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.
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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (Population)</td>
<td>Women complain urinary tract infection or cystitis</td>
</tr>
<tr>
<td>I (Intervention)</td>
<td>Administration of probiotic</td>
</tr>
<tr>
<td>C (Comparison)</td>
<td>Provision of placebo or none</td>
</tr>
<tr>
<td>O (outcome)</td>
<td>Reduction of complaints and other indicators related to the healing of urinary tract infections and cystitis</td>
</tr>
</tbody>
</table>

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. 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.

![Prisma Flow Chart](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

<table>
<thead>
<tr>
<th>Study design and studies</th>
<th>Assessment criteria</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative non randomized</td>
<td>Are the participants representative of the target population?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are measurements appropriate regarding both the outcome and intervention (or exposure)?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are there complete outcome data?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are the confounders accounted for in the design and analysis?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>During the study period, is the intervention administered (or exposure occurred) as intended?</td>
<td>N</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Is randomization appropriately performed?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are the groups comparable at baseline?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are there complete outcome data?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Are outcome assessors blinded to the intervention provided?</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Did the participants adhere to the assigned intervention?</td>
<td>N</td>
</tr>
</tbody>
</table>

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 characteristic. 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
Table 3. Research characteristics

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Study type</th>
<th>Type of disease</th>
<th>Number of samples</th>
<th>Probiotics type</th>
<th>Administration procedure</th>
<th>Outcome</th>
<th>Adverse effect</th>
<th>Finding/ statistical test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karada et al, 2019, India</td>
<td>Randomized double-blind, placebo-controlled, parallel group</td>
<td>Recurrent uncomplicated urinary tract infections</td>
<td>44 experiment / 45 placebo</td>
<td>BKPico-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 &gt;500 million live probiotic microorganisms (5 x 10^8 CFU/capsule)</td>
<td>Twice-daily for 28 weeks</td>
<td>Absence of UTI, UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria)</td>
<td>Not found in articles</td>
<td>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</td>
</tr>
<tr>
<td>Zippe et al, 2020, USA</td>
<td>Double-blind randomized controlled trial</td>
<td>Uncontrolled experimental pilot study</td>
<td>4 experiment / 3 placebo</td>
<td>Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at sum of 10^10 viable organisms</td>
<td>Twice daily</td>
<td>U/L ratio of daily voided urine</td>
<td>No</td>
<td>No difference mean U/L ratio, No changes in terms of microbiota diversity</td>
</tr>
<tr>
<td>Pugliese et al, 2020, Italy</td>
<td>Single-arm, open-label, phase II clinical trial</td>
<td>Vaginal suppositories containing the GAI 98322 strain of Lactobacillus crispatus</td>
<td>21 patients</td>
<td>Lactobacillus vaginal biofilm + 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.</td>
<td>1 year either every 2 days or three times per week</td>
<td>The primary endpoint was the response rate, as assessed by the number of episodes of recurrent cystitis during the year of administration. The secondary end points were the response rate, as assessed by episodes of recurrent cystitis during the year after completion of the administration period; the total number of episodes of recurrent cystitis before, during and after administration; adverse events; and changes in urine bacteria and microorganisms</td>
<td>No</td>
<td>An effective response (86%) during administration. The suppressive effects continued up to 1 year after the last suppository was administered. There was a significant reduction in the mean number of episodes of cystitis, both during and after administration of Lactobacillus vaginal suppositories</td>
</tr>
</tbody>
</table>
Stapleton et al., 2011, USA
Randomized, Placebo-Controlled Phase 2 Trial
Recurrent Urinary Tract Infection
One hundred young women
Lactin-V or placebo
Daily for 5 days, then once weekly for 10 weeks

the vaginal microbiome
Urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for L. crispatus

Adverse effects were reported by 56% of participants who received Lactin-V and by 50% of participants who received placebo; the most common adverse effects included vaginal discharge or itching of moderate abdominal discomfort

Recurrent UTI occurred in a small proportion of respondents. High-level vaginal colonization with L. crispatus was associated with a significant reduction in recurrent UTI only for Lactin-V.

Czaja et al., 2007, USA
Phase I Trial
Recurrent Urinary Tract Infection
30 women
L. crispatus CTV-05 or placebo vaginal suppositories
Daily for five days

The primary outcome of safety was assessed through self-reported symptoms, physical exam findings, and laboratory studies.

Secondary outcomes included shifts in urinary tract infection, recurrent side effects related to suppository use occur but do not affect compliance. L. crispatus CTV-05 may cause mild asymptomatic inflammation of the lower urinary tract.

Mild to moderate vaginal discharge

Czaja et al., 2019, USA
Randomized, Placebo-Controlled Parallel Group
Recurrent Urinary Tract Infection
One hundred young women
Lactin-V or placebo
Daily for 5 days, then once weekly for 10 weeks

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Sadahira et al., 2021, Japan
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 endpoint was the response rate, as assessed by the number of episodes of recurrent cystitis during the year of administration. The secondary endpoints were the response rate, as assessed by episodes of recurrent cystitis during the 1 year after completion of the administration period; the total number of episodes of recurrent cystitis before, during and after administration; adverse events; and changes in urine bacteria and the vaginal microbiome.

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44 experiment / 45 placebo
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Twice-daily for 26 days
Absence of UTI, UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria)
Not found in articles

Brite J. Wolf et al., 2019, USA
Double-blind randomized controlled trial
Acute cystitis
4 experiment / 3 placebo
Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at sum of 160 million live probiotic CFU/capsule.
Orally twice daily
U/L ratio of daily voided urine
No
No difference mean U/L ratio. No changes in terms of microbiota diversity.

Pugliese et al., 2020, Italy
Uncontrolled experimental pilot study
Acute cystitis
Thirty-three patients
A dose of a new combination of agents, (Probactis IVV, Omega Pharma, Canzi, Italy). Probactis IVV contains D. mannosae 2 g, Prebiotics (fructo-oligo-saccharide), 1g, pomegranate extract 250 mg (with 70% isation of ellagic acid 175 mg) and Prebiotics (Lactobacillus plantarum up115 ≥ 2 billion colony-forming unit).
Orally twice daily
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 decreased.

Sadahira et al., 2021, Japan
Single-arm, open-label, phase II clinical trial
Recurrent cystitis
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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. 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. 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.

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. Another meta-analysis corroborated these findings, asserting that cranberry supplementation significantly reduced UTI risk in susceptible populations. Certain vitamins, such as vitamin C, have also been linked to UTI management. Vitamin C is considered safe for post-kidney disease UTI treatment. However, conflicting studies suggest that ascorbic acid (vitamin C) might not be recommended for UTI prevention. 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.

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. Lactobacillus is the preferred probiotic agent for preventing and treating urogynecological infections due to properties such as hydrogen peroxide production and biosurfactant generation.

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.

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.

REFERENCES