Systematic Review

The Role of Probiotics in Urinary Tract Infections in Women

Peran Probiotik dalam Infeksi Saluran Kemih pada Perempuan

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Abstract

Objective: To review the role of probiotics in urinary tract infections in women

Methods: Systematic review was conducted by searching five databases with several keywords, namely "urinary tract infection", "cystitis", "women" and "probiotics". Articles that have gone through peer review are included in the study if they meet the inclusion and exclusion criteria. Reporting follows the PRISMA rules.

Results: The women included in this study varied from early adulthood to postmenopausal, most of whom were sexually active, used birth control methods, and had recurrent urinary tract infections. The results showed that the use of probiotics in varied outcomes, either positive or not showed significant results. This is also due to the differences in the outcomes studied and the additional materials used. This also contributed to the emergence of adverse effects.

Conclusion: The use of probiotics in the treatment of cystitis and urinary tract infections has hope, although not all studies show significant results. The side effects found are still tolerable although they need to be considered.

Keywords: cystitis, probiotic, urinary tract infection, women.

Abstrak

Tujuan: *Meninjau peran probiotik dalam infeksi saluran kemih pada perempuan.*

Metode: *Tinjauan sistematis dilakukan dengan mencari lima database dengan beberapa kata kunci, yaitu "infeksi saluran kemih", "sistitis", "perempuan" dan "probiotik". Artikel yang telah melalui peer review diikutsertakan dalam penelitian jika memenuhi kriteria inklusi dan eksklusi. Pelaporan mengikuti aturan PRISMA.*

Hasil: *Perempuan yang diikutsertakan dalam penelitian ini bervariasi mulai dari dewasa awal hingga pascamenopause, sebagian besar aktif secara seksual, menggunakan metode kontrasepsi, dan mengalami infeksi saluran kemih berulang. Hasil penelitian menunjukkan bahwa penggunaan probiotik pada infeksi saluran kemih menunjukkan hasil yang positif maupun tidak menunjukkan hasil yang signifikan. Hal ini juga disebabkan perbedaan outcome dan bahan tambahan yang digunakan. Penggunaan bahan juga berkontribusi pada munculnya efek samping.*

Kesimpulan: *Penggunaan probiotik dalam pengobatan sistitis dan infeksi saluran kemih memiliki harapan, walaupun tidak semua penelitian menunjukkan hasil yang signifikan. Efek samping yang ditemukan masih dapat ditoleransi meskipun perlu diperhatikan.*

Kata kunci: *infeksi saluran kemih, perempuan, probiotik, sistitis.*

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INTRODUCTION

One of the diseases that disproportionately affects women with a high risk of recurrence is Urinary Tract Infection (UTI). This disease can result in an economic burden due to the need for repeated health services[1]. Untreated urinary tract infections can lead to adverse conditions such as kidney stones, diabetes, complications from urethral catheterization, incontinence, and chronic diarrhea. The morbidity caused by UTIs is enormous, even though the chance of death is low[2] Moreover, compared to men, women have a 30 times higher chance of being affected [3]. Causes of UTI include clinical bacterial infections which account for as many as 50-60% every woman will have a chance of experiencing a UTI in her lifetime[4]. This occurrence is due to anatomical differences between women and men, as well as hormonal and behavioral effects[5]. UTI is a common infection that affects 150 million people per year. A study found an increase in UTI-related medical consultations among women over 18 years of age in France[6].

There are many types of causes for urinary tract infections. Pathogenic bacteria such as Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, and Staphylococcus saprophyticus are the main contributors[1]. UTIs do not occur in just one part but can involve various organs around the urinary tract[3]. One example is the case of cystitis, a specific inflammatory condition of the bladder[7]. Cystitis is characterized by the presence of bacteriuria. These bacteria cause complaints of dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria[8]. Properly treating UTIs can make the disease easy to manage and prevent further episodes[9]. Antibiotic exposure needs to be reduced due to the risk of recurrence. While initial treatment is antimicrobial therapy, using different prophylactic regimens and alternative strategies to reduce antibiotic exposure is suggested [10]. Complicated cystitis is associated with the virulence of infection or the potential for failure of antibiotic therapy [7]. Doctors face challenges in diagnosing and managing upper and lower UTIs due to the large number of cases, the risk of recurrence, and inappropriate treatment. Inaccurate history and diagnosis procedures can lead to antibiotic resistance[11].

Probiotics are live microorganisms that can provide health benefits when used in sufficient quantities[12]. Previous studies have shown that using probiotics is beneficial in boosting the immune system, preventing intestinal diseases, aiding lactose digestion, and balancing gut microbial levels. Apart from their role in digestion, probiotics contain anti-hypercholesterolemic agents and antihypertensive properties. They also help reduce postmenopausal disorders and diarrhea [13]. Although the use of probiotics has shown efficacy in various conditions, the optimal dose, frequency, and duration still need to be studied. Probiotics modulate various physiological functions in the body[14]. This study aims to review the role of probiotics in urinary tract infections in women.

METHODS

This systematic study examines the role of probiotics in urinary tract infections, including cystitis, in women. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed as a reference. Data was collected between July and August 2022. A search for English-language articles was conducted across five databases: Google Scholar, ScienceDirect, PubMed, ProQuest, and Scopus. The keywords used for the search included "urinary tract infection," "probiotics," "cystitis," and "women."

Table 1. PICO framework

Criteria	Determinants
P (Population)	Women complain urinary tract infection or cystitis
I (Intervention)	Administration of probiotic
C (Comparison)	Provision of placebo or none
O (outcome)	Reduction of complaints and other indicators related to the healing of urinary tract infections and cystitis

This study applies both inclusion and exclusion criteria. The research included in the study comprises observational and experimental studies written in English, discussing the role of probiotics in UTIs. The focus is on research published within the last twelve years, spanning from 2000 to 2022. Case reports, animal studies, letters to the editor, study reviews, preprints, and abstracts without full-text content were excluded from the review.

For title and/or abstract screening, the authors employed standard Microsoft Excel forms. The data collected were consolidated into a single folder, and subsequent assessment was

conducted. Each author individually analyzed all manuscripts, and the results were then compared. In cases of disagreement, a third external collaborator was consulted to reach a consensus.

The authors conducted a risk-of-bias assessment using critical appraisal tools. This process involved checking titles and/or abstracts independently using standard Microsoft Excel forms. When necessary, a third party was engaged to facilitate consensus when no agreement was reached. The risk-of-bias assessment utilized critical appraisal tools, specifically the Mixed Methods Appraisal Tool (MMAT) version 2018. The MMAT was employed for evaluating the quality of qualitative, quantitative, and mixed methods studies[15].The results of the critical appraisal are presented in table 2.

The authors extracted relevant results, organized, and analyzed them to identify sub-themes and overarching themes. Table 3 presents the characteristics of the research, including author, year, country, research type, disease type, sample size, probiotic type, administration method, results, side effects, and findings/ statistics. The impact of administering probiotics is evident through reductions in UTI symptoms and related indicators.

Flowchart study selection

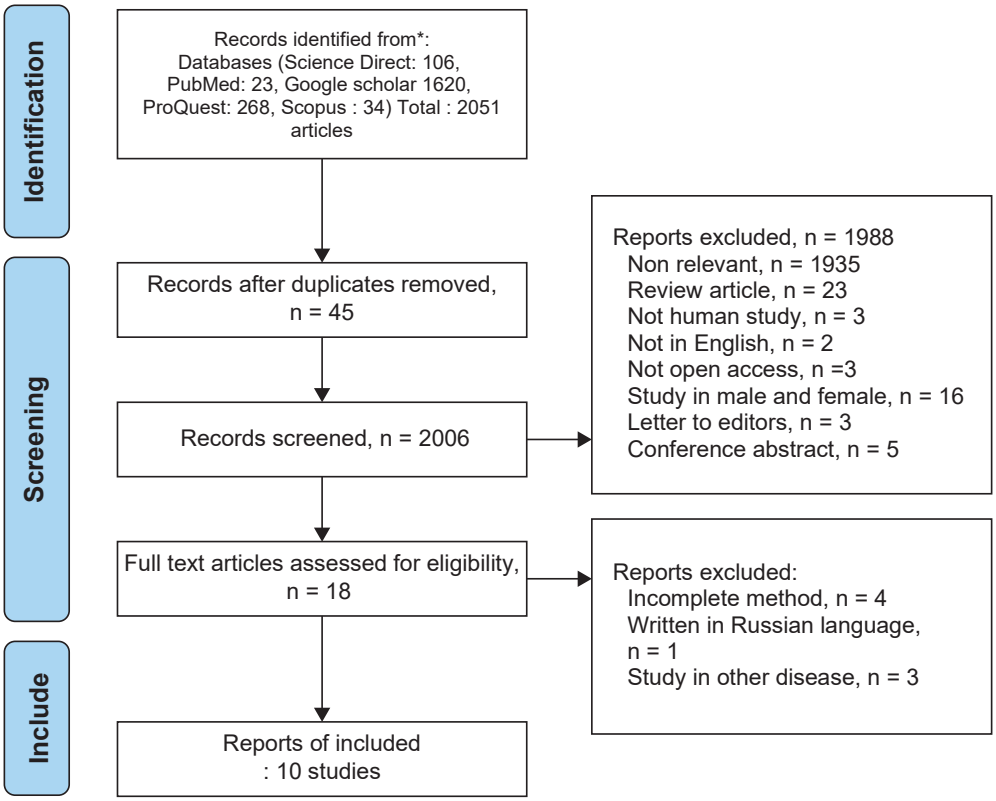


Figure 1. Prisma Flow Chart

RESULTS

The database search using keywords yielded a total of 2051 articles. Out of this initial pool, 1988 articles were screened and subsequently excluded as they did not meet the inclusion and exclusion criteria. A total of 18 full-text articles were evaluated for eligibility, and among them, 10 articles were included in the qualitative analysis. The article search process is illustrated in the PRISMA flowchart, as shown in Figure 1. The quality assessment results of the studies indicate that all articles fell within the moderate to good category. The detailed results of this assessment are presented in Table 1.

Table 2. Quality Assessment using MMAT

Study design and studies	Assessment criteria					Total Score
Quantitative non randomized	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analysis?	During the study period, is the intervention administered (or exposure occurred) as intended?	
Pugliese et al, 2020, Italy [16]	Y	Y	Y	Y	N	4
Uehara et al, 2006, Japan [17]	Y	Y	Y	Y/N	N	3.5
Montorsi et al, 2016, Italy [18]	Y	Y	Y	N	Y	4
Randomized controlled trials	Is randomization appropriately performed?	Are the groups comparable at baseline?	Are there complete outcome data?	Are outcome assessors blinded to the intervention provided?	Did the participants adhere to the assigned intervention?	
Koradia et al, 2019, India [19]	Y	Y	Y	Y	N	4
Czaja et al, 2007, USA [20]	Y	Y	Y	Y	N	4
Birte J. Wolf et al, 2019, USA [21]	Y	Y	Y	N	Y	4
Stapleton et al, 2011, USA [22]	Y	Y	Y	Y	N	4
Sadahira et al, 2021, Japan [23]	Y	Y	Y	Y/N	N	3.5
Kontiokari et al, 2001, Finland [24]	Y	Y	Y	Y	N	4
Beerepoot et al, 2012, Denmark [25]	Y	Y	Y	N	Y	4

A total of 2 articles discussed the role of probiotics in cystitis, while 8 articles discussed the role of probiotics in urinary tract infections. This study encompassed women of various ages. In the case of cystitis, two studies utilized samples with different average ages, namely 38 ± 11.2 years and 68.3 years. The study also included postmenopausal women, those with controlled diabetes mellitus, and those with cystocele. Among the studies focusing on urinary tract infections, there was considerable age variation and a wide age range. The average age was 21 years in some groups, with research also involving students in their 20s. Another study had a sample mean age ranging from 29.1 to 35 years. Some studies concentrated on postmenopausal women over 60 years old, while others included samples spanning ages 21 to 80 years. Most respondents were sexually active, with varying patterns of birth control usage, including some samples with less than 10% usage and others where the majority used birth control. Recurrent UTIs were common among the respondents.

The research results indicate diverse types, outcomes, and methodologies. Table 2 illustrates the journal characteristics. Researchers scrutinized the findings of each study to discern common themes. Conclusions were drawn regarding the potential and positive impact of probiotics. However, the results do not consistently indicate a significant role of probiotics, as their usage often involves combination with other ingredients. Positive improvements were observed in the prevention and treatment of recurrent urinary tract infections, such as reduced recurrence rates, extended intervals between recurrent UTIs, shorter active UTI durations, fewer subjects requiring antibiotics, and decreased antibiotic treatment durations. In cystitis cases, there were decreases in average ACSS scores and average cystic episode numbers. Yet, some studies demonstrated no significant difference in cumulative recurrence rates between the experimental and placebo groups. Similar mean U/L ratios were observed between placebo and probiotic groups. No discernible difference in microbiota diversity between the groups was found. There were also reported declines in

average quality of life scores.

Table 2 shows a comparison of study results, revealing disparities in terms of probiotic types (including various strains of Lactobacillus), additional therapies (such as cranberry, vitamins), and treatment dosages that varied. Lactobacillus, particularly Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus reuteri, and Lactobacillus crispatus Lactin, emerged as the most commonly used probiotics. Probiotics were combined with other ingredients like cranberry extract, vitamin A, D-mannose (2 g), prebiotics (fructo-oligosaccharide 1g), pomegranate extract, cranberry-lingonberry, vitamin C, and proanthocyanidins. The dosage and probiotic microbe count varied, as did the administration regimen, ranging from once to three times daily for up to a year. Moreover, administration methods spanned from oral intake to suppositories. The outcomes examined were diverse, encompassing the absence of UTIs, U/L ratio of daily voided urine, quality of life (QoL), Acute Cystitis Symptom Score (ACSS), changes in urine bacteria and vaginal microbiome, and development of antibiotic resistance. Outcome assessment involved self-reported symptoms, physical examination findings, and laboratory studies.

While most studies did not report side effects, further investigation is necessary to determine if these side effects stem from probiotics alone or from additional ingredients used. Side effects that were reported include vaginal discharge or itching, mild abdominal discomfort, mild asymptomatic inflammation of the lower urinary tract, diarrhea, or allergic reaction.

Table 3. Research characteristics

Authors, year, country	Study type	Type of disease	Number of samples	Probiotics type	Administration procedure	Outcome	Adverse effect	Finding/ statictical test results
Koradia et al, 2019, India [19]	Randomized double-blind, placebo-controlled, parallel group	Recurrent uncomplicated urinary tract infections	44 experiment / 45 placebo	BKPro-Cyan is a capsule formulation containing: cranberry extract (Vaccinium macrocarpon); probiotics (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47); and vitamin A (retinyl acetate; 160 µg/capsule). Each capsule contains a minimum of 18mg cranberry PACs and >500 million live probiotic microorganisms (>5 x 108 CFU/capsule).	Twice-daily for 26 weeks	Absence of UTI, UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria)	Not found in articles	Lower number recurrent UTIs, Improvements multiple secondary endpoints, longer time to first UTI, shorter duration of active UTI, Fewer subjects requiring antibiotics and shorter median duration of antibiotic treatment
Birte J. Wolf et al, 2019, USA[21]	Double-blinded randomized controlled trial	Urinary tract infection	4 experiment / 3 placebo	Lacctobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at sum of 10^9 viable organisms	Orally twice daily	U/L ratio of daily voided urine	No	No diference mean U/L ratio. No changes in terms of microbiota diversity
Pugliese et al, 2020, Italy[16]	Uncontrolled experimental pilot study	Acute cystitis	Thirty-three patients	A dose of a new combination of agents, (Prolactis IVU©, Omega Pharma, Cantù, Italy). Prolactis IVU contains D-mannose 2 g, Prebiotics (fructo-oligosaccharide 1g), pomegranate extract 250 mg (with 70% titration of ellagic acid 175 mg) and Probiotics (Lactobacillus plantarum Lp115 ≥ 2 billion colony-forming unit).	Twice daily for 5 days and then once a day for 10 days.	Changes in patients' symptoms, the therapeutic effects and changes in quality of life (QoL), the Acute Cystitis Symptom Score (ACSS) at the first visit (T0), 15 (T1) and 30 (T2) days later.	No	No symptoms or the majority of symptoms went. The mean score reported at all the ACSS sub-scales significantly decreased Typical symptoms decreased; Differential symptoms decreased QoL mean score also decrease
Sadahira et al, 2021, Japan[23]	Single-arm, open-label, phase II clinical trial,	Recurrent cystitis	21 patients	Vaginal suppositories containing the GAI 98322 strain of Lactobacillus crispatus	1 year either every 2 days or three times per week	The primary end-point was the response rate, as assessed by the number of episodes of recurrent cystitis during the year of	No	An effective response (86%) during administration. The suppressive effects continued up to 1 year after the last suppository was administered. There was
Authors, year, country	**Study type**	**Type of disease**	**Number of samples**	**Probiotics type**	**Administration procedure**	**Outcome**	**Adverse effect**	**Finding/ statictical test results**
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DISCUSSION

The study outcomes revealed varying results of using probiotics for urinary tract infections, with both positive outcomes and results that didn't show significant effects. Another study evaluated probiotic efficacy in preventing UTIs among premenopausal women. Systematic studies and meta-analyses demonstrated significant benefits in reducing recurrent UTIs compared to placebo in this group. However, more conclusive data are necessary to determine the effect of probiotics in strengthening the urogenital microbial barrier against pathogenic bacteria and protecting against UTI recurrence[26]. Other studies also yielded varying conclusions from the use of different probiotics. While two studies suggested that probiotics can reduce the risk of recurrent UTIs, others presented inconclusive results[27]. Results from another meta-analysis examining probiotics' impact on UTI incidence in children indicated that probiotic therapy had no significant beneficial effect on incidence or recurrence. Subgroup analysis indicated a reduction in UTI incidence when probiotics were used in combination with antibiotics[28].

The diverse results obtained stem from variations in usage methods and additional materials. This discrepancy also contributes to the appearance of side effects resulting from each ingredient. Other substances like cranberry extract, vitamin A, D-mannose, prebiotics (fructo-oligosaccharide 1g), pomegranate extract, cranberry-lingonberry, vitamin C, and proanthocyanidins can complicate decision-making regarding the overall role of probiotics in managing cystitis and urinary tract infections. For instance, cranberry extract, used prophylactically in UTIs among young and middle-aged women, demonstrated effectiveness in some studies, including findings by the Cochrane Collaboration[29]. Another meta-analysis corroborated these findings, asserting that cranberry supplementation significantly reduced UTI risk in susceptible populations [30]. Certain vitamins, such as vitamin C, have also been linked to UTI management. Vitamin C is considered safe for post-kidney disease UTI treatment[31]However, conflicting studies suggest that ascorbic acid (vitamin C) might not be recommended for UTI prevention [25]Other vitamins, like vitamin A, are also under discussion. Vitamin A supplementation appears effective for treating UTIs and reducing kidney injury and scarring following acute pyelonephritis in girls with initial acute pyelonephritis [32].

The results found indicated that Lactobacillus was the most widely used probiotic. In healthy premenopausal women, the female urogenital flora is predominantly dominated by Lactobacillus. This bacterial strain may offer protection against UTIs [33]. Lactobacillus is the preferred probiotic agent for preventing and treating urogynecological infections due to properties such as hydrogen peroxide production and biosurfactant generation[34].

The characteristics of the respondents in this study varied. UTI incidence spans from early adulthood to postmenopause. Most respondents were sexually active, and family planning practices varied, including both samples with less than 10% usage and those with the majority using family planning methods. Recurrent UTIs were common. Established risk factors for uncomplicated recurrent UTIs encompass frequent intercourse, vulvovaginal atrophy, changes in local bacterial flora, history of UTIs during premenopause or childhood, family history, and nonsecretory blood type. Complicated urinary tract infections manifest in patients with other medical conditions like diabetes, old age, pregnancy, or immunocompromised status[2].

This study is advantageous for exploring the potential and limitations of using probiotics in managing urinary tract infections, both in general and specifically in cystitis cases. However, various limitations, including variations in dosage, probiotic microbe count, and additional ingredient use, emphasize the need for further research focusing exclusively on probiotic utilization. Such research could enhance knowledge progression, as decades of study have yet to pinpoint an accurate dosage for optimal outcomes.

CONCLUSION

The utilization of probiotics for treating cystitis and urinary tract infections holds promise, even though not all studies yield significant results. The identified side effects, while generally tolerable, warrant consideration.

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