,44,63]. For example, *Enterobacteriaceae* were positively correlated with TNF- $\alpha$  and

515 reported a higher abundance in CHB-LC than in HBV carriers and control [44]. Moreover,  
516 patients with cirrhosis showed weakened intestinal tight junctions and reduced tight junction  
517 protein expression [111] assessed by zonulin, a robust tight junction regulator [112]. Patients  
518 with CHB-LC and HCC have significantly higher serum zonulin levels, which were  
519 proportional to HBV stages [113]. Interestingly, a correlation between zonulin levels and the  
520 abundance of certain bacterial species, such as pro-inflammatory *E. coli*, has been  
521 demonstrated [114].

522         However, another study reported an unpredicted decrease in pro-inflammatory  
523 bacteria like *Escherichia-shigella* in CHB-HCC patients compared to non-hepatitis-related  
524 HCC [63]. Both studies emphasize the role of gut microbiota in HBV infection and disease  
525 progression, where the authors attributed this phenomenon to a lack of protective memory T  
526 cells due to CHB infection.

527 **Beneficial genera:** *Lachnospira* was reported to consistently decrease in CHB, LC, and  
528 HCC in several studies [22,47,75,78,84]. *Lachnospiraceae* were found to play a role in the  
529 management of CHB via the reduction in LPS secretion and bacterial translocation [106,115].  
530 *Akkermansia*, was reported to increase in resolved CHB infection [116], but another study  
531 showed its increase in CHB-LC [78]. In addition, a study showed a restoration of  
532 *Akkermansia* in a mouse model receiving AVT [40]. These conflicting results indicate that  
533 additional research is required to determine how *Akkermansia* contributes to HBV-related  
534 infections compared to controls.

535 *Veillonella* and *Megamonas* genera were identified to be significantly contributed to the  
536 pathogenesis of liver disease in different studies. *Veillonella* increased in CHB [46,56,85],  
537 CHB-LC, and HCC [55,58,63,78], while *Megamonas* showed high abundance in CHB  
538 [24,53,101], but it declined in CHB-LC and HCC [64,70]. Both genera are known to produce  
539 butyrate and SCFAs [117], contributing to anti-inflammatory response in the host [118].

540 Additional *in vitro* evidence suggested that *Veillonella* LPS stimulated the release of  
541 inflammatory cytokines like IL-6, IL-1 $\beta$ , IL-10, and tumor TNF- $\alpha$  [119]. These results  
542 suggested intestinal *Veillonella* metabolites affect liver pathology and inflammation [120].  
543 Interestingly, a previous study found that the level of *Veillonella* was positively correlated  
544 with CTP score in patients with CHB-LC [55]. However, the elevated *Veillonella* and  
545 decreased *Megamonas* genera might suggest the unbalanced inflammatory status in patients  
546 with CHB-LC.

547 In summary, and according to the previous findings, we can propose a typical  
548 microbiota signature profile in HBV-associated infections based on the most reproducible  
549 results of reported microbiota changes, as demonstrated in (**Fig. 4**). This signature is  
550 characterized by a consistent increase along *Pseudomonadota* phylum including  
551 (*Gammaproteobacteria* class, *Enterobacteriales* order, *Enterobacteriaceae* family, *Klebsiella*,  
552 *proteus* and *Sutterella* genera and *Escherichia coli* species). However, Members of *Bacillota*  
553 (formerly *Firmicutes*) phylum showed a constant decrease among class *Clostridia* (except  
554 *Blautia* genus increased). Still, a consistent increase in class *Bacilli* members (including  
555 *Lactobacillales* order harboring *Streptococcus* and *Enterococcus* genera and *Veillonellaceae*  
556 family having *Veillonella* genus) (**Fig. 4**). Interestingly, *Bacteriodes eggerthi* decreased,  
557 unlike the constant increase in members of *Bacteroidia* class. This finding supports the  
558 importance of investigating HBV-associated dysbiosis to the species level that could show  
559 different abundance. In conclusion, the mechanisms by which the previous microbiota  
560 signature induces liver injury in HBV-associated dysbiosis are summarized in (**Fig. 5**).

561

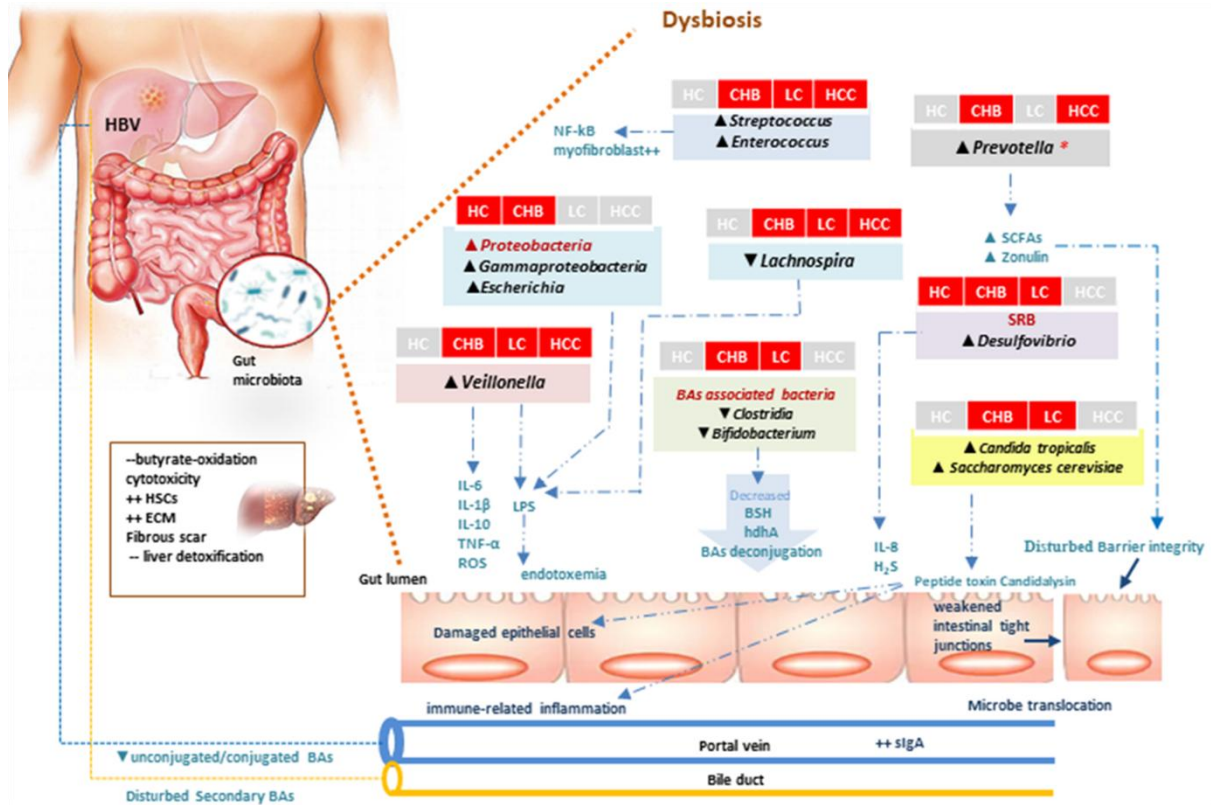
PHYLUM	CLASS	ORDER	FAMILY	GENUS	SPECIES
Pseudomonadota ▲	Gammaproteobacteria ▲	Enterobacteriales ▲	Enterobacteriaceae ▲	Escherichia ▲	Escherichia coli ▲
				Klebsiella ▲	
	Betaproteobacteria	Burkholderiales	Morganellaceae	Proteus ▲	
			Sutterellaceae	Sutterella ▲	
Bacteroidota	Bacteroidia ▲	Bacteroidales ▲	Rikenellaceae ▼		
			Prevotellaceae ▲	Prevotella ▲	
			Bacteroidaceae	Bacteroides	Bacteroides eggerthi ▼
Bacillota ▼	Clostridia ▼	Eubacteriales ▼	Lachnospiraceae ▼	Lachnospira ▼	
				Roseburia ▼	
				Blautia ▲	
				Clostridiaceae ▼	Clostridium ▼
	Bacilli ▲	Lactobacillales ▲	Lactobacillaceae ▲		
			Streptococcaceae ▲	Streptococcus ▲	
			Enterococcaceae	Enterococcus ▲	
Negativicutes	Veillonellales	Veillonellaceae ▲	Veillonella ▲		
Actinomycetota ▲	Actinomycetes ▲	Bifidobacteriales	Bifidobacteriaceae ▼	Bifidobacterium ▼	
		Coriobacteriales	Coriobacteriaceae ▼		
Thermodesulfobacteriota	Desulfovibrionia	Desulfovibrionales	Desulfovibrionaceae	Desulfovibrio ▲	

562

563

564 **Figure. 4 Identified microbiota signatures in HBV-associated gut dysbiosis.**

565 Pathobiont taxa with a high abundance are highlighted in red, while symbiont species with a low abundance are  
 566 marked in green. Taxa highlighted in grey are either not reported in the reviewed publications but included in  
 567 the graphic to better represent the taxonomy profile, or the reported results were inconclusive.



568

569 **Figure. 5** Possible pathophysiological mechanisms induced by identified signature microbiota in HBV-  
 570 associated diseases. Gradually decreased *Lachnospira* and increased *Streptococcus*, *Enterococcus*, *Prevotella*,  
 571 and *Veillonella* seem to play essential roles in the progression from LC to HCC, which could be considered the  
 572 potential microbial markers for the early diagnosis of HCC. \* *Prevotella* produces SCFAs that maintain gut  
 573 barrier integrity; however, it also correlates to increased zonulin serum levels [114], causing weakened intestinal  
 574 tight junctions. **NF-kB**: Nuclear factor-kB; **SRB**: Sulfate-reducing bacteria; **SCFAs**: Short chains fatty acids;  
 575 **LPS**: Lipopolysaccharides; **IL**: Interleukin; **TNF**: Tumor necrosis factor; **ROS**: Reactive oxygen species; **H<sub>2</sub>S**:  
 576 Hydrogen sulfide; **BSH**: Bile salt hydrolase; **hdhA**: 7-alpha-hydroxysteroid dehydrogenase; **BAs**: Bile acids;  
 577 **HSCs**: hepatic stellate cells; **ECM**: Extracellular matrix; **sIgA**: Secretory immunoglobulin A. ++: proliferation;  
 578 --: Inhibition. Predominant taxa in different disease stages are illustrated (red squares) as follows: **HC**: HBV-  
 579 carriers, **CHB**: Chronic HBV infection, **LC**: liver cirrhosis, **HCC**: hepatocellular carcinoma.

## 580 5 NON-BACTERIAL MICROBIOTA IN HBV-ASSOCIATED DYSBIOSIS

581

### 582 5.1 Gut virome

583 In the human body, the gastrointestinal system is home to most viruses [120], forming viral  
584 fingerprints unique for each individual and primarily comprising bacteriophages [121].

585 Viruses, in general, and phages, specifically, are modulated through the presence and  
586 abundance of their bacterial hosts [122].

587 Phages can control bacterial population density and facilitate the lysis of bacterial  
588 cells. According to a recent study, *Streptococcus* species were the primary interface between  
589 bacteria and phages in patients with LC and HE [123]. Since *Streptococcus* species have been  
590 reported to be consistently highly abundant in CHB and HBV-related complications  
591 [46,47,56,100], this could suggest that HBV infection could be related to gut viruses.

592 However, the precise role of gut virome in the etiology of HBV infection remains  
593 unknown, owing to the complex pathogenesis of HBV and a lack of relevant studies. A pilot  
594 study was conducted to investigate the frequency of Human herpesvirus-6 (HHV-6)  
595 reactivation in viral HBV and its impacts on the course of the primary disease. According to  
596 the serological and immunohistochemical findings, HBV infection has higher autoantibody  
597 formation once HHV-6 is present [124].

598 Interestingly, two studies have investigated gut virome as a potential therapeutic  
599 target in cirrhosis. One study reported that phages linked with bacterial species such as  
600 *Escherichia* and *Lactobacillus* increased with LC progression, while those related to health,  
601 such as crAssphages were lower [123]. In addition, there were stronger positive linkages  
602 between *Faecalibacterium* phage and *Microviridae* spp and potentially beneficial SCFA-  
603 producing taxa after rifaximin treatment [123]. Moreover, *Microviridae*, predominantly  
604 *Enterobacteriaceae* phages, increased in patients with LC receiving rifaximin. Their positive

605 linkages with otherwise beneficial bacterial species may suggest a proper post-rifaximin  
606 context associated with lower *Enterobacteriaceae* [125].

607 In conclusion, it is challenging to determine whether the changes in the gut virome are  
608 a cause or a result of the disease, especially since LC severity is more correlated with bacteria  
609 than viruses. However, modulating LC progression as a complication of CHB infection by  
610 affecting bacteria through phages or modified medication is essential to analyze.

611

## 612 **5.2 Gut mycobiome**

613 Fungi are believed to be a crucial part of the human microbiota, interacting with other  
614 microorganisms in the gut [126]. However, due to their low abundance in the human body,  
615 research studies on mycobiota have been far fewer than those on microbiota for the past two  
616 decades [127]. The gut fungi in adults mainly comprise three phyla: *Ascomycetes* (harboring  
617 *Aspergillus*, *Penicillium*, and *Candida*), *Basidiomycetes*, and *Zygomycetes* [128].

618 There has been little research on the relationship between gut mycobiota and HBV  
619 infection, with changes in the mycobiome linked to the progression of HBV infection in  
620 patients with and without LC. Only *three* studies, all from China, have been reported and  
621 discussed in this review (**Table 1**). One study reported a higher richness of fungal species in  
622 patients with CHB-LC than in CHB [115]. Only *Candida* spp. and *Saccharomyces*  
623 *cerevisiae* were obtained by culture-dependent approach. Enteric fungal diversity showed  
624 little difference between HBV carriers and controls [115]. Another study reported a high  
625 prevalence of *Aspergillus*, *Candida*, *Galactomyces*, *Saccharomyces*, and *Chaetomium* in  
626 patients with CHB-LC [129]. Moreover, Guo et al. noted a high abundance of *C.*  
627 *parapsilosis*, *C. glabrata*, *C. tropicalis*, and *S. cerevisiae* in patients with CHB-LC [130].  
628 Those findings show that the diversity of enteric fungi is positively related to HBV disease  
629 progression.



630           Recent studies have proven that *C. albicans* could secrete a peptide toxin called  
631 Candidalysin, which directly damages epithelial membranes and activates host immune  
632 responses [131]. Since *Candida* species were highly abundant in CHB, this mechanism could  
633 have a role in HBV-related liver injury (**Fig. 5**).

634           Interestingly, a prior study conducted on patients with LC (cause of cirrhosis not  
635 mentioned) reported that *Ascomycota* was negatively correlated with *Bacteroidetes*;  
636 moreover, a significant reduction of *Basidiomycota/Ascomycota* ratio (used to define the  
637 fungal dysbiosis) was reported in LC compared to controls [132]. In addition, the worsening  
638 of the Model for End-Stage Liver Disease (MELD) score (used as a predictor of survival in  
639 LC) was correlated negatively with *Basidiomycota/Ascomycota* ratio [132]. This implies that  
640 both mycobiome and bacterial microbiome need to be considered to improve prognostication.

641           In conclusion, the high abundance of *C. tropicalis* and *S. cerevisiae* was a  
642 reproducible finding in HBV-related infections (detected in at least two studies (**Table. 1**)).  
643 However, a recent study revealed that most strains of *Saccharomyces* and *non-*  
644 *Saccharomyces* yeasts are safe microorganisms, and could be regarded as probiotic yeast  
645 [133]. Therefore, prescribing such yeast species as probiotics should be cautiously applied,  
646 especially in HBV-infected patients.

647           The above findings demonstrate that fungi are significant modulators of the overall  
648 gut microbial dysbiosis in LC. However, the studies of interacting microorganisms are  
649 limited. Hence, more studies are needed to determine such interactions to identify better the  
650 role of bacterial-fungal correlation networks in disease pathogenesis and progression.

651

652 **Table 1.** Mycobiota changes in human HBV-related diseases

Author	Cohort (n)	Methodology	Mycobiota changes	Relevant findings
<b>Chen et al., 2011</b> [115]	HBV carriers (n = 33) CHB (n = 35) CHB-LC (n = 38) Healthy controls (n = 55)	-Culture -PCR-RFLP -18S rDNA clones and sequencing	<i>Aspergillus versicolor</i> ↑ <i>Aspergillus penicillioides</i> ↑ <i>Candida solani</i> ↑ <i>Candida albicans</i> ↑ <i>Candida austromarina</i> ↑ <i>Candida intermedia</i> ↑ <i>Candida milleri</i> ↑ <i>Candida tropicalis</i> ↑ <i>Saccharomyces paradoxus</i> ↑ <i>Saccharomyces cerevisiae</i> ↑ <i>Galactomyces geotrichum</i> ↑ <i>Simplicillium obclavatum</i> ↑ <i>Simplicillium lanosoniveum</i> ↑ <i>Chaetomium globosum</i> ↑ <i>Hyphozyma variabilis</i> ↑ <i>Aureobasidium pullulans</i> ↑ <i>Doratomyces stemonitis</i> ↑ <i>Wallemia muriae</i> ↑ <i>Asterotremella albida</i> ↑ <i>Cryptococcus fragicola</i> ↑ <i>Rhizopus microsporus var.</i> ↑ <i>Malassezia pachydermatis</i> ↓ <i>Penicillium freii</i> ↓ <i>Candida krissii</i> ↓	<ul style="list-style-type: none"> <li>➤ Both fungal abundance and fungal diversity ↑</li> <li>➤ All OTUs belonged to the <i>three</i> major fungal taxa: <i>Zygomycetes</i> (2.7%), <i>Ascomycetes</i> (78.4%), and <i>Basidiomycetes</i> (18.9%).</li> <li>➤ Only <i>five</i> species were identified by the culture-dependent method: <i>C. albicans</i> and <i>C. krusei</i> were detected in all groups, <i>C. glabrata</i> detected in HBV-LC, CHB, and control groups; <i>C. tropicalis</i> was detected in the HBV-LC group; <i>S. cerevisiae</i> was detected in CHB group.</li> <li>➤ The culture-independent method did not identify <i>C. krusei</i> and <i>C. glabrata</i> from fecal samples, which was found by the culture-dependent method.</li> <li>➤ Patients with CHB-LC and CHB shared greater fungal diversity than HBV carriers and controls and patients with CHB-LC had the highest fungal diversity and composition among all groups.</li> </ul>
<b>Mou et al., 2018</b> [129]	CHB (n = 52) HBV-LC (n = 52) Healthy controls (n = 40)	Culture	<b>Genus:</b> <i>Saccharomyce</i> ↑	<ul style="list-style-type: none"> <li>➤ <i>Saccharomyces</i> in the CHB and CHB-LC groups were significantly greater than in the control group (P&lt;0.05).</li> <li>➤ <i>Saccharomyces</i> showed a weak correlation with serum IL-17A and a negative correlation with vitamin D levels in patient groups.</li> </ul>
<b>Guo et al., 2010</b> [130]	HBV carriers (n = 66) CHB (n = 68) CHB-LC (n = 80) Healthy controls (n = 84)	qPCR	<b>Species: (Prevalence)</b> <i>Candida parapsilosis</i> ↑ <i>Candida glabrata</i> ↑ <i>Candida tropicalis</i> ↑ <i>Candida krusei</i> ↑ <i>Saccharomyces cerevisiae</i> ↑	<ul style="list-style-type: none"> <li>➤ The sensitivity of the qPCR assays is significantly higher than the traditional isolation and culture method (P&lt;0.001).</li> <li>➤ Frequency of fungal species (DNA copy numbers) <ul style="list-style-type: none"> <li>▪ <i>C. glabrata</i>, <i>C. tropicalis</i>, and <i>S. cerevisiae</i> were more frequently found in HBV carriers than controls (P&lt;0.05).</li> <li>▪ Although copies of target DNA for <i>C. albicans</i> were significantly</li> </ul> </li> </ul>

different among the groups (especially LC  $P<0.01$ ), the prevalence values were not significantly different

- For *C. glabrata* and *C. tropicalis*, no significant difference in DNA copy numbers was observed among four groups,

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653

654 **HBV:** Hepatitis B virus; **CHB:** Chronic hepatitis B virus infection; **CHB-LC:** Chronic hepatitis B-associated liver cirrhosis; **PCR:** Polymerase chain reaction; **RFLP:**

655 Restriction fragment length polymorphism; **qPCR:** Quantitative polymerase chain reaction; **OTUs:** Operational taxonomic units and **IL:** Interleukin.

## 656 6. GUT MICROBIOTA-TARGETED TREATMENT

657 Antiviral medication has been acknowledged as an efficient method for treating and even  
658 reversing liver fibrosis and cirrhosis [134]. In addition, host health is dependent on the  
659 balance of the composition of the entire microbial community rather than one or a few  
660 dominant organisms [135]. Hence, with increasing evidence of the link between HBV  
661 infection and gut dysbiosis, several studies focused on manipulating the gut microbiota to  
662 treat CHB or slow disease progression by applying different treatment options (**Table. 2**).

663

### 664 6.1 Reverse HBV-associated dysbiosis with medications

#### 665 A. Antiviral treatment (AVT)

666 The main goal of all current treatment strategies is to suppress HBV replication [3].  
667 Interferon alpha and nucleoside analogs (NAs), such as ETV, are the principal AVT choices  
668 with low resistance and long-acting effects [136].

669 A previous study reported that ETV therapy could reverse gut microbiota in HBV-  
670 associated dysbiosis in a mouse model [40]. Reduced HBV DNA levels were documented in  
671 addition to restoration of specific beneficial bacteria such as *Akkermansia*, *Lacnospiracea*,  
672 and *Marvinbryantia* to proportions similar to controls [40]. Moreover, a recent study reported  
673 a marked increase of *Clostridium* and *Erysipelotrichaceae* after *eight* weeks of ETV  
674 treatment, while *Streptococcus*, *Atopobium*, and *Murdochiella* were markedly decreased  
675 [137]. Although adding *Clostridium butyricum* (CB) to ETV did not improve serum  
676 biochemical, immunologic, or virologic variables, it did affect the gut microbiota in CHB  
677 patients treated with ETV [138]. At the phylum level, significant differences in abundance  
678 between the untreated group and the ETV + CB group included *Firmicutes*, *Actinobacteria*,  
679 *Cyanobacteria*, *Euryarchaeota*, and *Synergistetes* [138] (**Table 2**). However, dynamic and

680 synergistic research on liver fibrosis outcomes and gut microbiota changes during AVT is  
681 still limited and needs further investigation.

682

## 683 **B. Antibiotics**

684 Rifaximin is a rifamycin-based nonsystemic antibiotic with low gastrointestinal absorption  
685 and good antibacterial activity [139]. Rifaximin has been used to prevent and treat HE [140].  
686 Current research investigates how rifaximin could treat liver complications by acting on gut  
687 microbiota (**Table 2**).

688         In a randomized trial, patients with LC and ascites were assigned to one of two  
689 groups: rifaximin or placebo for *four* weeks. Rifaximin group showed a decrease in gut  
690 microbiota abundance with a remarkable difference in *Pseudomonadales* abundance [141].  
691 Another two studies found that rifaximin also had some effect on gut microbiota abundance,  
692 where a slight decrease in *Veillonellaceae* and an increase in *Eubacteriaceae* were noticed  
693 [142]. Yet, the metabolite levels changed, endotoxemia was relieved, and serum fatty acid  
694 levels were increased significantly [143]. Conversely, prophylactic rifaximin did not improve  
695 SBP and was associated with *Escherichia coli*, *Enterococci*, and *Klebsiella* species in  
696 cirrhotic CHB patients with ascites [144]. In conclusion, rifaximin appears to directly impact  
697 bacterial function and pathogenicity rather than having a bactericidal effect.

698

## 699 **6.2 Bacterial probiotics**

700 Probiotics are nonpathogenic microorganisms that live in the gut, and when applied at  
701 treatment doses (at least 10<sup>6</sup> viable CFU/g), they may help to balance the gut microbiota  
702 [145]. *Lactobacillus* and *Bifidobacterium* genera are commonly reported as clinically  
703 available probiotics [146]. The protective mechanisms include reduced endotoxin levels,

704 antimicrobial production, improved gut barrier function, and modulation of local and  
705 systemic immunity [56].

706         The role of probiotics in HBV-related complications has been established in several  
707 studies. Probiotic therapy by *Lactobacillus acidophilus* was reported to improve blood  
708 ammonia and psychometric tests in HE [147]. Moreover, after *three* months of probiotic  
709 administration of *Clostridium butyricum* mixed with *Bifidobacterium infantis*, a previous  
710 study showed a significant improvement in venous ammonia and cognition levels. In  
711 addition, the abundance of pathogenic *Enterococcus* and *Enterobacteriaceae* was reduced  
712 [148] (**Table 2**). Interestingly, probiotics were effective in primary HE prevention in 26.3%  
713 of cirrhotic patients via replacing the pathogenic pro-inflammatory  
714 (*Veillonellaceae*, *Enterococcus*, and *Megasphaera*) and urease-producing organisms  
715 (*Alcaligenaceae* and *Porphyromonadaceae*) [149]. Moreover, a randomized controlled study  
716 showed that the combination of probiotics and lactulose was helpful for the prevention of HE  
717 patients with CHB-LC [150]. However, CHB patients treated with a probiotic containing  
718 LAB, *three* strains of *B. lactis*, *L. rhamnosus*, and *L. acidophilus* showed a significant  
719 increase in the treated group ( $p = 0.001$ ). However, CTP scores and liver functions did not  
720 significantly change [151].

721         Notably, due to recent advancements in synthetic biology, further engineered  
722 microorganisms, such as engineered *Escherichia coli* Nissle 1917 (Ecn), have been developed  
723 to lower blood ammonia levels and eventually reduce the incidence of HE [152,153].  
724 However, these strains have not progressed to clinical studies in hyperammonemia patients,  
725 and the clinical effects need further investigation.

726         In conclusion, probiotics could present potential therapeutic approaches for modifying  
727 HBV-associated dysbiosis. However, some studies have shown inconsistent results,

728 indicating the need for more clinical studies in HBV-infected patients with larger  
729 populations.

730

### 731 **6.3 Probiotic fungi**

732 Despite some intriguing recent discoveries about how the gut mycobiota contributes to the  
733 development of liver disease, there have been few promising studies of fungal novel  
734 therapeutic options for liver disease.

735 *Saccharomyces boulardii* is probably the most commonly used probiotic fungi.

736 Animal studies have indicated the protective and therapeutic role of *S. boulardii* in liver  
737 diseases via gut microbiota change and attenuating liver inflammation [154]. As mentioned  
738 earlier, most *Saccharomyces* and non-*Saccharomyces* yeasts strains were reported to be safe  
739 microorganisms and could be applied as an alternative to the probiotic yeast *S. boulardii*  
740 [133]. However, some side effects of *S. boulardii*, such as fungemia, were documented in  
741 clinical settings with immunosuppressed patients [155]. Therefore, probiotic fungi should be  
742 prescribed with caution.

743 Interestingly, macrofungi, known as mushrooms, such as *Agaricus bisporus* [156]  
744 and *Pleurotus ostreatus* [157], have shown their medicinal properties in proving  
745 hepatoprotective activity in mice models.

746 In conclusion, the probiotic effects of some fungal species have yet to be fully  
747 explored. Furthermore, probiotic fungus supplementation to prevent or treat HBV-related  
748 diseases can be anticipated; nevertheless, their medical application needs to be carefully and  
749 thoroughly investigated.

#### 750 **6.4 Faecal microbiota transplantation (FMT)**

751 Fecal microbiota transplantation is an emerging treatment method that transfers the gut  
752 microbiota from a healthy donor to a patient [158]. It is one of the most promising therapies  
753 in many diseases because it reshapes gut microbial communities [117].

754 Studies of FMT on animal models show promising results. Neuroinflammation was  
755 reduced in cirrhotic mice model treated with FMT [159]. Moreover, human studies on  
756 cirrhotic patients have shown promising FMT results in improving HE [160]. Several studies  
757 evaluating FMT in CHB patients are summarized in **Table 2**.

758 In a pilot study on treated CHB patients with HBeAg-positive status, the FMT arm  
759 experienced a significant decline in HBeAg titer compared to controls [161]. The previous  
760 findings imply that FMT can induce HBeAg seroclearance with high efficacy. The previous  
761 results were consistent with another clinical trial on HBeA-positive patients receiving AVT  
762 for over a year. The results showed that 16.7% of the FMT arm patients achieved HBeAg  
763 seroclearance [162].

764 Interestingly, a case report evaluated FMT in HBsAg-positive woman with LC  
765 reported a decrease in CTP score with an increase in beneficial bacteria like  
766 *Faecalibacterium* after FMT [163]. Surprisingly, some researchers have proposed that FMT  
767 of some potential beneficial bacteria can change the occurrence of disease, and HBV carriers  
768 might be the most suitable donors for slightly higher microbiota abundance [57]. However,  
769 such finding needs to be further validated.

770 Furthermore, in a randomized clinical trial, FMT helped reduce hospitalizations and  
771 improve cognition and dysbiosis for LC with recurrent HE [160]. Additionally, the same  
772 authors later verified the safety of FMT capsules through a phase 1, randomized, and  
773 placebo-controlled clinical trial [164].



774 Overall, using FMT as a therapy for HBV-associated dysbiosis showed promising  
775 results. Further research into this technique is already currently in progress, with the hope of  
776 providing future guidance in its clinical application. However, due to the limitations of a  
777 small number of participants and a lack of randomized clinical trials, further extensive, well-  
778 designed studies and trials are warranted to confirm the initial assumptions and promote the  
779 clinical practicability of such therapeutic options. The clinical trials conducted to date on  
780 FMT effectiveness in CHB have been summarized in **Table 3**.

781 **Table. 2** Microbiota-targeted treatment in HBV-associated dysbiosis

Study type	Reference	Cohort (n)	Treatment protocol	Relevant findings
<b>AVT</b>				
Human study	Lu et al., 2021 [137]	CHB (n = 30); Healthy controls (n =30).	Eight weeks of daily ETV; (n = 30).	<ul style="list-style-type: none"> <li>➤ After ETV treatment, gut microbiota abundance significantly increased.</li> <li>➤ Significant improvement in ALT, IL-6, IL-8, TNF-<math>\alpha</math>, and HBV DNA levels.</li> </ul>
Human study	Lu et al., 2021 [138]	CHB (n = 60); Healthy controls (n =30).	Eight weeks of daily ETV + CB; ETV (n = 30), ETV + CB (n =30).	<ul style="list-style-type: none"> <li>➤ Marked differences in <i>Firmicutes</i>, <i>Actinobacteria</i>, <i>Cyanobacteria</i>, <i>Euryarchaeota</i>, and <i>Synergistetes</i> before initial treatment and after ETV + CB treatment.</li> <li>➤ Significant differences in <i>Actinobacteria</i>, <i>Fusobacteria</i>, <i>Pseudomonadota</i>, <i>Saccharibacteria</i>, and <i>Synergistetes</i> between the ETV group and ETV + CB group.</li> <li>➤ No improvement in blood biochemical, immunological, and virological parameters.</li> </ul>
Mouse model	Li et al., 2020 [40]	HBV-infected mice at six weeks old (total n= 10); HBV infected (n = 5), HBV + ETV (n = 5).	35 days after HBV infection, four weeks of daily ETV, ETV (n = 5).	<ul style="list-style-type: none"> <li>➤ ETV reversed dysbiosis.</li> <li>➤ Changes in bacteria proportions of <i>Akkermansia</i>, <i>Lacnospiracea</i>, and <i>Marvinbryantia</i> in the ETV-treated group.</li> </ul>
<b>Antibiotics</b>				
Randomized trial	Kimer et al., 2018 [141]	LC (n = 54); CHB (not mentioned).	Four weeks of rifaximin 550-mg BD or placebo BD; Rifaximin (n = 36), Placebo (n = 18).	<ul style="list-style-type: none"> <li>➤ Rifaximin had minor effects on gut microbiota.</li> <li>➤ Rifaximin showed little impact on the inflammatory markers TNF-<math>\alpha</math>, IL-6, IL-10, IL-18, and CRP.</li> </ul>
Human study	Kaji et al., 2020 [142]	LC (n = 30).	Four weeks of rifaximin 1200 mg/d, rifaximin (n= 30)	<ul style="list-style-type: none"> <li>➤ Rifaximin relieved HE endotoxemia with improved intestinal hyperpermeability.</li> <li>➤ Rifaximin didn't affect serum proinflammatory cytokine levels (TNF-<math>\alpha</math>, IL-6, IFN-<math>\gamma</math>, IL-10).</li> </ul>
Human study	Bajaj et al., 2013 [143]	LC patients with MHE (n =20).	Eight weeks of rifaximin 550-mg BD, rifaximin (n= 20)	<ul style="list-style-type: none"> <li>➤ Minor effect on gut microbiota with little decrease in <i>Veillonellaceae</i> and increase in <i>Eubacteriaceae</i>.</li> <li>➤ Rifaximin significantly improved cognition and endotoxemia.</li> <li>➤ Increase in serum fatty acids.</li> </ul>
Human study	Lutz et al., 2014 [144]	LC with ascites (n =152).	Prophylactic antibiotic treatment before the time of paracentesis; rifaximin (n =27), other systemic antibiotics (n	<ul style="list-style-type: none"> <li>➤ Prophylactic rifaximin did not improve SBP.</li> <li>➤ Prophylactic rifaximin was associated with the dominant bacteria in ascites: <i>Escherichia coli</i> and <i>Enterococcus</i>.</li> <li>➤ <i>Klebsiella</i> species were mainly recovered from the rifaximin group.</li> </ul>

= 17).

**Probiotics**

Human study	Xia et al., 2018 [148]	CHB-LC with MHE (n=30).	Three months of probiotics 1500-mg TD, which contained CB combined with <i>Bifidobacterium infantis</i> . Probiotics group (n =30).	<ul style="list-style-type: none"> <li>➤ Significant improvements in ALT, AST, bilirubin, albumin, and decreased ammonia levels.</li> <li>➤ Considerable improvement in psychometric tests.</li> <li>➤ Significant decrease in venous ammonia, LPS, D-lactate, and diamine oxidase.</li> <li>➤ The beneficial bacteria were significantly enriched, while <i>Enterococcus</i> and <i>Enterobacteriaceae</i> were decreased.</li> </ul>
Human study	Kwak et al., 2014 [151]	Chronic liver disease patients: HBV (8/25), ALD (14/25), HCV (2/25), Cryptogenic (1/25).	<p>- Probiotic containing six LAB species once per day for four weeks.</p> <p>- Six bacterial species included: <i>Bifidobacterium bifidum</i>, <i>Bifidobacterium lactis</i>, <i>Bifidobacterium longum</i>, <i>Lactobacillus acidophilus</i>, <i>Lactobacillus rhamnosus</i>, <i>Streptococcus thermophilus</i>.</p>	<ul style="list-style-type: none"> <li>➤ Small intestinal bacterial overgrowth, measured by hydrogen breath test, was present in 26% of the patients and improved in 24% of the probiotic group, while 16% worsened in the placebo group.</li> <li>➤ Liver chemistry, CTP scores, and intestinal permeability did not significantly change between groups.</li> </ul>
Human study	Agrawal et al., 2012 [150]	LC patients with recovered HE (n = 235).	Three months of lactulose 30–60 mL/d, or three probiotics capsules per day, contained four strains of <i>Lactobacillus</i> ; Lactulose (n = 80), Probiotics (n = 77).	<ul style="list-style-type: none"> <li>➤ Lactulose and probiotics were effective for secondary prophylaxis of HE in cirrhotic patients.</li> </ul>
Human study	Ziada et al., 2013 [147]	LC patients with MHE (n =90); CHB (not mentioned).	Four weeks of lactulose 30–60 mL/day, or three probiotics capsules per day, contained <i>Lactobacillus acidophilus</i> ; Lactulose (n = 30), Probiotics (n = 30).	<ul style="list-style-type: none"> <li>➤ Probiotic was more tolerated than lactulose.</li> <li>➤ Both of them can improve blood ammonia and psychometric tests and reduce the risk of developing HE.</li> <li>➤ The levels of brain neurometabolites were improved in the probiotic group.</li> </ul>
Animal model	Nicaise et al., 2008 [165]	Ornithine-transcarbamoylase deficient Sparse-fur mice; Carbon-tetrachloride-rats;	NCIMB8826 (wild-type strain <i>Lactobacillus plantarum</i> ),	<ul style="list-style-type: none"> <li>➤ EV101 administration was effective in controlling hyperammonemia in constitutive animal models with a significant effect on survival.</li> </ul>

		Thioacetamide-induced acute liver failure mice	or EV101 (engineered <i>Lactobacillus plantarum</i> ) oral and intrarectal administration	
Mouse model	Kurtz et al., 2019 [152]	Ornithine transcarbamylase-deficient <i>spfash</i> mice; Thioacetamide-induced acute liver failure mice; Healthy human controls ( $n = 52$ ) for phase 1 trial.	Non-modified <i>Escherichia coli</i> Nissle 1917 (EcN), SYNBI020 administration	<ul style="list-style-type: none"> <li>➤ SYNBI020 reduced systemic hyperammonemia and improved survival in mouse models.</li> <li>➤ SYNBI020 was well tolerated in healthy controls.</li> </ul>
Mouse model	Ochoa-Sanchez et al., 2021 [153]	Bile-duct ligated rats.	Non-modified EcN, S-ARG, or S-ARG <sup>+</sup> administration	<ul style="list-style-type: none"> <li>➤ S-ARG was further modified to synthesize butyrate, which had the potential to prevent HE.</li> </ul>
<b>FMT</b>				
Human study	Ren et al., 2017 [161]	CHB patients ( $n = 18$ ) with positive HBeAg status for less than three years were treated with ETV or TDF. <i>Five</i> patients elected to receive FMT, and <i>four</i> finished the trial. The other 13 who refused FMT were enrolled as a Control group ( $n = 13$ ).	FMT was performed by gastroscopy into the duodenum every <i>four</i> weeks until HBeAg clearance.	<ul style="list-style-type: none"> <li>➤ HBeAg titer declined after each round compared to controls in 75% (3/4) of patients.</li> <li>➤ FMT was effective in HBeAg clearance in CHB, especially in patients who could not cease the oral AVT even after long-term treatment.</li> <li>➤ Gut microbiota revealed some changes with each FMT, but no clear pattern was observed among all patients.</li> </ul>
Human study	Sun et al., 2019 [163]	One 45-year-old woman with CHB-LC with hepatic myelopathy.	The patient underwent <i>three</i> rounds of FMT from <i>four</i> healthy donors, the 1st by colonoscopy, and the last two by gastroscopy	<ul style="list-style-type: none"> <li>➤ Improvement of hepatic myelopathy score.</li> <li>➤ CTP score decreased from 8 to 6, and the patient showed marked improvement in her paraparesis.</li> <li>➤ Increase in beneficial genera like <i>Faecalibacterium</i> and decrease in harmful bacteria like <i>Fusobacterium</i>.</li> </ul>
Human study	Chauhan et al., 2021 [162]	HBeAg(+) CHB patients on oral AVT for >1 year ( $n = 12$ ).	<i>Six</i> FMTs by gastroscopy with antivirals every <i>four</i> weeks ( $n = 12$ )	<ul style="list-style-type: none"> <li>➤ 16.7% (2/12) of patients developed HBeAg clearance compared to none in the AVT arm.</li> <li>➤ <i>Six</i> patients reported one minor adverse event, while one was hospitalized for severe abdominal pain.</li> </ul>
Human study	Bajaj et al., 2017 [160]	DC patients with recurrent HE ( $n = 20$ ); CHB (not mentioned).	After <i>five</i> days of antibiotics, FMT was performed by enema, or SOC, (rifaximin/lactulose) was applied; FMT ( $n = 10$ ),	<ul style="list-style-type: none"> <li>➤ FMT increased diversity and beneficial gut microbiota taxa, improved cognition, and showed better tolerance than SOC.</li> </ul>

Human study	Guo et al., 2021 [166]	CHB (n=18); CHB-LC (n=17).	SOC (n = 10). All patients underwent gastroscopy FMT treatment using a freshly prepared bacterial solution.	<ul style="list-style-type: none"> <li>➤ FMT treatment improved liver function tests, controlled the replication of HBV-DNA, relieved liver fibrosis, and postponed the progression of CHB.</li> <li>➤ The fecal microbiota of the patients gradually approached the composition of the controls.</li> </ul>
Randomized controlled trial	Bajaj et al., 2019 [164]	DC patients with recurrent HE (n = 20); CHB (not mentioned).	FMT was performed by enema, or SOC, (rifaximin/lactulose) was applied; FMT (n= 10), SOC (n = 10).	<ul style="list-style-type: none"> <li>➤ Oral FMT capsules are safe and well tolerated.</li> <li>➤ The diversity in post-FMT increased with higher <i>Ruminococcaceae</i> and <i>Bifidobacteriaceae</i> and lower <i>Streptococcaceae</i> and <i>Veillonellaceae</i>.</li> </ul>
Mouse model	Liu et al., 2020 [159]	Germ-free mice.	Sterile supernatant or entire stool from pre-FMT and post-FMT cirrhotic patients with HE was transplanted to germ-free mice.	<ul style="list-style-type: none"> <li>➤ In mice, fecal microbial colonization from LC patients resulted in greater levels of neuroinflammation and neuronal activation regardless of LC. Reducing neuroinflammation by colonizing germ-free mice with samples from post-FMT patients revealed a direct effect of fecal microbiota irrespective of ongoing hepatic inflammation or injury.</li> </ul>
Mouse model	Wang et al., 2022 [167]	Six to eight-week-old male BALB/c and C57BL/6 mice.	The gut microbiota in BALB/c mice was depleted using broad-spectrum antibiotics and then reconstituted with fecal microbiota from BALB/c or C57BL/6 mice to evaluate the effect of FMT on the outcomes of the immune response to HBV infection.	<ul style="list-style-type: none"> <li>➤ Mice receiving fecal microbiota from BALB/c or C57BL/6 mice displayed different HBV infection outcomes.</li> <li>➤ The fecal microbiota from C57BL/6 mice induced immune tolerance in the liver and prolonged HBV infection.</li> <li>➤ The host genetic background shapes the gut microbiota composition, and commensal bacteria from FMT do not entirely but selectively colonize the gut of the new host.</li> <li>➤ FMT can modulate the host immune response and alter host susceptibility to HBV infection.</li> </ul>

782 **HBV:** Hepatitis B virus; **CHB:** Chronic hepatitis B infection; **LC:** Liver cirrhosis; **CHB-LC:** Chronic hepatitis B-associated liver cirrhosis; **MHE:** Minimal hepatic  
783 encephalopathy; **ALD:** Alcohol-related liver disease; **HCV:** Hepatitis C virus; **FMT:** Fecal microbiota transplantation; **HBeAg:** Hepatitis B e antigen; **CB:** *Clostridium butyricum*; **AVT:** Antiviral  
784 treatment; **DC:** Decompensated cirrhosis; **ETV:** Entecavir; **CB:** *Clostridium butyricum*; **BD:** Twice a day; **TD:** Three times daily; **LAB:** Lactic acid bacteria; **SOC:** standard  
785 of care; **ALT:** Alanine transaminase; **IL:** Interleukin; **TNF:** Tumor necrosis factor; **CRP:** C-reactive protein; **SBP:** Spontaneous bacterial peritonitis; **AST:** Aspartate  
786 transferase; **LPS:** Lipopolysaccharides; **CTP:** Child-Turcotte-Pugh, and **HE:** Hepatic encephalopathy.

787 **Table. 3** Clinical trials evaluating FMT efficacy in CHB patients

Study title	Status	Country	Identifier/ Completion Date	Study Population (n)	Intervention	Evaluation
Study on Gut Microbiota in Chronic HBV Infected Patients	NA	China	NCT03587467 (December, 2020)	CHB (n=90)	16S rRNA gene sequencing of fecal samples.	<b>Primary outcome measure:</b> Gut microbiota shift of patients in different stages.
Efficacy of Addition of Fecal Microbiota Transplant (FMT) and Plasma Exchange to Tenofovir in Comparison to Monotherapy With Tenofovir in ACLF-HBV	Recruiting	India	NCT04431375 (June 10, 2022)	ACLF-HBV (n=70)	Study whether adding plasma exchange & FMT adds benefit compared to tenofovir treatment alone.	<b>Primary outcome measure:</b> 28-day overall survival. <b>Secondary outcome measures:</b> <i>Three</i> -month survival. Reduction in HBV DNA level. Reduction in CTP and MELD scores.
Study on Effect of Intestinal Microbiota Transplantation in Chronic Hepatitis B (CHB)	NA	China	NCT03429439 (November 2020)	CHB (n=60)	Proposing IMT combined with AVT over 26 weeks.	<b>Primary outcome measure:</b> Changes in serum HBsAg, <b>Secondary outcome measures:</b> Changes in anti-hepatitis B antigens. Relief of gastrointestinal symptoms. Fecal microbiota before and after IMT.
Study on Effect of Intestinal Microbiota Transplantation in Hepatitis B Virus Induced Cirrhosis	NA	China	NCT03437876 (December 2020)	HBV-LC (n=60)	Patients will be randomized to either a control or IMT group over 12 months, applying four IMT at 2-week intervals for all patients.	<b>Primary outcome measure:</b> Change of liver Fibroscan score <b>Secondary outcome measures:</b> Relief of gastrointestinal symptoms. Changes in gut microbiota at <i>three</i> , <i>six</i> , and <i>twelve</i> months.
Randomized Controlled Trial Comparing the Efficacy and Safety of FMT in Hepatitis B Reactivation Leads to Acute on Chronic Liver Failure.	Completed	India	NCT02689245 (March 13, 2018)	ACLF-HBV (n=64)	Group 1:Tenofovir Group 2:Tenofovir with FMT  Tenofovir would be given 300 mg once daily; FMT through a naso-jejunal tube for <i>seven</i> days.	<b>Primary outcome measure:</b> 3-month Transplant free survival <b>Secondary outcome measures:</b> Reduction in HBV DNA level $\geq 2$ log. Improvement in MELD and CTP scores. Improvement in clinical parameters. Change in gut microbiome in both. Assessment of organ failures.

788 **HBV:** Hepatitis B virus; **CHB:** Chronic hepatitis B; **ACLF:** Acute-on-chronic liver failure; **CHB-LC:** Chronic hepatitis B-associated liver cirrhosis; **FMT:**  
789 Fecal microbiota transplantation; **IMT:** Intestinal microbiota transplant; **AVT:** Antiviral treatment; **MELD:** Model for End Stage Liver Disease; **CTP:** Child-  
790 Pugh Turcotte, and **HBsAg:** Hepatitis B surface antigen. Data collected from the official website <https://ClinicalTrials.gov> (Accessed June, 2023).  
791

## 792 7. CONCLUSIONS AND PERSPECTIVES

793 Hepatitis B is one of the most common liver diseases worldwide, and studies  
794 describing HBV-associated dysbiosis lack consensus on a signature microbiota profile in  
795 most disease stages. Therefore, this review provided a comprehensive overview of the most  
796 recent research on HBV-associated dysbiosis investigating microbiome, mycobiome, and  
797 virome studies. The results were heterogeneous, particularly in patient subgroups. This could  
798 be due to factors influencing gut microbiota, such as genetics, age, environmental exposures,  
799 and diet, which were not adjusted in many cases.

800 Eventually, reproducible results of a signature microbiota profile in most HBV-related  
801 diseases were obtained. An increase in *Pseudomonadota*, *Bacilli*, *Prevotella*, *Streptococcus*,  
802 *Veillonella* and a decrease in *Clostridia*, *Lachnospiraceae*, and *Roseburria* characterizes this  
803 signature. High abundance of *Saccharomyces cerevisiae*, and *Candida tropicalis* was a  
804 constant finding. Notably, dysbiosis was observed in all groups except for HBV carriers, who  
805 seemed similar to the control group. This indicates the role of microbiota in the pathogenesis  
806 of HBV infection.

807 It is challenging to determine whether the changes in gut microbiota are a cause or a  
808 result of HBV infection or which is the initiating factor between gut microbiota alteration and  
809 HBV disease progression to LC and HCC. Hence, well-established animal models may help  
810 elucidate the causality effect, especially in the acute stage. Moreover, modulating CHB-LC  
811 progression affecting bacteria through phages or fungi is essential to analyze. Therefore,  
812 more studies investigating microbiota changes to the species level are needed in a more  
813 geographically diverse population.

814 Probiotics and FMT are promising gut microbiota-targeted therapies. However,  
815 probiotic fungi should be carefully prescribed, and more extensive FMT randomized clinical  
816 trials are needed to confirm the practicability in clinical settings. Hence, synthetic probiotics



817 and selective microbiota transplantation may make these therapies more precise and bring  
818 fewer side effects.

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### 823 **AUTHOR CONTRIBUTIONS**

824 R.M.W contributed to independent literature search and review, analysis, original draft  
825 writing, and visualization. M.T.A reviewed the final version. S.R reviewed the mycobiome  
826 studies. P.B and R.G performed a critical review of the manuscript. D.R contributed to  
827 conceptualization and project administration. M.M supervised the study, performed the  
828 methodological quality assessment for the studies, and revised the results. All authors  
829 reviewed and approved the final version of the manuscript.

### 830 **Declaration of generative AI and AI-assisted technologies in the writing process**

831 During the preparation of this work, the authors declare that no AI tools or any AI-assisted  
832 technologies have been used in the writing process or data extraction/analysis for the  
833 included studies in this review. The only AI tools used are [Semantic Scholar] and [Scite] in  
834 order to deeply investigate our systematic review by searching broad non-traditional  
835 databases to retrieve all the related studies for our topic. The authors reviewed the content  
836 and take full responsibility for the content of the publication.

### 837 **Data, scripts, code, and supplementary information availability**

838 All the data and supplementary tables are available on the HAL portal  
839 <https://amu.hal.science/hal-04608814> [31].

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