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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

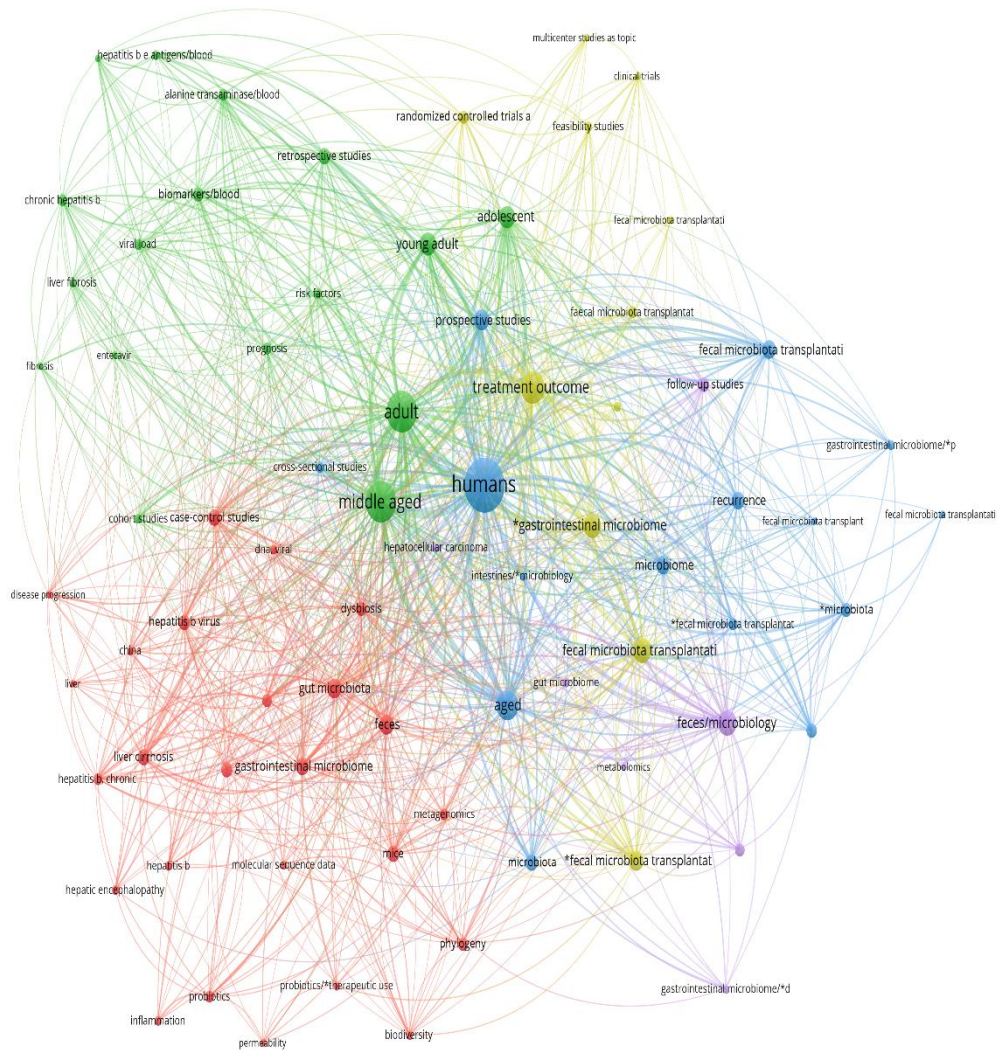
93 **1. DATA COLLECTION**

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].

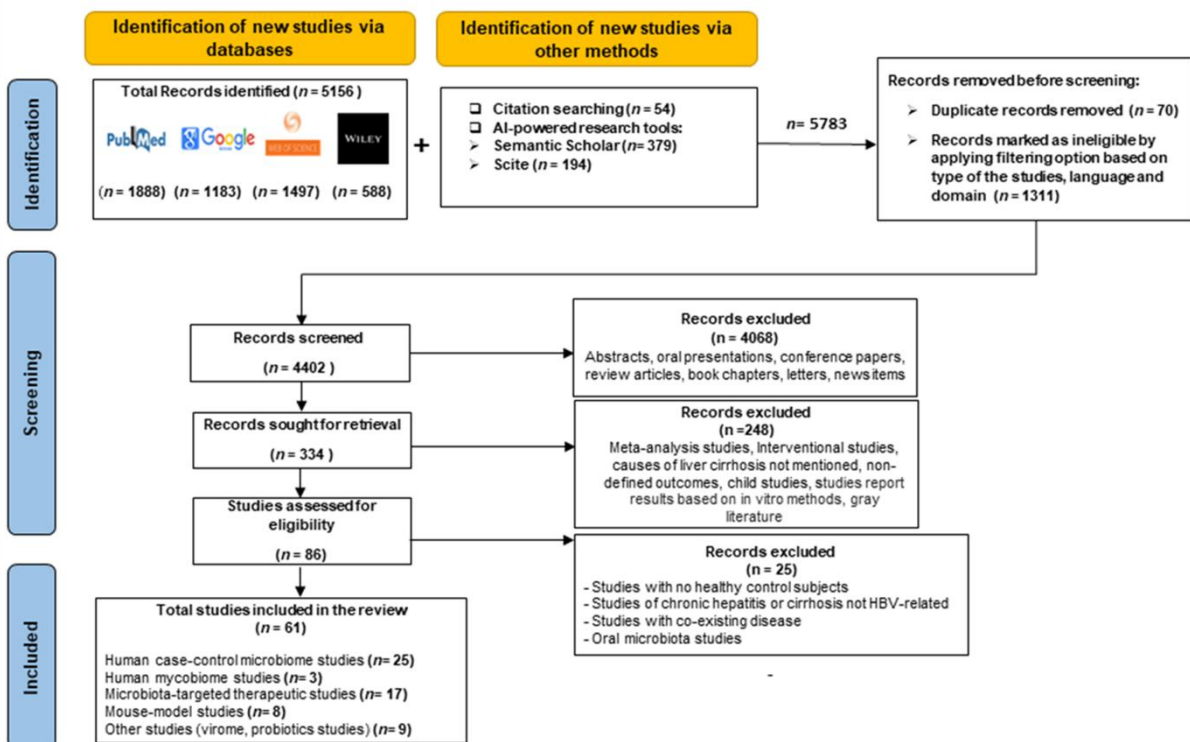
172 Different molecular methods were used to characterize gut microbiota, including denaturing
173 gradient gel electrophoresis (DGGE), Quantitative PCR (qPCR), and sequencing of the 16s
174 rRNA genes. All microbiota analyses were investigated in adults. All microbiome studies

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 α 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 (CH₃SH) production, whereas the control group resembled hydrogen sulfide
306 (H₂S) 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
Phylum					
<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)
Class					
<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)
Order					
<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)
Family					
<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
Genus					
<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)
Species					
<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- α 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- α 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 (H₂S), 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 H₂S
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- α 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 β , IL-10, and tumor TNF- α [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

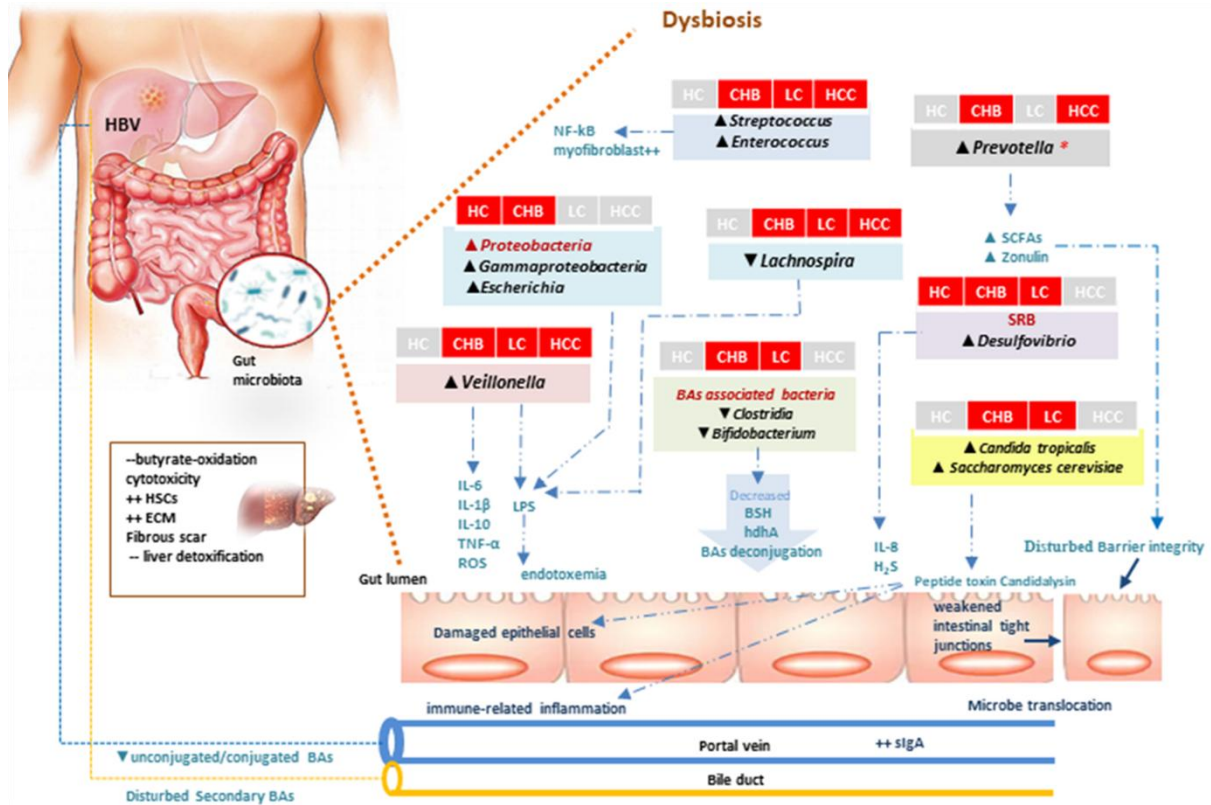
PHYLUM	CLASS	ORDER	FAMILY	GENUS	SPECIES
Pseudomonadota ▲	Gammaproteobacteria ▲	Enterobacteriales ▲	Enterobacteriaceae ▲	Escherichia ▲	Escherichia coli ▲
				Klebsiella ▲	
	Betaproteobacteria	Burkholderiales	Morganellaceae	Proteus ▲	
			Sutterellaceae	Sutterella ▲	
Bacteroidota	Bacteroidia ▲	Bacteroidales ▲	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; **H₂S**:
 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
Chen et al., 2011 [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"> ➤ Both fungal abundance and fungal diversity ↑ ➤ 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%). ➤ 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. ➤ 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. ➤ 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.
Mou et al., 2018 [129]	CHB (n = 52) HBV-LC (n = 52) Healthy controls (n = 40)	Culture	Genus: <i>Saccharomyce</i> ↑	<ul style="list-style-type: none"> ➤ <i>Saccharomyces</i> in the CHB and CHB-LC groups were significantly greater than in the control group (P<0.05). ➤ <i>Saccharomyces</i> showed a weak correlation with serum IL-17A and a negative correlation with vitamin D levels in patient groups.
Guo et al., 2010 [130]	HBV carriers (n = 66) CHB (n = 68) CHB-LC (n = 80) Healthy controls (n = 84)	qPCR	Species: (Prevalence) <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"> ➤ The sensitivity of the qPCR assays is significantly higher than the traditional isolation and culture method (P<0.001). ➤ Frequency of fungal species (DNA copy numbers) <ul style="list-style-type: none"> ▪ <i>C. glabrata</i>, <i>C. tropicalis</i>, and <i>S. cerevisiae</i> were more frequently found in HBV carriers than controls (P<0.05). ▪ Although copies of target DNA for <i>C. albicans</i> were significantly

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,

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 10⁶ 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
AVT				
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"> ➤ After ETV treatment, gut microbiota abundance significantly increased. ➤ Significant improvement in ALT, IL-6, IL-8, TNF-α, and HBV DNA levels.
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"> ➤ 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. ➤ 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. ➤ No improvement in blood biochemical, immunological, and virological parameters.
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"> ➤ ETV reversed dysbiosis. ➤ Changes in bacteria proportions of <i>Akkermansia</i>, <i>Lacnospiracea</i>, and <i>Marvinbryantia</i> in the ETV-treated group.
Antibiotics				
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"> ➤ Rifaximin had minor effects on gut microbiota. ➤ Rifaximin showed little impact on the inflammatory markers TNF-α, IL-6, IL-10, IL-18, and CRP.
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"> ➤ Rifaximin relieved HE endotoxemia with improved intestinal hyperpermeability. ➤ Rifaximin didn't affect serum proinflammatory cytokine levels (TNF-α, IL-6, IFN-γ, IL-10).
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"> ➤ Minor effect on gut microbiota with little decrease in <i>Veillonellaceae</i> and increase in <i>Eubacteriaceae</i>. ➤ Rifaximin significantly improved cognition and endotoxemia. ➤ Increase in serum fatty acids.
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"> ➤ Prophylactic rifaximin did not improve SBP. ➤ Prophylactic rifaximin was associated with the dominant bacteria in ascites: <i>Escherichia coli</i> and <i>Enterococcus</i>. ➤ <i>Klebsiella</i> species were mainly recovered from the rifaximin group.

= 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"> ➤ Significant improvements in ALT, AST, bilirubin, albumin, and decreased ammonia levels. ➤ Considerable improvement in psychometric tests. ➤ Significant decrease in venous ammonia, LPS, D-lactate, and diamine oxidase. ➤ The beneficial bacteria were significantly enriched, while <i>Enterococcus</i> and <i>Enterobacteriaceae</i> were decreased.
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"> ➤ 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. ➤ Liver chemistry, CTP scores, and intestinal permeability did not significantly change between groups.
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"> ➤ Lactulose and probiotics were effective for secondary prophylaxis of HE in cirrhotic patients.
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"> ➤ Probiotic was more tolerated than lactulose. ➤ Both of them can improve blood ammonia and psychometric tests and reduce the risk of developing HE. ➤ The levels of brain neurometabolites were improved in the probiotic group.
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"> ➤ EV101 administration was effective in controlling hyperammonemia in constitutive animal models with a significant effect on survival.

		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"> ➤ SYNBI020 reduced systemic hyperammonemia and improved survival in mouse models. ➤ SYNBI020 was well tolerated in healthy controls.
Mouse model	Ochoa-Sanchez et al., 2021 [153]	Bile-duct ligated rats.	Non-modified EcN, S-ARG, or S-ARG ⁺ administration	<ul style="list-style-type: none"> ➤ S-ARG was further modified to synthesize butyrate, which had the potential to prevent HE.
FMT				
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"> ➤ HBeAg titer declined after each round compared to controls in 75% (3/4) of patients. ➤ FMT was effective in HBeAg clearance in CHB, especially in patients who could not cease the oral AVT even after long-term treatment. ➤ Gut microbiota revealed some changes with each FMT, but no clear pattern was observed among all patients.
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"> ➤ Improvement of hepatic myelopathy score. ➤ CTP score decreased from 8 to 6, and the patient showed marked improvement in her paraparesis. ➤ Increase in beneficial genera like <i>Faecalibacterium</i> and decrease in harmful bacteria like <i>Fusobacterium</i>.
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"> ➤ 16.7% (2/12) of patients developed HBeAg clearance compared to none in the AVT arm. ➤ <i>Six</i> patients reported one minor adverse event, while one was hospitalized for severe abdominal pain.
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"> ➤ FMT increased diversity and beneficial gut microbiota taxa, improved cognition, and showed better tolerance than SOC.

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"> ➤ FMT treatment improved liver function tests, controlled the replication of HBV-DNA, relieved liver fibrosis, and postponed the progression of CHB. ➤ The fecal microbiota of the patients gradually approached the composition of the controls.
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"> ➤ Oral FMT capsules are safe and well tolerated. ➤ The diversity in post-FMT increased with higher <i>Ruminococcaceae</i> and <i>Bifidobacteriaceae</i> and lower <i>Streptococcaceae</i> and <i>Veillonellaceae</i>.
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"> ➤ 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.
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"> ➤ Mice receiving fecal microbiota from BALB/c or C57BL/6 mice displayed different HBV infection outcomes. ➤ The fecal microbiota from C57BL/6 mice induced immune tolerance in the liver and prolonged HBV infection. ➤ 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. ➤ FMT can modulate the host immune response and alter host susceptibility to HBV infection.

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 B virus; **FMT:** Fecal microbiota transplantation; **HBeAg:** Hepatitis B e antigen; **CB:** **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.	Primary outcome measure: 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.	Primary outcome measure: 28-day overall survival. Secondary outcome measures: <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.	Primary outcome measure: Changes in serum HBsAg, Secondary outcome measures: 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.	Primary outcome measure: Change of liver Fibroscan score Secondary outcome measures: Relief of gastrointestinal symptoms. Changes in gut microbiota at <i>three</i> , <i>six</i> , and twelve 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.	Primary outcome measure: 3-month Transplant free survival Secondary outcome measures: Reduction in HBV DNA level ≥ 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.

819 **CONFLICT OF INTEREST**

820 The authors have no conflict of interest to be disclosed.

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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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