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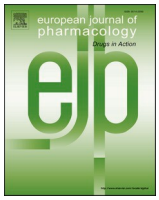

Efficacy of probiotics on improvement of health outcomes in cirrhotic liver disease patients: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Summary: Liver cirrhosis is a chronic condition of the liver and is the 14th most common cause of death around the world; yet it remains an incurable disease. Probiotics have gained significant popularity as a potential treatment option for liver cirrhosis.

Methods: A systematic review and meta-analysis was conducted to assess the effects of probiotics on liver cirrhosis. PubMed, Scopus, Cochrane Central Register for Controlled Trials (CENTRAL) and ProQuest Dissertation and Thesis were searched from 2000 to January 2024 for studies that evaluated the effects of probiotics on a variety of outcomes of liver disease.

Results: A total of 22 randomised controlled trial studies were included in the meta-analysis. Probiotics significantly decreased Gamma-glutamyl transferase (effect size: 0.307, $p = 0.024$, 95% CI [-0.572, −0.040]) and Aspartate aminotransferase ($p = 0.013$, 95% CI [-17.927, −2.128]). Significant reduction in serum ammonia levels (effect size = −1.093, $p = 0.000$, 95% CI [-1.764, −0.423]) and endotoxin levels (effect size = −0.961, $p = 0.000$, 95% CI [-1.537, −0.385]) were also found.

Summary: Overall probiotics could be recommended as a potential adjunct therapy for patients with cirrhosis, as they appear to have some benefit in improving liver function, and are well tolerated with minimal adverse effects. More comprehensive research with larger sample sizes is recommended to understand more about the widespread effects of probiotic use.

1. Introduction

Liver cirrhosis is a chronic condition of the liver, and is the 14th most common cause of death around the world (Tsochatzis et al., 2014). Liver cirrhosis is characterised by histological development of regenerative nodules surrounded by fibrous bands that occur secondary to long term damage of the liver (Schuppan and Afdhal, 2008). Some of the prevailing aetiologies of liver cirrhosis include alcoholic liver disease, non-alcoholic liver disease, hepatitis B, hepatitis C, Wilson disease and sclerosing cholangitis (Lee and Suk, 2020). In the early stages of liver cirrhosis, the disease is usually compensated. An individual is considered to have decompensated liver cirrhosis when they develop ascites, oesophageal variceal bleeding, hepatic encephalopathy, and in some instances, increased bilirubin concentrations (GBD 2017 Cirrhosis Collaborators, 2020). Mortality and morbidity resulting from cirrhosis increase significantly once an individual develops decompensated cirrhosis; depending on the aetiology of the cirrhosis, the one-year case fatality rate can be near 80% (GBD 2017 Cirrhosis Collaborators, 2020). The only curative treatment option for cirrhotic patients is to receive a liver transplant, which is a high burden option for patients and the healthcare system (Jiang et al., 2022). Recently, microbiome-targeted therapies (MTTs) have developed an increased popularity as a potential treatment option for multiple chronic diseases including cirrhosis by changing the gut microbiome (Chi et al., 2020; Dixon et al., 2020; Tranah et al., 2021).

The human gut microbiota consists of bacteria, fungi, protozoa, archaea, and viruses. It is a complex ecosystem that drives diverse nutritional, immune and metabolic functions within the host (Lee and

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Suk, 2020; Sun and Buys, 2015; Taylor et al., 2017). Its composition can be affected by a variety of factors such as an individual's diet, age, gender, stress levels, and geographical location (Sun and Buys, 2015). Recently, dysbiosis has been associated with numerous health conditions, including a number of liver conditions. This association is postulated to be due to the bidirectional relationship between the gut microbiota and the liver known as the gut-liver axis (Schwenger et al., 2019). Dysbiosis is associated with an increase in intestinal permeability, that causes damage to the liver through exposure to pathogen associated molecular patterns and damage associated molecular patterns (Qin et al., 2014; Schwenger et al., 2019).

Microbiome-targeted therapies (MTTs) can regulate the exposure of the liver to harmful substances by replenishing the 'good' bacteria missing from the microbiota of liver disease patients (Won et al., 2022). Probiotics are typically supplied from outside the human body and are live organisms usually in the form of spores that when ingested in adequate dosages are believed to have beneficial effects on the host (Sharma et al., 2013). The beneficial effects, however, depend on whether the probiotics can tolerate the acidic gastric environment and alkaline bile juices exposed to on their journey from the mouth to the intestines (Sharma et al., 2013). Many studies have looked at the efficacy of MTTs on the outcomes of cirrhotic liver disease complications which support the integral role of the gut microbiota on the progression of cirrhotic liver disease (Milosevic et al., 2019; Shukla et al., 2011). One meta-analysis assessing the effects of probiotics on liver cirrhosis was completed prior to our publication (Cao et al., 2018). The study focussed primarily on the effects of probiotics on hepatic encephalopathy and unlike our meta-analysis did not include the effects of probiotics on liver transaminases, albumin, creatinine, IL-6 and IL-10. Furthermore, our study included randomised control trials that were not included in the aforementioned meta-analysis, giving a more thorough insight into the effects of probiotics in patients with liver cirrhosis. Another meta-analysis did assess the effects of probiotics on liver function; however, their population was not specific (Khalesi et al., 2018). In contrast, our meta-analysis looked at the effects of probiotics in a specific population of individuals with liver cirrhosis.

This systematic review and meta-analysis seek to provide relevant evidence for the effects of prebiotics, probiotics and synbiotics compared to placebo, on the serological markers, quality of life, and adverse event outcomes in patients with liver cirrhosis.

2. Materials and methods

2.1. Search strategy

This systematic review and meta-analysis followed the PRISMA guidelines. To create the search strategy, the population, intervention, control and outcome (PICO) principle was utilised. Population was adults >18 years with a diagnosis of cirrhosis. Intervention was probiotics/prebiotics or synbiotics. Control was administration of a placebo or no treatment. Primary outcomes were Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), minimal hepatic encephalopathy (MHE) and serum albumin. Secondary outcomes included serum endotoxin, interleukins (IL-6 & IL-10), ammonia, creatinine, international normalised ratio (INR), TNF-α, bilirubin, MELD score, Child-Pugh score, quality of life scores and adverse effects.

The keywords for the search strategy were: (Probiotic OR prebiotic OR Bfidobacter* OR Lactobacill* OR Saccharomyces* OR Streptococcus* OR Enterococcus*) AND (cirrhosis OR cirrhotic) AND (randomised controlled trial OR RCT). In cases where data were insufficiently reported, the authors of that paper were contacted to retrieve the relevant data.

2.2. Inclusion criteria

Studies were included in the meta-analysis if they fit the following inclusion criteria: (1) participants were adults >18 years with cirrhosis; (2) probiotics/prebiotics/synbiotics were used as the intervention; (3) a placebo or no treatment was the control; (4) primary outcomes assessed liver function (GGT, AST, ALT and serum albumin) or features of MHE (cognitive outcomes); (5) published in a peer-reviewed journal since January 2000; (6) a randomised controlled trial. Exclusion criteria were: (1) patients <18 years; (2) any other additional liver pathology; (3) GI comorbidities; (2) <20 participants at baseline.

2.3. Data collection

If articles presented data, which were not appropriate for raw data extraction, the authors were contacted in an attempt to retrieve the necessary data. No authors responded to provide the required information, and therefore these data were not extracted or used in the analysis.

2.4. Data extraction

The search was completed by two reviewers, with disagreements resolved via discussion. The databases used to complete the search were: PubMed, Scopus, Cochrane Central Register for Controlled Trials (CENTRAL) and ProQuest Dissertation and Thesis. All citations and abstracts were downloaded to EndNote X9 for review by UL and AB. Duplicates were removed, and the remaining articles underwent title and abstract screening. Disagreements were resolved via discussion. Articles chosen for inclusion via title and abstract screening were then assessed via full-text screening, to create a final list of included articles. Bibliographies of similar review papers were assessed, and any relevant sources found from these were included into the final list.

Data extraction was completed by three reviewers: UL, AB and SP. The following data were extracted from the included articles: Study setting, location, participant demographics (age, sex), comorbidities, severity of cirrhosis, Child-Pugh score, form and content of probiotic, route of administration, dose, duration of treatment, type of control, measured outcomes, information for completion of risk of bias assessment, and any major findings of the study.

2.5. Quality assessment

The Physiotherapy Evidence Database tool (PEDro scale) was used to assess the quality of the included papers after full-text screening, as they were solely randomised controlled trials. Criteria 2–9 of the scale were used to assess internal validity, criteria 1 was used to assess external validity, and criteria 10–11 were used to assess sufficient statistical information. According to assessment, papers were categorised into three levels of quality: high quality (≥8 points), moderate quality (4–7 points) and low quality (≤3 points). Each paper was assessed independently by two reviewers, and any disparities were discussed and resolved between the reviewers. Articles deemed low quality via PEDro assessment were excluded from the study.

The 11 criteria within the PEDro scale were: (1) eligibility criteria specified; (2) subjects were randomly allocated to groups; (3) allocation was concealed; (4) groups were similar at baseline; (5) blinding of all subjects; (6) blinding of therapists; (7) blinding of assessors; (8) primary outcome measurement for ≥85% of initially enrolled subjects; (9) intention-to-treat analysis; (10) between-group statistical comparison; (11) measures of variability.

2.6. Statistical analysis

Data expressed through median (IQR), or median (min, max) were converted to estimated mean with standard deviation (SD), via Luo et al.

(2018) for estimated mean, and Wan et al. (2014) for estimated SD. The pooled effect size method was used to determine the effect of probiotics on outcomes in patients with cirrhosis, using a random-effect analysis. Some data were converted to allow for standardised units of measurements within each variable, allowing for the use of standardised mean difference within the pooled effect size. Mean difference and SD were used to indicate the effect size for the various outcome variables, including serum ammonia, GGT, AST, ALT, albumin, bilirubin, interleukins, TNF-α, ammonia, creatinine, MELD score and Child-Pugh score. For each of these outcome variables, the confidence interval (CI) and weighted mean difference were calculated. Inconsistencies were assessed within each study by visually assessing overlap between the CIs, and through use of I^2 statistics for heterogeneity.

Subgroup analyses were performed, which included the form of probiotic (capsule, yoghurt, powder, liquid), duration of intervention (<3 months, ≥3 months), strain (single vs. multiple strains) and type of intervention (prebiotic, probiotic, synbiotic), dose (<$4x10^{10}$, $4x10^{10}$ – $4x10^{11}$, >$4x10^{11}$. Publication bias was assessed using Egger's test, for variables which had ≥3 studies during analysis.

3. Results

A total of 503 studies were identified via the search strategy, with other 3 sources found via bibliography search. Duplicates were removed (141), which resulted in 365 articles to screen. Title and abstract screening resulted in 66 papers to screen via full-text, with reasons for exclusion provided (see Fig. 1). After full-text screening, 22 papers were chosen for inclusion and eligibility assessment via the PEDro scale (see Table 1). These papers met the eligibility criteria, and therefore, 22 studies were included in the analysis (see Table 2) (Agrawal et al., 2012; Bajaj et al., 2008, 2014; Dhiman et al., 2014; Grąt et al., 2017; Horvath et al., 2016; Jayakumar et al., 2013; Koga et al., 2013; Liu et al., 2004; Lunia et al., 2014; Macnaughtan et al., 2020; Maslennikov et al., 2022; Mittal et al., 2011; Perananthan et al., 2021; Pereg et al., 2011; Ramachandran et al., 2023; Riordan et al., 2007; Román et al., 2019; Saji et al., 2011; Sharma et al., 2014; Shi and Li, 2023; Vidot et al., 2019).

Subgroup analysis was conducted for ammonia only, as there were insufficient data for all other variables (≥3 studies per subgroup). Some heterogeneities were found for most of the included studies. This could be explained by the differences in sample size, length of probiotics

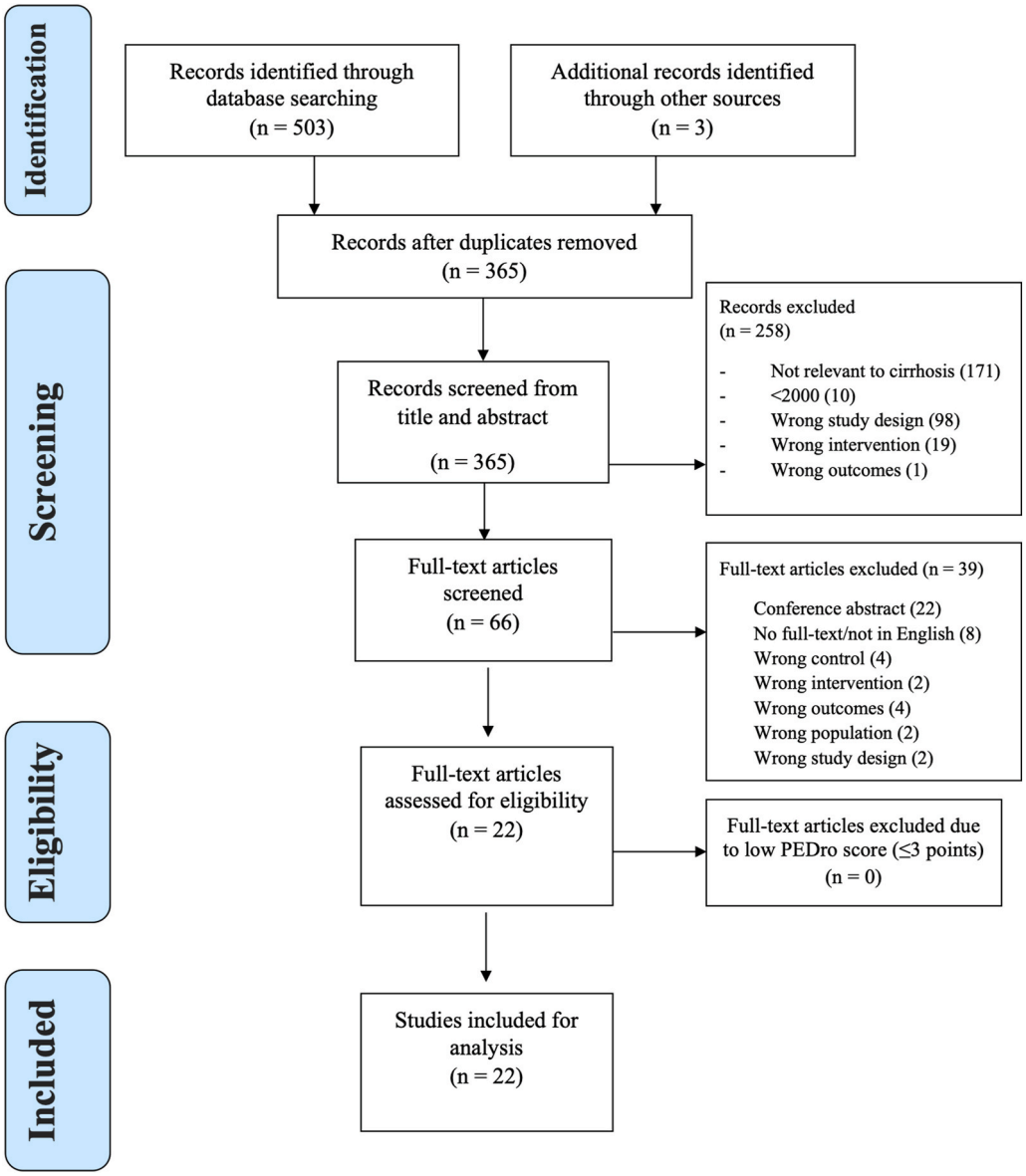

Fig. 1. Prisma flow diagram.

Table 1
Study characteristics.

Author (year)	Location	Sample Size (I/C)	*Age*I/C	Sex *n* (I/C) (M; F)	Cause of Cirrhosis Intervention	Cause of Cirrhosis Control	Control	Type of intervention	Intervention Strain/s	Form of intervention	Dose (CFU)	PEDro Score
Agrawal et al. (2012)	India	77/78	45.4 (±11.7)/46 (±11.2)	70; 7/ 61; 17			No therapy	Probiotic	4 strains of Lactobacillus; 3 strains of Bifidobacterium; 1 strain of Streptococcus salivarius	Capsule	11.2x10^10	6
Bajaj et al. (2014)	United States	14/16	58.4 (±3.8)/58.5 (±4.5)	10; 4/ 12; 4	Alcohol (1); HCV (7); HCV + Alcohol (2); NASH (2); Other (2)	Alcohol (0); HCV (8); HCV + Alcohol (1); NASH (5); Other (2)	Placebo	Probiotic	*lactobacillus* GG AT strain 53103 (LGG)	Capsule	51/61/53 billion	7
Bajaj et al. (2008)	United States	17/8	52 (±8)/54 (±4)		Autoimmune hepatitis (2); HCV (12); Primary Sclerosing Cholangitis (1); Other (3)	Autoimmune hepatitis (0); HCV (5); Primary Sclerosing Cholangitis (1); Other (2)	Placebo	Probiotic	*S. thermophilus, L. bulgaricus, L. acidophilus*, *Bifidobacteria*, and *L. casei*.	Yoghurt		9
Dhiman et al. (2014)	India	66/64	48/50.1	56; 10/ 54; 10	Alcohol (50); HBV (4); HCV (9); Other (7)	Alcohol (44); HBV (4); HCV (4); Other (13)	Placebo	Probiotic	4 Lactobacillus (*L paracasei* DSM 24733, *L plantarum* DSM 24730, *L acidophilus* DSM 24735, and *L delbrueckii ssp bulgaricus* DSM 24734); 3 Bifidobacterium (*B longum* DSM 24736, *B infantis* DSM 24737, and *B breve* DSM 24732), and *Streptococcus thermophilus* DSM 24731	Powder	9 × 10^11	10
Grąt et al. (2017)	Poland	24/26	52 (43; 58)/ 48 (35; 61)	18; 6/ 20; 6	Alcohol (8); HBV (6); HCV (7); Other (8)	Alcohol (6); HBV (4); HCV (8); Other (11)	Placebo	Probiotic	*Lactococcus lactis* PB411, *Lactobacillus casei* PB121, *Lactobacillus acidophilus* PB111, and *Bifidobacterium bifidum* PB211	Capsule	3 × 10^9 CFU	9
Horvath et al. (2016)	Austria	44/36	60 (54; 64)/ 56 (50; 63)	32; 12/ 26; 10	Alcohol (24); HCV (8); Other (12)	Alcohol (20); HCV (5); Other (11)	Placebo	Probiotic	*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52 *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	Powder	2.5 × 10^9	10
Jayakumar et al. (2013)	Canada	7/8	50 (46; 58)/ 53.5 (50; 55)	5; 2/7; 1	Alcohol (5); HCV (2)	Alcohol (6); HCV (2)	Placebo	Probiotic	4 strains of *Lactobacillus;* 3 strains of *Bifidobacterium; Streptococcus salivarus* ssp *thermophilus*	Powder	3600 × 10^9	10
Koga et al. (2013)	Japan	18/19	52.6 (±11.8)/ 53.9 (±14.9)	15; 3/ 15; 4	Alcohol (18)	Alcohol (19)		Probiotic	*Lactobacillus casei Shirota* YIT 9029	Liquid	80 × 10^9	7
Liu et al. (2004)	China	20/15	55 (±12)/ 57 (±12)	20; 0/ 14; 1	Alcohol (4); HBV (14); HCV (0); Other (2)	Alcohol (3); HBV (11); HCV (1); Other (0)	Placebo	Synbiotic	*Pediacoccus pentoseceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1, *Lactobacillus paracasei* ssp *paracasei* 19, *Lactobacillus plantarum* 2592	Powder	40^10	8
Lunia et al. (2014)	India	86/74	48.5 (±10.5)/ 49.4 (±11.5)	52; 34/ 44; 30	Alcohol (42); Cryptogenic (15); HBV (18); HCV (6); Other (5)	Alcohol (40); Cryptogenic (13); HBV (13); HCV (5); Other (3)	Placebo	Probiotic	*Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus* and *Streptococcus thermophilus*	Capsule	33 × 10^10	7
Macnaughtan et al. (2020)	UK	44/43	56.16 (±8.47)/ 58.16 (±9.18)	32; 12/ 30; 13	Alcohol (21); HBV (4); HCV (6); NASH (8); Other (5)	Alcohol (24); HBV (2); HCV (12); NASH (3); Other (2)		Probiotic	*Lactobacillus casei* ssp *Shirota*	Liquid	19.5x10^9	10

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Location	Sample Size (I/C)	*Age*I/C	Sex *n* (I/C) (M; F)	Cause of Cirrhosis Intervention	Cause of Cirrhosis Control	Control	Type of intervention	Intervention Strain/s	Form of intervention	Dose (CFU)	PEDro Score
Maslennikov et al. (2022)	Russia	24/16	48.5 (42.5; 59)/53.5 (44.5; 59)	8:16/ 9; 7	Alcohol (12); Cryptogenic (2); HBV (2); HCV (3); Mixed (3)	Alcohol (9); Cryptogenic (3); HBV (0); HCV (2); Mixed (3)	Placebo	Probiotic	*Lactobacillus casei* ssp *Shirota*		250 mg	8
Mittal et al. (2011)		34/31	44.25 (±11.8)/ 41.20 (±11.9)		Alcohol (18); Viral (13); Other (9)	Alcohol (14); Viral (14); Other (12)		Probiotic	Unknown	Capsule	22x10^10	7
Perananthan et al. (2021)		11/10	56.3 (±7.8)/54.5 (±7.2)	10; 1/ 9; 2	Alcohol (2); Cholestatic (0); NASH (2); Viral (5); Other (2)	Alcohol (3); Cholestatic (1); NASH (1); Viral (5); Other (0)		Prebiotic -Probiotic	*Lactobacillus plantarum, leuconostoc mesenteroides, pediococcus pentosaceus*		40x10^11	9
Pereg et al. (2011)	Israel	18/18	63.2 (±10.5)/ 65.9 (±8.4)		HCV (9); Other (Alcohol, Cryptogenic, HBV) (9)	HCV (10); Other (Alcohol, Cryptogenic, HBV) (8)	Placebo	Probiotic	*Lactobacillus acidophilus, Lactobacillus bulgaricus, Bfidobacterium bifidum, Streptococcus thermophiles*	Capsule	2x10^10	10
Ramachandran et al. (2023)	India	108/107	45.24 (±30.81)/ 49.76 (±39.83)	102; 6/94; 15	Alcohol (75); Cryptogenic (10); NASH (6); Viral (17)	Alcohol (68); Cryptogenic (12); NASH (5); Viral (20)	Placebo	Probiotic	*L paracasei DSM 24733, L plantarum DSM 24730, L acidophilus DSM 24735, L delbrueckii subspecies bulgaricus DSM 24734, B Longum DSM 24736, B infantis DSM 24737, B breve DSM 24732, Streptococcus thermophilus DSM 24731.*	Capsule	112.5 billion	10
Riordan et al. (2007)	Australia	15/15	56/55	9; 6/ 10; 5	Alcohol (6); HCV (7); Other (2)	Alcohol (7); HCV (7); Other (1)	Placebo	Synbiotic	*Pediacoccus pentoseceus 5-33:3, leuconostoc mesenteroides 32-77:1, lactobacillus paracasei subspecies paracasei 19 and lactobacillus plantarum 2592*	Powder	10^10	5
Román et al. (2019)	Spain	17/18	65.8 (±3.1)/64 (±2.6)	6; 12/ 8; 10	Alcohol (9); HBV (1); HCV (3); Other (4)	Alcohol (10); HBV (1); HCV (3); Other (2)	Placebo	Probiotic	*Streptococcus thermophilus* DSM 24731, *Bfidobacterium breve (B. breve)* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *Lactobacillus paracasei* DSM 24733, *L. acidophilus* DSM 24735, *L. delbrueckii* subspecies *bulgaricus* DSM 24734, *L. plantarum* DSM 24730.	Powder	450 billion	10
Saji et al. (2011)	India	20/20	50.6 (±5.81)/ 52.15 (±10.18)	19; 1/ 18; 2	Alcohol (34/40); Other (6/40)		Placebo	Probiotic	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum, Sacharomyces boulardi*	Powder	1.25 billion	10
Sharma et al. (2014)	India	32/30	33.87 (±13.2)/38 (±11.8)	17; 5/ 20; 10	Alcohol (4); HBV (5); HCV (7); Other (16)	Alcohol (10); HBV (7); HCV (4); Other (9)	Placebo	Probiotic	*Lactobacillus acidophilus, lactobacillus rhamnosus, lactobacillus plantarum, lactobacillus casei, Bifidobacterium longum, bifidobacterium infantis, bifidobacterium breve, Saccharomyces boulardi, Streptococcus thermophilus*	Capsule	5 billion	8
Shi and Li (2023)	Mongolia	44/44	59.6 (±6.4)/58.4 (±4.7)	36; 8/ 35; 9	Alcohol (7); HBV (32); Other (5)	Alcohol (8); HBV (30); Other (6)	Lactulose	Probiotic	*Bacillus subtilis, Enterococcus faecium*	Capsule	500 probiotics	7
Vidot et al. (2019)	Australia	12/12	56.7 (±7.5)/54.1 (±6.7)	11; 1/ 11; 1	Alcohol (2); NASH (3); Viral (5); Other (2)	Alcohol (3); NASH (1); Viral (6); Cholestatic (2)	Placebo	Synbiotic	*Lactobacillus paracasei* ssp *saracasei Lactobacillus plantarum Leuconostoc mesenteroides Pedicoccus pentosaceus*	Powder	40x10^11	11

Table 2
Mean Difference and Hedge's G effect size. p values in bold indicate statistical significance.

Variable	Studies	Mean difference (95% CI)	*p* for mean difference	Hedge's G effect size (95% CI)	*p* for Hedge's G	*Q* test	*p* for Q test	I^2
GGT	4	−29.252 (−55.567, −3.938)	**0.029**	−0.307 (−0.572, −0.040)	**0.024**	2.360	0.501	0.000
AST	5	−10.028 (−17.927, −2.128)	**0.013**	−0.340 (−0.849, 0.169)	0.191	23.860	0.000	83.236
ALT	7	−4.711 (−11.327, 1.904)	0.163	−0.326 (−0.838, 0.185)	0.211	47.113	0.000	87.265
Albumin	8	0.030 (−0.072, 0.132)	0.568	0.142 (−0.037, 0.321)	0.121	8.18	0.317	1.470
Endotoxin	5	−0.233 (−0.458, −0.009)	**0.041**	−0.961 (−1.537, −0.385)	**0.001**	45.042	0.000	91.119
IL-6	5	−3.755 (−12.985, 5.475)	0.425	−0.356 (−1.384, 0.672)	0.497	52.90	0.000	91.490
Creatinine	9	0.007 (−0.042, 0.055)	0.792	0.000 (−0.174, 0.173)	0.999	5.608	0.691	0.000
Ammonia	7	−11.091 (−17.498, −4.683)	**0.001**	−1.093 (−1.764, −0.423)	**0.001**	56.695	0.000	89.417

intervention, number of probiotic strains, dosages of probiotics, and placebo given between the studies.

3.1. Primary outcomes

3.1.1. Liver function tests

Four studies with a sample size of 223 adults were included in the meta-analyses assessing the effect of probiotics on GGT (Horvath et al., 2016; Macnaughtan et al., 2020; Maslennikov et al., 2022; Román et al., 2019). According to the analyses, probiotic supplementation did significantly reduce GGT levels with an overall mean difference of −29.252 U/L (effect size: 0.307, p = 0.024, 95% CI [−0.572, −0.040]) in five studies with no apparent heterogeneity (I^2 = 0%). Five studies were included in the meta-analyses assessing the effect of the probiotics on AST, with a sample size of 428 adults (Horvath et al., 2016; Macnaughtan et al., 2020; Maslennikov et al., 2022; Ramachandran et al., 2023; Sharma et al., 2014). A statistically significant reduction was noted with a mean difference of −10.028 U/L (effect size: 0.340, p = 0.191, 95% CI [−0.849, 0.169], I^2 = 83.236%), demonstrating a moderate effect size, with substantial heterogeneity.

The effect of probiotics on ALT was analysed in 7 of the included studies (sample size = 530). A reduction in ALT levels was more significant in the intervention arms of these studies, with an effect size in a fixed-effect model of −0.255 (p = 0.004; 95% CI = −0.43, −0.08). Substantial heterogeneity was found within these studies (I^2 = 87.27). (see Fig. 2)

Non-significant primary outcomes.

3.1.2. MHE

Agrawal et al. (2012) found that the use of probiotics had a greater effect in secondary prophylaxis of hepatic encephalopathy (HE) compared with no therapy. Over the 12-month follow-up period, out of 77 patients that developed HE, 22 of those patients were in the probiotic's intervention group compared to 37 being in the placebo group. Bajaj et al. (2008) found a similar trend in which a higher percentage of participants who were randomised into the probiotics group reversed MHE, compared with the no therapy group. Furthermore, 25% of the participants in the no therapy group developed overt hepatic

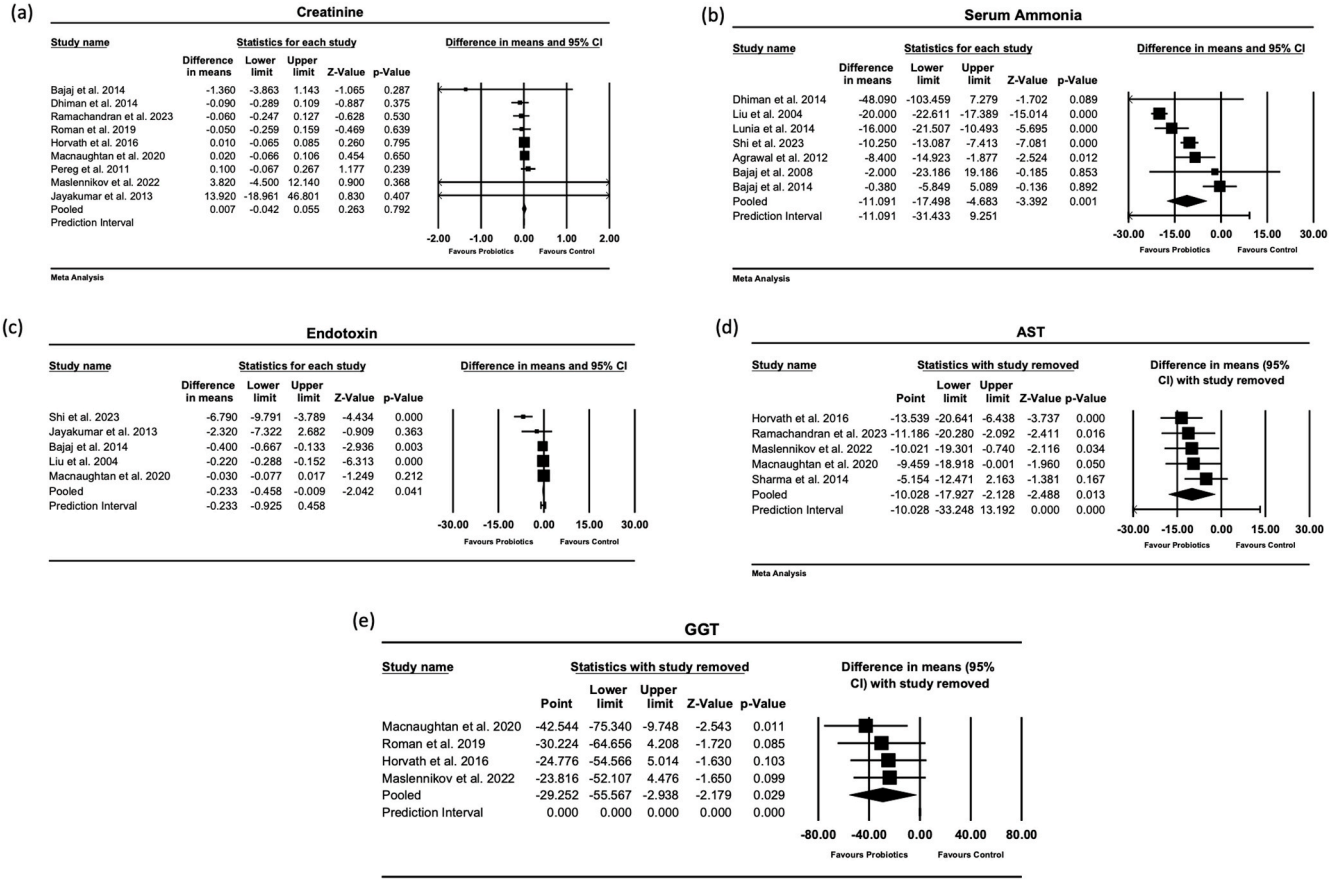

Fig. 2. Forest plots of meta-analysis for (a) Cretinine (b) ammonia (c) endotoxin (d) AST (e) GGT.

encephalopathy compared with 0% of participants in the probiotics group (Bajaj et al., 2008). Compared with placebo, 10/23 patients experienced low grade breakthrough HE in the probiotics group, which were managed in outpatients. In the placebo group however, 29/33 patients experienced high-grade HE that required hospitalisation (Bajaj et al., 2008). In Liu et al. (2004), MHE was reversed in 10/20 participants in the probiotics group, which was significantly higher than those in the no therapy group (2/15). Using intention to treat analysis, Lunia et al. (2014) found that a significantly smaller number of patients in the probiotics group developed HE compared to placebo. Similarly, Mittal et al. (2011) found that at 3 months recovery from MHE was significantly higher in the probiotics group versus placebo group. Conversely, Horvath et al. (2016) reported no difference in HE at baseline and end of study in both probiotic and control groups.

3.1.3. Serum albumin

The effect of probiotics on serum albumin was analysed in 8 of the included studies, with a sample size of 206 adults (Bajaj et al., 2014; Horvath et al., 2016; Jayakumar et al., 2013; Macnaughtan et al., 2020; Maslennikov et al., 2022; Pereg et al., 2011; Ramachandran et al., 2023; Román et al., 2019). The analyses indicates that probiotics did not have a statistically significant effect on increasing serum albumin (overall effect size = 0.142, p = 0.121, 95% CI [−0.037, 0.321]) in 8 mostly homogenous studies [I^2 = 1.470%].

3.2. Secondary outcomes

3.2.1. Serum ammonia

The effect of probiotics on serum ammonia was analysed in 7 of the included studies (Agrawal et al., 2012; Bajaj et al., 2008, 2014; Dhiman et al., 2014; Liu et al., 2004; Lunia et al., 2014; Shi and Li, 2023), with a sample size of 505 adults. Results showed that the effect of probiotics on decreasing serum ammonia levels was significant in pooled analysis, with a mean difference of −11.091 μmol/L (overall effect size = −1.093, p = 0.001, 95% CI [−1.764, −0.423] in 8 heterogenous studies (I^2 = 89.417%). Subgroup analysis showed significant differences between subgroups regarding type of intervention (capsule, yoghurt, liquid) and strain (single strain, multiple strains). A significantly larger decrease in ammonia levels was seen in studies utilising capsule or liquid formulations compared to yoghurt, and in studies using multiple strains compared to a single strain (seeTable 4).

3.2.2. Endotoxin

The effect of the probiotics on endotoxin was analysed in 5 of the included studies, with a sample size of 236 adults (Bajaj et al., 2014; Jayakumar et al., 2013; Liu et al., 2004; Macnaughtan et al., 2020; Shi and Li, 2023). The analysis indicated that there was a statistically significant effect on decreasing endotoxin levels, with a mean difference of −0.233 EU/ml (overall effect size = −0.961, p = 0.001, 95% CI [−1.537, −0.385]). The included studies were considerably heterogenous (I^2 = 91.119%).

Non-significant secondary outcomes.

3.2.3. Serum creatinine

The effect of probiotics on serum creatinine was analysed in 9 of the included studies, with a sample size of 516 adults. (Bajaj et al., 2014; Dhiman et al., 2014; Horvath et al., 2016; Jayakumar et al., 2013; Macnaughtan et al., 2020; Maslennikov et al., 2022; Pereg et al., 2011; Ramachandran et al., 2023; Román et al., 2019). Results indicate that probiotics did not have a statistically non-significant effect on reducing serum creatinine (overall effect = 0.000, p = 0.999, 95% CI [−0.174, 0.173]) in 9 homogenous studies [I^2 = 0%].

3.2.4. IL-6

The effect of probiotics on IL-6 was analysed in 5 of the included studies, with a population of 221 adults (Bajaj et al., 2008, 2014; Jayakumar et al., 2013; Macnaughtan et al., 2020; Shi and Li, 2023). The analysis indicated a non-significant decrease in IL-6 levels with a mean difference of −3.755 pg/mL, correlating to a medium effect size (effect size: 0.356, p = 0.497, 95% CI [−1.384, 0.672], I^2 = 91.490).

3.2.5. Adverse effects

Six studies reported no adverse events in the probiotic's groups (Jayakumar et al., 2013; Koga et al., 2013; Lunia et al., 2014; Macnaughtan et al., 2020; Mittal et al., 2011; Perananthan et al., 2021). Román et al. (2019), reported that adverse event incidence numbers were comparable between the two groups and adverse events were not attributable to the study product. Similarly, Grąt et al. (2017) reported a similar rate of adverse events in probiotics and control groups. Common minor adverse events were reported in Agrawal et al. (2012) and Horvath et al. (2016) including abdominal distention, constipation, gastric pain, diarrhoea, and nausea. In Agrawal et al. (2012), minor adverse events were easily managed by dietary advice and on and off use of proton pump inhibitors. A higher incidence of diarrhoea in the probiotics group compared to placebo was reported by Bajaj et al. (2014), which were not associated with the need to stop the study intervention.

3.3. Publication bias

Results of the Egger's test and publication bias (Table 3, Figure 3) (Albumin: p = 0.326; Ammonia: p = 0.566; Creatinine: p = 0.989; Endotoxin: p = 0.151; ALT: p = 0.580; AST: p = 0.229; GGT: p = 0.065; IL-6: p = 0.220) indicated that there was no significant publication bias present within any of the assessable variables.

4. Discussion

4.1. Effect of probiotics on liver function and disease severity

Liver transaminases such as GGT, ALT, and AST are commonly elevated in liver conditions such as liver cirrhosis. Although ALT and AST are more specific to liver function, trends of elevated GGT are also commonly seen. Our meta-analyses indicated a significant reduction in all three enzymes – ALT, AST and GGT. Furthermore, the participants included all had relatively low Child-Pugh scores with only a few having hepatic encephalopathy (Pereg et al., 2011). Strict exclusion criteria also resulted in Román et al. (2019) to have a study population with relatively well reserved liver function which would have made it difficult for improvement of mildly impaired liver function. To further emphasise a trend in improvement from probiotics, our pooled analysis for the effects of probiotics on serum ammonia levels showed a statistically significant decrease (p = 0.057). Ammonia, which is a breakdown product of glutamine, is metabolised and cleared by the liver (Deutsch-Link et al., 2022). Therefore, an improvement in serum ammonia levels would be expected in patients showing liver function improvement. On inspection of the studies, there were mixed results, with some studies finding a statistically significant effect (Agrawal et al., 2012; Liu et al., 2004; Lunia et al., 2014; Mittal et al., 2011), and others not reaching statistical significance (Bajaj et al., 2008; Perananthan et al., 2021; Pereg et al., 2011; Saji et al., 2011; Vidot et al., 2019). These mixed individual results could have been due to a small sample size, short therapy duration (Perananthan et al., 2021; Saji et al., 2011), moderate probiotic dosages (Saji et al., 2011), and loss of follow up (Vidot et al., 2019). However, the pooled significant reduction in ammonia reinforces the evidence that probiotics have a role in improving the functional capability of the liver in cirrhotic patients.

Endotoxin was also found to be significantly reduced by probiotics in our pooled analysis (Bajaj et al., 2014; Jayakumar et al., 2013; Liu et al., 2004; Macnaughtan et al., 2020; Shi and Li, 2023). Endotoxins are produced by gram negative bacteria found in the intestines. In healthy individuals, the intestinal mucosa functions as a barrier and prevents translocation of endotoxins into the portal system (Fukui, 2015). Studies

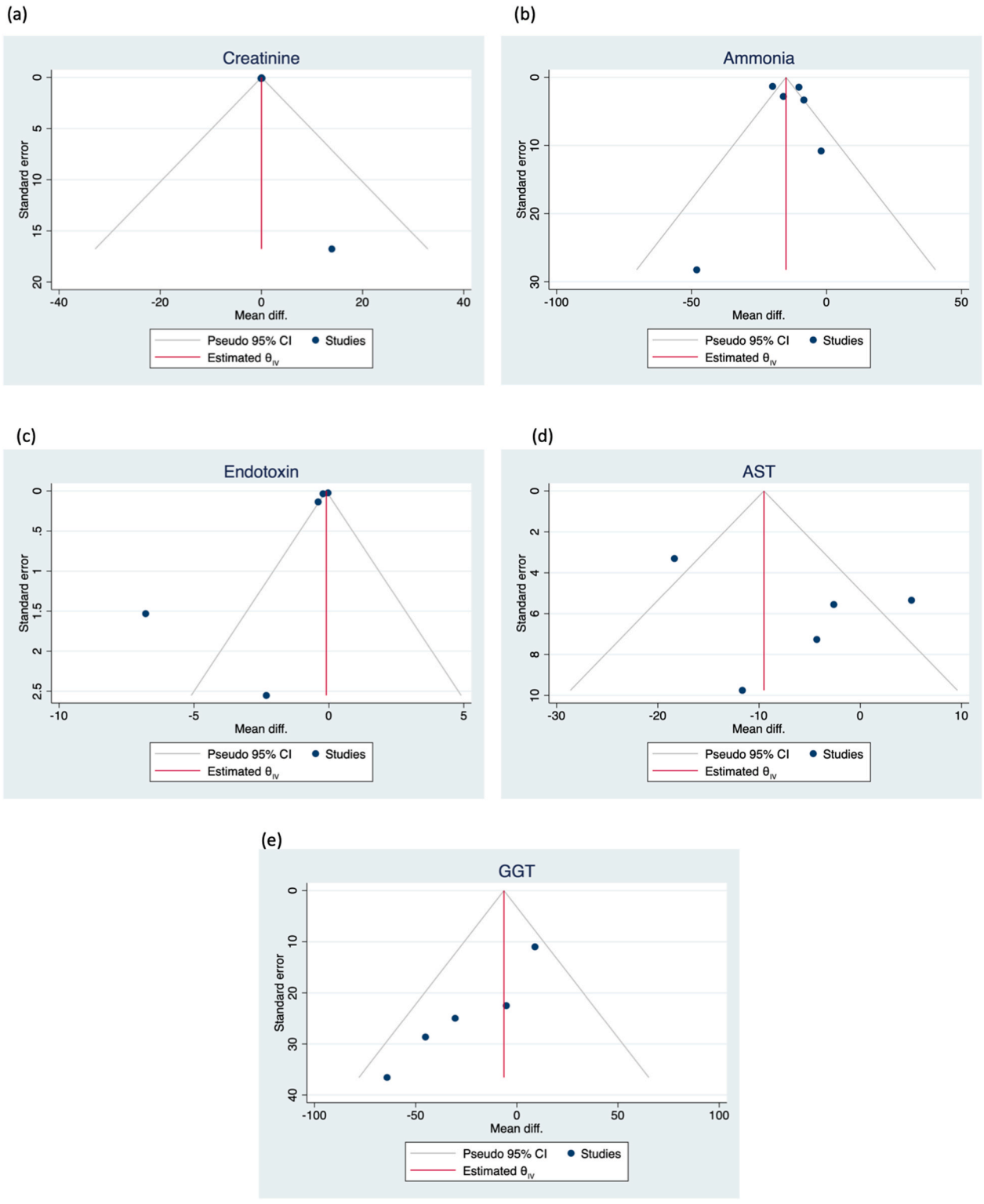

Fig. 3. Funnel plots for (a) creatinine (b) ammonia (c) endotoxin (d) AST (e) GGT.

have found that patients with cirrhosis have structural and functional changes to their intestinal mucosa that increases intestinal permeability (Fukui, 2015). Probiotic supplementation has been widely studies for its effects on intestinal health and have been found to improve intestinal permeability by increasing tight junction integrity, mucous production, IgA and antimicrobial peptides, which explains the significant reduction in endotoxin levels found in our analysis (Chaiyasut et al., 2022). The sample size used for our pooled analyses was still relatively small, therefore future research with larger population sizes should be completed to further explore the effects of probiotics on serum endotoxin levels, and therefore offer a more comprehensive insight.

IL-6 is a pro-inflammatory cytokine that is involved in a wide variety of biological functions. IL-6 is primarily produced by monocytes and macrophages (Naseem et al., 2018); however, its receptors are primarily expressed on hepatocytes and leukocytes. Levels of IL-6 have been found to be increased in patients with liver cirrhosis (Labenz et al., 2019).

Table 3
Egger's test for publication bias.

Variable	Studies, *n*	t-value (95% CI)	*p*
GGT	4	3.737 (−9.049, 0.636)	0.065
AST	5	1.506 (−2.193, 6.136)	0.229
ALT	7	0.591 (−12.339, 7.726)	0.580
Albumin	8	1.07 (−1.381, 3.524)	0.326
Endotoxin	5	1.914 (−8.174, 2.034)	0.151
IL-6	5	1.55 (−7.352, 21.250)	0.220
Ammonia	7	0.615 (−4.265, 6.947)	0.566
Creatinine	9	0.014 (−1.082, 1.070)	0.989

While the exact mechanism is not completely understood, the increased levels of IL-6 may be due to increased inflammation and tissue damage. Higher levels have been associated with an increased risk of complications such as malignancy and MHE (Labenz et al., 2019). Our analysis did not demonstrate a significant change in serum IL-6 levels, however there was an overall downward trend in the intervention arms compared to placebo. Further research is necessary to make a reliable comment on the effect of probiotics on IL-6 in patients with cirrhosis, as the small sample size in this meta-analysis may not be indicative of a larger population. Further research is also recommended to help identify the role of IL-6 in the context of liver cirrhosis, as it is still not widely understood.

The Child-Pugh scoring system was originally designed to predict mortality in cirrhotic patients. It is broken down into three categories: A - good hepatic function, B - moderately impaired hepatic function and C - advanced hepatic dysfunction. Three studies (Dhiman et al., 2014; Liu et al., 2004; Riordan et al., 2007) reported a trend of improvement in Child-Pugh score post-probiotic intervention. This is contradicted by Grat et al. (2017) that found no significant change in Child-Pugh score. A mixed result was reported in Horvath et al. (2016) as 6/16 patients improved in Child-Pugh score, 7/16 did not have a change in their Child-Pugh score and 3/16 had a worsened Child-Pugh score. MELD score is another method used to determine the severity of liver disease. Although our study found no significant difference in MELD score between the probiotic's population and placebo population, it is worth noting the importance of MELD scores for future research. If probiotics have the capacity to improve liver function as noted by the significant improvement in liver transaminases and ammonia levels, MELD scores should as a result also be improved secondary to probiotics intervention. One of the studies included in our analysis found a significant improvement in MELD score in the probiotic group compared with that in placebo group. This was contradicted by Bajaj et al. (2008) that found no significant differences. However, the study population used had an average MELD score of 9, thus the stability of the MELD score is not surprising (Bajaj et al., 2008). It is clear that further research with larger population sizes should be conducted to ensure that the effects of probiotics on the severity of liver cirrhosis is properly explored.

4.2. Effect of probiotics on quality of life (QOL)

QOL: Eight of the included studies assessed QOL. The included papers by Bajaj et al. (2008), Dhiman et al. (2014) and Macnaughtan et al. (2020), used the short form, 36-item health survey version 2 (SF-36) to assess health-related QOL (HRQOL). No change in the SF-36 physical and mental scores were observed between baseline and study end in Bajaj et al. (2008). Macnaughtan et al. (2020) found no significant differences in SF-36 scores between placebo and probiotics groups in post-test analysis. Furthermore, Perananthan et al. (2021) also did not find a difference at baseline compared to post intervention in the probiotics group. Conversely, Dhiman et al. (2014) reported a significant improvement in the physical function and role physical domains, and in the physical component summary of the SF-36 after probiotic treatment. Although Roman et al. (2019) did not observe a significant change in QOL using the Nottingham health profile, they found a trend of improvement in the domain of social isolation in the prebiotic group. Another two studies assessed HRQOL using the sickness impact profile, both finding no improvement (Bajaj et al., 2014; Mittal et al., 2011).

4.3. Adverse events

Probiotics have gained significant popularity as a potential treatment option for patients who have cirrhotic liver disease. We have found that probiotics are well-tolerated by individuals with numerous studies indicating no adverse events occurring when consumed (Jayakumar et al., 2013; Lunia et al., 2014; Macnaughtan et al., 2020; Mittal et al., 2011; Perananthan et al., 2021). Other two studies (Agrawal et al., 2012; Horvath et al., 2016) reported minor side effects including abdominal distention, constipation, gastric pain, diarrhoea and nausea. Our study indicated that consuming probiotics improved liver function evident by a significant reduction in serum ammonia and liver transaminases. Furthermore, we showed probiotics can improve MHE in cirrhotic patients, whilst also improving endotoxin levels.

4.4. Strengths, limitations and implications

This present study represents an important contribution to the current literature on the effects of probiotics on the outcomes of liver cirrhosis. It has assessed a large number of outcomes related to the health and liver function in patients with cirrhosis. Reviewer bias was minimised by ensuring all papers were independently screened by two reviewers to decide on the finalised inclusion list. This study does have a few limitations worth noting. Firstly, due to the limited number of randomised controlled trials on this topic, subgroup analyses were unable to be completed. The small number of studies also resulted in a smaller total sample size. Thus, caution should be taken when interpreting the results of certain analyses with small sample sizes. In addition, seven of the studies included in the meta-analysis were only of moderate quality according to the PEDro quality assessment, with blinding being a problem in majority of these studies.

5. Conclusion

This systematic review and meta-analysis found that the administration of probiotics in patients with cirrhotic liver disease improved

Table 4
– Subgroup analysis: Ammonia.

Subgroup	Group 1	Effect size (95% CI)	Group 2	Effect size (95% CI)	Group 3	Effect size (95% CI)	Q-value	df (Q)	*p*-value
Type of Intervention	Capsule	−9.391 (−11.552, −7.230)	Yoghurt	−2.000 (−23.186, 19.186)	Liquid	−20.062 (−22.670, −17.454)	39.304	2	0.000
Duration of intervention	<3 months	−13.779 (−15.585, −11.973)	≥3 months	−13.040 (−17.236, −8.844)			0.100	1.000	0.751
Strains	Single strain	−0.380 (−5.849, 5.089)	Multiple strains	−15.009 (−16.750, −13.269)			56.695	6	0.000
Dose	$4x10^{10}$-$4x10^{11}$	−13.704 (−15.369, −12.040)	$>4x10^{11}$	−48.090 (−103.459, 7.279)			2.652	2	0.266

overall liver function. This was determined through a statistically significant decrease in the liver transaminases GGT and AST and ALT, alongside a decrease in endotoxins and serum ammonia. These pieces of evidence indicate that probiotics may be beneficial for the liver's toxin filtering capabilities, as well as improving intestinal permeability. While being statistically not significant, an increase in serum albumin may reinforce the improvement in overall liver function, allowing it to more effectively produce necessary proteins. This review has also found that numerous studies have reported resolution of MHE or a decrease in the severity of MHE through the administration of probiotics. Probiotics appear to be a very well tolerated intervention, with little side-effects reported as a direct result of their use. More research should be conducted to more accurately determine the overall effects on broader liver function and QOL. However, their tolerability and benefits determined from this review suggest that probiotics should be a beneficial adjunct treatment in patients with cirrhosis. Therefore, the use of probiotics is recommended as adjunctive intervention when treating cirrhotic liver disease in clinical and community settings. The liquid format of intake containing multiple probiotic strains in relatively large doses (greater than 4×10^{11} CFU per kilogram in total) is recommended for daily use as a component of treatment measures.

CRediT authorship contribution statement

Unnah Leitner: Writing – original draft, Formal analysis, Data curation. **Anita Brits:** Writing – review & editing. **Dawei Xu:** Writing – review & editing, Formal analysis. **Sasha Patil:** Writing – review & editing. **Jing Sun:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors do not declare any conflicts of interest relevant to this manuscript.

Data availability

Data will be made available on request.

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Authorship: The authors' responsibilities were as follows – UL: Search strategy, paper screening, bias assessment, data extraction, writing methods, formulation of tables and figures, referencing, manuscript drafting, updating of manuscript – AB: Search strategy, paper screening, writing of abstract, data extraction, writing of results and discussion, referencing – DX: updating of manuscript, formatting statistical figures, revise manuscript – SP: data extraction, contributed to Table 2, PEDro quality assessment (Table 1) – JS: Supervision of research team, conceptualization, statistical analysis, write, revise, edit and review manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2024.176874.

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