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Probiotics Therapy for the Constipation in Children: An Overview of Systematic Reviews

Chao Xu[a,*], Li Liu[b]

Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 710246, China
[a]1252741690@qq.com, [b]1016911627@qq.com
[*]Corresponding author

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Abstract: Objective: To evaluate the methodological bias and the reliability of the conclusions of systematic reviews on constipation. Methods: CNKI, CBM, VIP, WanFang Data, The Cochrane Library, PubMed and EMbase databases were searched to collect systematic reviews or meta-analyses of probiotics therapy for constipation from inception to March, 2022. Two researchers independently screened literature and extracted data. Then, AMSTAR 2 tool and PRISMA statement were used to evaluate the methodological quality and reporting quality of included systematic reviews. Results: A total of 5 systematic reviews were included. The results of AMSTAR 2 suggested that 1 systematic reviews were of extremely low quality, 3 of middle quality, and 1 of high quality. The PRISMA score ranged from 20 to 26. 3 studies were relatively complete, 7 studies had certain defects and one study had serious defects. Conclusions: The existing systematic reviews evidence shows that probiotics may have a certain curative effect in the treatment of constipation in children, but the quality of research methodology, reporting quality and evidence quality still needs to be improved.

Constipation is a disease with the main clinical manifestations of difficulty in defecation, reduced frequency of defecation, dry and hard stools or a feeling of incomplete defecation [1]. At present, the global incidence of constipation is 11%~20% [2], the incidence rate in China is 10.9% [3]. Although constipation does not directly cause death in patients, it may increase the risk of death from acute myocardial infarction, hypertension, and cerebrovascular accidents [4]. A global multicenter study showed that the quality of life of patients with constipation was significantly lower than that of the non-chronic constipated population [5]. Constipation costs the United States $235 million a year [6]. This brings a huge financial burden to the families of patients.

Constipation is closely related to the imbalance of intestinal flora, and studies have shown that the number of dominant flora in patients with constipation is significantly reduced, and potentially pathogenic bateria increase [7-8], supplement specific probiotics, can increase intestinal flora, promote intestinal motility, reduce intestinal pH, and thus improve constipation symptoms [9]. Chinese chronic constipation expert consensus points out that probiotics can be used for chronic constipation [10]. There have been many systematic reviews (SRs) expioring the efficacy and safety of probiotics in the treatment of constipation [11-15]. However, their methodological and reporting

quality are unclear. Systematic evaluation re-evaluation is a comprehensive research method to re-evaluate the treatment, etiology, diagnosis and prognosis of the same disease or health problem [16].

Therefore, this study will re-evaluate the SRs of probiotics in the for constipation, and evaluate the methodological quality and reporting quality of the included SRs, in order to improve the evidence support for its clinical practice.

1. Data and Methods

1.1 Data Sources

We searched PubMed, Embase, and Cochrane Library, China Journal Full-text Database (CNKI), China Biomedical Literature Database (CBM), Wanfang Data and VIP database to collect SRs of probiotics for constipation. The retrieval time was from March 1, 2022, and the publication time and language were not restricted. The search terms included: microecological agents, constipation, systematic review, meta-analysis; probiotics, prebiotics, probiotic bacteria, beneficial bacteria, etc. Take PubMed as an example. See Figure 1 for specific strategies.

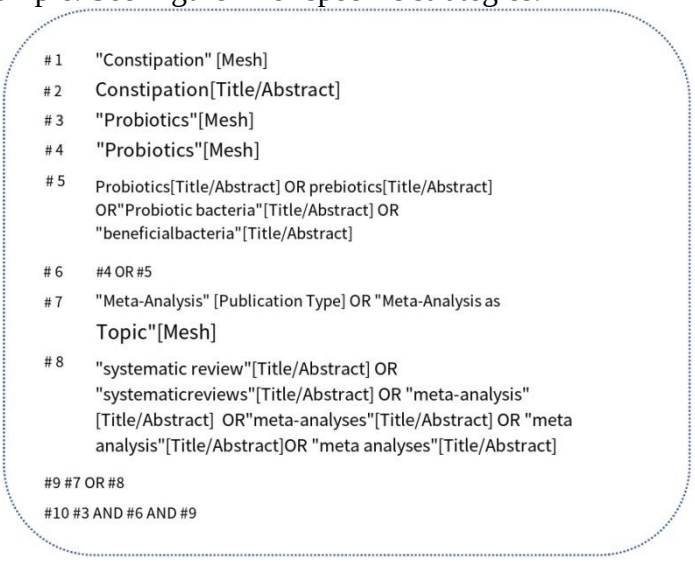

Figure 1: PubMed retrieval strategy

1.2 Inclusion Criteria

Study type: Systematic review/meta-analysis

Study subjects: Constipation patients, regardless of gender, disease course and age.

Interventions: The treatment group was probiotics or probiotics combined with conventional Western medicine, and the control group was conventional Western medicine or placebo, etc. There is no restriction on the type, usage and dosage of probiotics.

Outcome: All outcomes

Exclusion criteria: Repeated studies Conference papers; traditional reviews.

1.3 Literature Selection and Data Extraction

Two researchers independently screened the literature, extracted the data and cross-checked the data. Negotiated and discussed or consulted a third party in case of disagreement. Data extraction included: first author, publication time, disease name, sample size, interventions, bias risk

assessment tools and meta-analysis results.

1.4 Quality Evaluation

Two researchers independently used AMSTAR 2 (A Measurement Tool to Assess Systematic reviews 2) [17] and PRISMA 2009 (Preferred reporting items for systematic reviews and meta-analyses) [18] Evaluate the quality of methodology and reporting included in the SRs. Application GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Evaluate the level of evidence for outcome indicators and cross-check, and consult a third party in case of disagreement. AMSTAR 2 has a total of 16 entries, seven of which are key entries. Each item was evaluated as "yes" (full report), "partially yes" (partial report), and "no" (unreported). Combining the evaluation results of key items and non-key items, the quality of each system evaluation was given: high, medium, low, and very low [17]. PRISMA includes 27 entries. Each item and scoring criteria: 1 point for complete report, 0.5 point for partial report, 0 point for non-report. A score of 21-27 is a relatively complete report, a score of 15-21 is a certain defect, and a score below 15 is a relatively serious information defect [19].

1.5 Statistical Analysis

Excel 2019 was used to sort out the extracted data, and descriptive statistical analysis was conducted by frequency, percentage and 95% CI. The results of AMSTAR 2 evaluation were presented in percent-stacked bar chart, PRISMA evaluation was presented in bar chart.

2. Results

2.1 Literature Search

A total of 421 studies were obtained by searching the Chinese and English databases, and 5 SRs were finally included after multiple screening [11-15]. The screening process is shown in Figure 2.

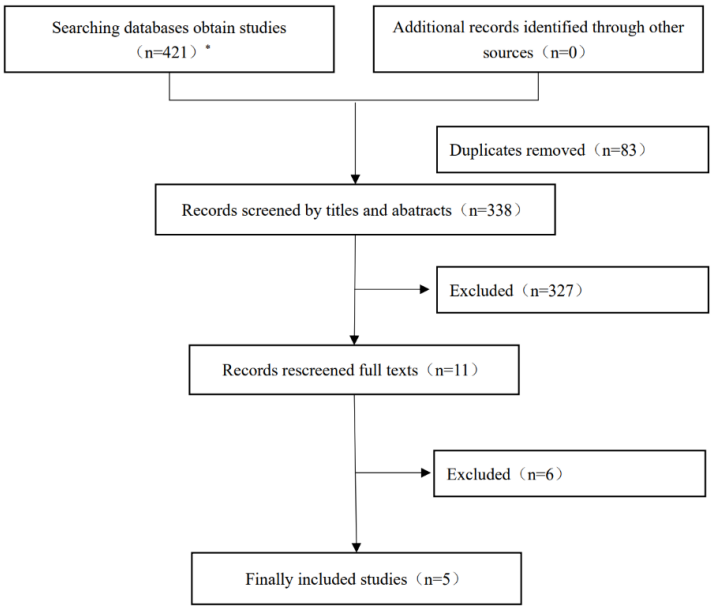

Figure 2: Literature screening process

2.2 Studies Charateristics

The basic information included in the study is shown in Table 1. Total Included 5 SRs, 4 SRs [11-14]. For English studies, 1 SRs [15] for Chinese studies all SRs [11-15] for constipation in children.3 SRs [13-15] use The Cochrane ROB bias risk assessment tool and 2SRs [11-12] used Jadad scale.

Table 1: Studies charateristics

Study ID	Disease	Type of Research	Intervention Measures		Data analysis methods	Sample size	Risk of bias tool	Outcome
			Experimental group	Control group				
Huang R 2017 [11]	FC	SR	Probiotics	Placebo	MA	6 (498).	Jadad	(2), (12)
Jin L 2018 [12]	FC	SR	Probiotics	Placebo	MA	4 (382).	Jadad	(1),(2),(3), (4),(5),(6), (7),(8),(9), (10),(11)
Wojtyniak K 2017 [13]	FC	SR	Lactobacillus rhamnosus	Placebo	MA	7 (515).	Cochrane ROB	(1),(2), (6), (8), (11)
Harris R G 2019 [14]	FC	SR	Probiotics + WM	Placebo + WM	MA	17 (1408).	Cochrane ROB	(1), (2)
Wang Junli 2014 [15]	FC	SR	Probiotics	Placebo	MA	7 (421).	Cochrane ROB	(1),(2),(3), (6),(7),(8), (9),(10),(11)

(1) Treatment success, (2) stool frequency, (3) hard stools, (4) lactulose, (5) glycerin enema, (6) abdominal pain, (7)laxatives, (8) Fecal incontinence, (9) painful stool, (10) flatulence, (11) adverse effects, (12) stool consistency, WM: Western medicine.

2.3 Methodological Quality Evaluation for Inclusion of SRs

The evaluation results of AMSTAR 2 are shown in Figure 3. 1 SR [14] for high quality, 3 SRs [11-13] Medium quality, 1 SRs [15] is of very low quality. There are 7 items (item 1, item 15, item6, item 9, item 11, item 13, item15) with a complete reporting rate of 100%.There are 2 items with full reporting rate ≥80% (item 8, item 17). 3 items with a full reporting rate < 20% (item 2, item 7, item 12).

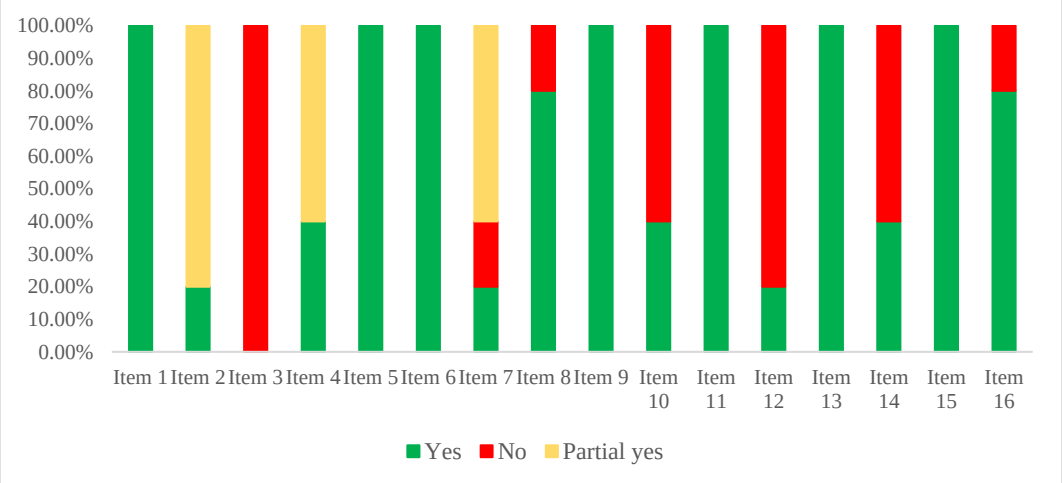

Figure 3: Methodological quality of SRs inclusion

2.4 Report Quality Evaluation Included in SRs

The evaluation results of PRISMA entries are shown in Figure 4, the average score of 22.2, with a range of 20 to 26. 2 SRs (40%) reports were relatively complete. 3 SRs reports (60%) had some defects; No SRs report (0%) had serious defects. There were 6 entries with a 100% complete reporting rate(item 3, item 4, item6, item 7, item 9, item 10, item 11, item 13, item14, item15, item18, item 20, item 21), complete report rate is more than 80% of entries has 10 (item 1, item 2, item 12, item 16, item 17, item 19, item 22, items 23, item 26, item 27,), 1 items had a complete reporting rate < 30% (item 5).

Figure 4: Report quality incorporated into SRs

2.5 Efficacy Outcome

The efficacy outcomes of the included studies are shown in Table 2. A total of 12 outcomes. These outcomes were used to compare the effect of probiotics and other interventions for constipation in children in terms of symptoms, efficacy and adverse effects.

Table 2: Outcome

Author	Outcome	Interventions	Control	Sample size	I2	P values	Effect value [95% CI]
Huang R 2017	stool frequency	Probiotics	Placebo	6 (444).	84.00 %	0.02	MD = 0.73 [0.14,1.31]
	stool consistency	Probiotics	Placebo	3 (267).	92.00 %	0.27	MD = -0.07 [-0.21,0.06]
Jin L 2018	Treatment success.	Probiotics	Placebo	4 (382).	55.70 %	0.697	RR = 1.05 [0.81, 1.38]
	stool frequency	Probiotics	Placebo	-	95.00 %	0.571	WMD = 0.89 [-2.18, 3.95]
	Hard stools	Probiotics	Placebo	-	-	0.408	WMD = -0.30 [-1.01,

							0.41]
	lactulose	Probiotics	Placebo	-	-	0.238	WMD = -1.80 [-4.79, 1.19]
	glycerin enema	Probiotics	Placebo	-	-	0.004	WMD = -2.40 [-4.03, -0.77]
	Abdominal pain	Probiotics	Placebo	-	-	< 0.001	WMD = -4.80 [-7.08, -2.52]
	laxatives	Probiotics	Placebo	-	-	0.19	RR = 0.72 [0.44, 1.18]
	Fecal incontinence	Probiotics	Placebo	-	-	0.139	RR = 0.75 [0.51, 1.10]
	Pain during defecation	Probiotics	Placebo	-	-	0.41	RR = 1.16 [0.81, 1.66]
	flatulence	Probiotics	Placebo	-	-	0.109	RR = 0.65 [0.39, 1.10]
	adverse effects	Probiotics	Placebo	-	-	0.979	RR = 1.01 [0.62, 1.63]
Wojtyniak K 2017	Treatment success	Probiotics	Placebo	4 (336).	56.00 %	0.7	RR = 1.05 [0.81, 1.38]
	stool frequency	Probiotics	Placebo	2 (108).	96.00 %	0.95	MD = 0.16 [-4.38, 4.69]
	fecal incontinence	Probiotics	Placebo	2 (108).	0.00%	0.86	MD = -0.05 [-0.63, 0.53]
	abdominal pain	Probiotics	Placebo	2 (108).	94.00 %	0.4	MD = -2.13 [-7.12, 2.87]
	adverse effects	Probiotics	Placebo	6 (-)	0.00%	-	RR = 0.58 [0.25, 1.31]
Harris R G 2019	stool frequency	Probiotics + WM	Placebo + WM	14 (1043).	77.40 %	0.165	WMD = 0.28 [-0.12, 0.69]
	Treatment success	Probiotics	Placebo	11 (943).	73.70 %	0.024	RR = 1.24 [1.03, 1.50]
Wang Jun li 2014	Treatment success.	Probiotics	Placebo	6 (421).	54.00 %	0.48	RR = 1.11 [0.83, 1.50]
	Abdominal pain	Probiotics	Placebo	3 (293).	0.00%	0.75	OR = 1.09 [0.65, 1.82]
	painful stool	Probiotics	Placebo	2 (209).	0.00%	0.23	OR = 1.46 [0.79, 2.72]
	laxatives	Probiotics	Placebo	2 (76).	0.00%	0.51	OR = 0.83 [0.47, 1.45]
	Stool consistency	Probiotics	Placebo	2 (93).	80.00 %	0.12	0R = 0.42 [0.14, 1.27]
	Flatulence	Probiotics	Placebo	1 (143).		0.38	RR = 0.72 [0.34, 1.50]
	stool frequency	Probiotics	Placebo	4 (320).	81.00 %	0.28	SMD = 0.31 [-0.25, 0.86]
	Fecal incontinence	Probiotics	Placebo	3 (177).	43.00 %	0.84	SMD = 0.04 [-0.61, 0.25]
	Hard stools	Probiotics	Placebo	1 (84).		0.41	SMD = -0.18 [-0.61, 0.25]

3. Discuss

The AMSTAR 2 tool and the PRISMA 2009 Statement were used to evaluate the methodological quality and reportage quality.

The methodological quality evaluation showed that the overall quality of the included SRs was fair. The following are problems with the included articles: ①Lacked of advance registration without a proposal may cause the actual study process to deviate significantly from expectations, increasing the risk of study bias; 2. None of the included literature explained the reasons for including such studies. ③Insufficient search of gray literature during the search, which may produce publication bias. ④Lacked of a detailed list of excluded literature during the literature screening process may have risked screening omissions and made the included literature incomplete.

⑤ Insufficient description of the source of funding for the included studies makes it difficult for readers to assess whether there is a potential interest in SR, and the difference played by the funder in the trial may affect the results or even overestimate the results [31].

The results of the PRISMA 2009 statement showed the following problems with the quality of the report: no protocol and registration information was provided, and there was a lack of awareness of SRs protocol development and registration, which reduced the reliability of the study (item 5); No retrieval example is provided, and the article retrieval process lacks repeatability, which may lead to the risk of retrieval omission (item 8). The evidence strength of GRADE was not summarized, which reduced its convenience of use.

The analysis and summary of the outcome indicators showed that probiotics can effective in treating constipation in children. However, different conclusions were drawn by different SRs in terms of outcome indicators, such as efficacy, hard stools, and number of stools, forced defecation and abdominal pain. Possible reasons for the analysis include: ① Currently, there is no unified probiotic treatment plan for constipation in the world, and indications of treatment, selection of probiotic strains, dosage and course of treatment are still being explored. Therefore, there is great clinical heterogeneity in clinical application; ② the etiology and severity of constipation are different, which may lead to different therapeutic effects of probiotics. The included study did not assess the severity of constipation or give appropriate treatment strategies. ③The measurement methods and standards of outcome indicators are inconsistent, which leads to a large bias in the judgment of patient outcome indicators and affects the judgment of results; ④ There is a bias in the methodology and report quality of the included studies, and the quality of the original studies and the small sample size of some SRs also lead to poor consistency of the conclusions.⑤ Differences in the inclusion of SRs in the exclusion criteria may lead to heterogeneity in patient selection, disease diagnosis basis and other aspects, resulting in inaccurate results.

There are some limitations in this study: ① only Chinese and English literatures were included, and the lack of data in other languages may affect the results to some extent; ② The search period was up to January 1, 2022, and the updating of evidence may affect the results; ③ There is inevitably some subjectivity in the process of evaluation and analysis, which may lead to bias.

In conclusion, based on the current SRs evidence, the efficacy of probiotics in the treatment of constipation has not been fully determined, which only suggests that probiotics may have certain advantages in some aspects (intestinal transport time, ease of defecation, recurrence rate, constipation symptom score, etc.), and the safety is reasonable. In the future, it is suggested to carry out more high-quality studies, standardize the practical program of probiotics, standardize the evaluation system of constipation, and find the specific advantageous population for the treatment of probiotics, so as to provide high-quality evidence for the application of probiotics in constipation.

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