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Probiotic Supplementation's Efficacy and Safety in Preventing Healthcare-Associated Infections: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Infections that people may get while seeking treatment in health facilities are known as healthcare-associated infections (HAIs). The application of probiotics represents a forefront approach in ongoing research and development for the prevention of HAIs. Probiotics' effectiveness has been the subject of several prior research, although the findings have not always been consistent. **Objectives:** This research aims to determine the efficacy and safety of probiotic supplementation in lowering HAIs when compared to a placebo. **Methods:** The PRISMA 2020 guidelines were followed in this investigation. Using the keywords "Healthcare-Associated Infections", "Nosocomial Infection, and "Probiotic", a search of the literature was done in July 2023 on the Cochrane Library, Google Scholar, PubMed, Proquest, Science Direct, Springer Link, and the ClinicalTrial.gov registry, with a focus on Randomized Clinical Trials from the previous ten years that compared the efficacy and safety of probiotics and placebos in preventing HAIs. The University of Oxford CEBM sheet, the Cochrane Risk of Bias Tools and Modified Jadad Score were used to evaluate the RCTs included. Meta analysis is carried through using RevMan Software 5.4. **Results:** Three RCTs that included 542 adult patients were qualified. The patient's ages varied from 18 to 80, with 304 men (67.26%) and 148 women (32.74%) present. Probiotics significantly reduced HAIs compared to placebo (OR 1.92; 95% CI 1.10-3.35; p=0.02). Probiotics were administered to patients without causing any significant negative effects**. Conclusion:** In comparison to a placebo, probiotics are effective and safe in lowering the frequency of HAIs.
Keywords: Healthcare-Associated Infections, Placebo, Probiotics

ABSTRAK

Latar Belakang: Infeksi yang diperoleh pasien saat berobat ke fasilitas pelayanan kesehatan dikenal sebagai *healthcare-associated infections* (HAIs). Penggunaan probiotik merupakan pendekatan terdepan dalam penelitian dan pengembangan saat ini untuk upaya pencegahan HAIs. Efektivitas probiotik telah menjadi subjek beberapa penelitian sebelumnya, meskipun temuan yang diperoleh tidak selalu konsisten. **Tujuan:** Penelitian ini bertujuan untuk mengetahui efikasi dan keamanan suplementasi probiotik dalam menurunkan HAIs jika dibandingkan dengan plasebo. **Metode:** Penelitian ini mengikuti pedoman PRISMA 2020. Penelusuran literatur dilakukan menggunakan kata kunci *"Healthcare-Associated Infections", "Nosocomial Infection"*, dan *"Probiotic"* pada bulan Juli 2023 di *database* Cochrane Library, Google Scholar, PubMed, Proquest, Science Direct, Springer Link, dan

ClinicalTrial registri.gov, dengan fokus artikel *Randomized Clinical Trials* (RCT) terpublikasi sepuluh tahun terakhir yang membandingkan efikasi serta keamanan probiotik dan plasebo dalam mencegah HAIs. Lembar *The University of Oxford CEBM*, instrumen deteksi risiko bias *Cochrane*, dan skor Jadad yang dimodifikasi digunakan untuk mengevaluasi artikel RCT terpilih. Meta Analisis dilakukan dengan menggunakan *Software* RevMan versi 5.4. **Hasil:** Tiga artikel RCT yang mencakup sebanyak 542 pasien dewasa memenuhi syarat untuk disertakan dalam penelitian. Usia pasien bervariasi dari 18 hingga 80 tahun, terdiri dari 67,26% pasien pria dan 32,74% pasien wanita. Probiotik secara signifikan mengurangi HAIs dibandingkan dengan plasebo (OR 1.92; 95% CI 1.10-3.35; p=0.02). Probiotik diberikan kepada pasien tanpa menimbulkan efek negatif yang signifikan **Kesimpulan:** Dibandingkan dengan plasebo, probiotik efektif dan aman dalam menurunkan frekuensi HAIs.
Kata Kunci: *Healthcare-Associated Infections*, Plasebo, Probiotik

1. Introduction

To lower the frequence of HAIs, several ways have been cooked. Exercising probiotics as a precautionary measure is one of the current strategies being used to lower the circumstance of HAIs.[8] Live bacteria known as probiotics have beneficial impacts on intestinal flora balance, local and systemic immune responses, digestive tract protection, antimicrobial resistance, and the length of time that antibiotics are used.[9–12] In addition to being effective, probiotic treatment is also more cost-effective than attempts to create new classes of antibiotics, making it a viable strategy for reducing HAIs and resistance to antibiotics.[9,12]

Probiotic therapy has been proven to reduce a variety of HAIs in multiple RCTs [9,10,12,13], however other investigations have shown contradictory findings.[3,14] Without taking into account the whole variety of HAIs, several earlier meta-analyses and methodical reviews concentrated exclusively on one specific form of HAIs and neglected to estimate safety factors.[8,11,15] The current study's objective was to thoroughly compare probiotic supplementation to a placebo in order to assess its safety and effectiveness in reducing HAIs using the most recent data.

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2. Method

This meta-analysis adheres to the standards of the Cochrane and is presented in accordance with PRISMA 2020 methodology.[16,17]

2.1. Data Sources and Search

The keywords "Healthcare-Associated Infections", "Nosocomial Infection", and "Probiotic" were used in a literature search on the databases of Cochrane Library, Google Scholar, ProQuest, PubMed, Springer Link, Science Direct, and ClinicalTrial.gov in July 2023, with the RCTs comparing the efficacy and safety of probiotics and placebo in preventing HAIs in the previous 10 years as the focus. The University of Oxford CEBM and risk of bias tools by Cochrane were used to evaluate RCTs included.

2.2. Eligibility Criteria

The inclusion criteria encompass the following: 1) Study design: RCTs conducted within the past decade; 2) Population: adults (age more than 18 years) who experience HAIs (respiratory tract infections, digestive tract infections, surgical wound infections, bloodstream and urinary tract infections); 3) Intervention: probiotics compared with placebo in patients with HAIS; 4) Outcome: HAIs incident and safety aspects of probiotics; 5) Studies with the Odds Ratio statistical measure. The following are the exclusion criteria: 1) All studies with designs other than RCTs such as observational studies, *in vitro*, *in vivo* and *ex vivo* studies, case reports and reviews; 2) All studies with statistical measures other than Odds Ratio; 3) Non-english language studies.

2.3. Article Selection and Data Extraction

Zotero reference manager program, version 6.0.26, was used to import and eliminate duplicate articles found through online database and registry searches. Irrelevant publications was removed after independently screening the titles and abstracts. A comprehensive examination of the full texts of the remaining studies was then conducted. Articles were selected according to predetermined eligibility criteria. Following the instructions on the University of Oxford for therapy study CEBM sheet, the chosen studies were next submitted to a critical assessment. Article selection procedure in the PRISMA flow chart was illustrated using the Shiny app and the online R Package tools.[18] The Excel Spreadsheet tab contains data that has been taken from the associated articles. The extracted data is compared next, and any inconsistencies that are discovered are discussed and addressed. Data on study features (author, study population, study design, year of publication, study site, probiotics and dose utilized, route of administration, comparison, effectiveness, and safety) are also included in the information that was retrieved.

2.4. Outcome Measurement

The prevalence of HAIs (respiratory tract infections, digestive tract infections, surgical wound infections, bloodstream and urinary tract infections) was the primary outcome evaluated. The secondary outcome is the safety of utilizing probiotics, specifically whether or not probiotic medication results in serious adverse effects.

2.5. Assessment of Bias Risk

Bias risk was assessed by the Cochrane risk of bias tools.[19] The tools encompasses five domains, including bias arising form deviations in the planned intervention, bias stemming from the randomization process, bias in outcome evaluation, bias arising from the selection of reported outcomes, and bias due to missing outcome data. The researchers individually categorized each included study's bias risk as low, high, or with some bias concerns. Any disparities in bias assessment were resolved through discussion and consensus.

2.6. Determining Article Quality

The quality of the papers was estimated by experimenters using the modified Jadad score.[20] The assessment results were divided into two categories, grounded on eight criteria, with each study entering a total score ranging from 0 to 8 points. If an composition receives 0–3 points, it is rated as low quality, and if it receives 4–8 points, it is rated as good quality.

2.7. Data Synthesis

For every RCTs, the data is displayed as odds ratios (OR) along with 95% CI for binary outcomes. Statistical analysis was performed using the RevMan version 5.4 software. A Mantel-Haenszel method was used with fixed effects analysis model, following the Cochrane.[16] Chi^2 values of $p \geq 0.05$ and I^2 values of <50% indicate low/moderate heterogeneity for each synthesis. For the total impact of the effectiveness outcome, $p < 0.05$ was used as the significant level. Safety outcomes are analyzed in narrative form. The study's findings and article characteristics are supplied in tabular format.

3. Result

Figure 1 shows the comprehensive literature screening procedure. After deduplication and screening, three studies were included in the review. The three trials examined the effectiveness of probiotic supplementation in lowering the incidence of HAIs to a placebo. The respiratory tract (ventilator-associated pneumonia, hospital-acquired pneumonia), the digestive tract *(Clostridium difficile*-associated diarrhoea), the urinary tract, surgical wounds, and the blood stream are among the types of HAIs. The trials included 542 eligible patients who are adults within the

age range of 18 to 80 years old, with 304 men (67.26%) and 148 women (32.74%) participating. Table 1 displays specific details about the studies included.

3.1 Assessment of Bias Risk in the Study

Out of the complete set of studies, 2 studies, Litton *et al.*[14] and Tsilika *et al.*[21] (representing 66.7%) exhibited bias with a low risk, whereas 1 study, Salomao *et al.*[22] (constituting 33.3%) showed some concerns related to bias, particularly concerning the selection of reported outcomes, outcome measurement, and missing outcome data. The detailed assessment of bias risk for each study is provided in Figure 2.

3.2 Treatment Effects

3.2.1 Primary Outcome: Incidence of HAIs

The results of this meta-analysis show that probiotic therapy demonstrated a significant decrease in the incidence of HAIs when compared to a placebo (OR 1.92; 95% CI 1.10-3.35; p=0.02). Figure 3 presents several forest plots. The synthesis of data reveals that the studies included exhibited low to moderate levels of heterogeneity, with a Chi-squared (Chi2) value of 0.32 (p = 0.85) and an I-squared (I2) value of 0%. Based on Jadad's modified score, the overall quality of the study was determined to be excellent (Table 2).

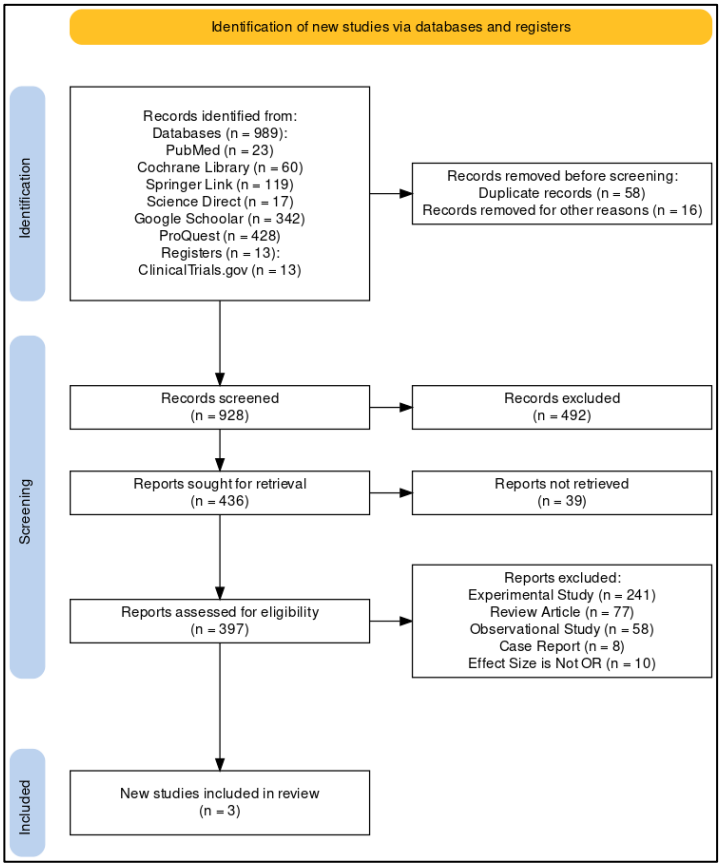

Figure 1. PRISMA 2020 Flow Chart[17]

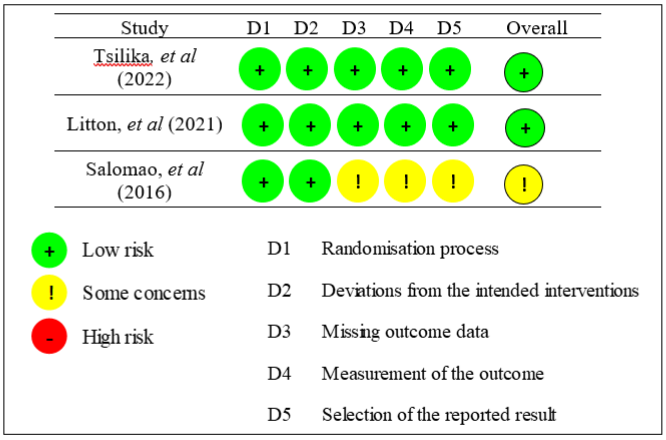

Figure 2. Evaluation of Bias Risk in Each Individual Study

Table 1. Attributes of the Studies Encompassed in the Review

Author	Research Design/Population/Location	Probiotics & Dosage	Administration	Comparison	Efficacy Probiotic compared to Placebo	Safety
Tsilika *et al.*[21]	Multicenter, RCT, Double Blind/Patients with multitrauma (aged 18-80) treated in ICU using ventilators/University Hospital of Thessaloniki, Greece	*Lactobacillus plantarum* (0.5 x 10^9 CFU); *Saccharomyces boulardii* (1.5 x 10^9 CFU); *Bifidobacterium lactis* (1.75 x 10^9 CFU); *Lactobacillus acidophilus* (1.75x10^9 CFU);	In sachet preparations, the frequency is given 2x2 per day for 15 days (1 sachet through the NGT/gastrotomy, 1 sachet through the oropharynx. The sachet is mixed in water of 100 ml.	Placebo: contains Glucose Polymer flour	OR 0.34; 95% CI 0.13-0.92; P=0.034	No SAE
Litton *et al.*[14]	Randomized, placebo-controlled/Adult patient admitted to ICU/Perth, Western Australia	*Lactobacillus plantarum* 299v (2x10^{10} CFU)	Capsule preparation (60 capsules per bottle), given with a frequency of 1x1 for 60 days.	Placebo: contains Microcrystalline Cellulose	OR 1.62; 95% CI 0.51-5.10; p=0.57	No SAE
Salomao *et al.*[22]	RCT, double blind/Inpatient adults aged >18/University Hospital of Ribeirao Preto Medical School	*Lactobacillus bulgaricus* (1 x 10^{10} CFU), *Lactobacillus rhamnosus* (1 x 10^{10} CFU) suspended in Fructo-oligosaccharides (FOS)	Probiotics are given with a frequency of 2x for 7 days, orally/naso enterally tube.	Placebo: the shape, color, consistency and taste are the same as probiotics so they cannot be differentiated	adjusted OR 1.95; 95% CI 0.69-5.50; p=0.21	No SAE

CFU, Colony-Forming Units; NGT, Nasogastric Tube; OR, Odds Ratio; CI, Confidence Interval; SAE, Serious Adverse Effect

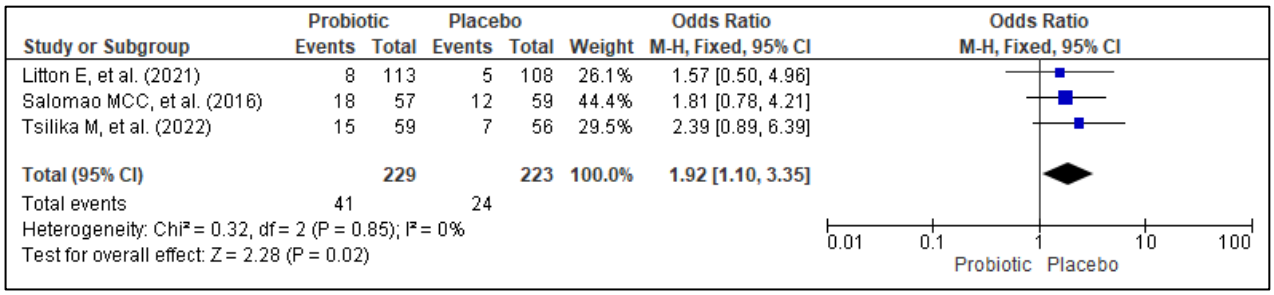

Figure 3. Assessment of HAIs Occurrence in Patients Receiving Probiotics vs. Placebo

Table 2. Study Quality Assessment Using Modified Jadad Score

No	Study	8 Item								Total Score	Quality
		1	2	3	4	5	6	7	8		
1	Tsilika *et al.*[21]	1	1	1	1	1	1	1	1	8	High
2	Litton *et al.*[14]	1	1	1	1	1	1	1	1	8	High
3	Salomao *et al.*[22]	1	1	1	1	1	1	1	1	8	High

Note:
Item 1. Labeled study as randomized
Item 2. Randomization method suitability
Item 3. Incorporating blinding state in the study
Item 4. Accuracy of blinding technique
Item 5. Documented account of participant withdrawals
Item 6. Criteria for including/excluding participants
Item 7. Procedure employed to assess adverse effects
Item 8. Statistical analysis outlined

3.2.2 Secondary Outcome: Safety Aspects of Probiotics

All three studies (as shown in Table 3) reported no significant adverse events. Tsilika *et al.*[21] findings indicated that there was no noticeable distinction in the occurrence of adverse effects between the probiotic and placebo (OR 0.44; 95% CI 0.11-1.82; p = 0.328). Salomao *et al* [22] (4/53; 7.5% in the placebo group and 3/48; 6.2% in the probiotic group; p = 1.000) also made a comparable assertion.

Table 3. Safety Aspects of Probiotics

Probiotic Safety Parameters	Study		
	Tsilika *et al.*[21]	Litton *et al.*[14]	Salomao *et al.*[22]
Serious Adverse Effect	None	None	None

4. Discussion

The incidence of HAIs was shown to decrease with the use of probiotics as a supplemental treatment in this meta-analysis research comprising three RCT studies encompassing 542 adult patients. It also had favorable safety characteristics. These findings are in line with other meta-analyses, which found that probiotics can prevent Ventilator-Associated Pneumonia (VAP) and reduce bacterial colonization of the oropharynx and stomach in all age groups, from newborns to adults.[8,23–26]

A description of the gut-lung axis is used by Virk to explain how probiotics and VAP, a kind of HAIs, are related. Critical illness and VAP worsen the dysbiosis of the gut and lungs' microbiota, impair immunological function,

dysregulate immune regulation, and lessen the gut's capacity to defend against invading pathogenic microorganisms.[27] Probiotics have the potential to enhance the population of regulatory T cells, as well as the function of IL-10 and TGF- β, increase anti-inflammatory capabilities

through increasing short-chain fatty acid immunomodulation, which has a positive impact on maintaining the function of the intestinal barrier, and decrease cytokines produced by Th cells 2, such as IL-13, IL-5, and IL-4, maintain the epithelial barrier and increase tight junction protein expression.[10,13,27] Probiotics have the power to improve the microbial ecology in the stomach and intestines and stop intestinal bacteria from spreading to other, more distant organs. A managed microbiome environment will also benefit the immune response outside of the gut.[28–30]

The papers included in the study had low quality, publication bias, and substantial heterogeneity, which made it challenging to draw trustworthy results in prior meta-analyses.[8,11,23,24] This study made an effort to follow standardized procedures, screen papers using stringent inclusion criteria, and include high-quality, bias-free studies. However, the review was limited to a small number of RCT investigations. There is a need for further RCT studies with comparable themes that use Intention to Threat (ITT) analysis and have high quality, sufficiently randomized samples, big sample sizes, double-blind designs, and thorough follow-up.[3]

5. Conclusion

As a consequence of our study of the effectiveness and safety of probiotic supplementation in this meta-analysis, the utilization of probiotics has been demonstrated to be both effective and safe in reducing the occurrence of HAIs when contrasted with a placebo.

Acknowledgments

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Conflict of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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