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A Systematic Review and Meta-Analysis of Non-Antibiotic Agents in Comparison to Antibiotic Therapies for Prevention of Recurrent Urinary Tract Infection

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Introduction. Prolonged antibiotic usage can lead to modifications in the normal gastrointestinal tract and vaginal microbiome, which contributes to the UTI recurrence. This study aims to assess the impact of non-antibiotic therapies compared to antibiotic interventions in the prevention of recurrent urinary tract infections (UTIs).
Methods. A systematic literature search was carried out from the PubMed, Google Scholar, Cochrane, and ScienceDirect databases published from 2013–2023, adjusted for inclusion and exclusion criteria. Keywords and Medical Subject Headings (MeSH) used were urinary tract infection, UTI, recurrent UTI, antibiotics, anti-bacterial agents, antimicrobial versus non antibiotic agents, probiotics, cranberries, D-mannose, vitamins, NSAID, prevention, treatment. The RevMan 5.3 program was used to analyze the risk of recurrent UTIs. Forest plot analysis was used to present relative risk estimates from individual studies and combined meta-analysis results.
Results. Six studies were deemed eligible for quantitative synthesis and were included in this meta-analysis. This meta-analysis study showed a large heterogeneity, with p= 0.006 and I^2= 85%. Pooled analysis using a fixed effect model showed the development of recurrent UTI was significantly lower in women with symptomatic UTI who were given non-antibiotic interventions compared to antibiotic interventions, with a relative risk of 0.75 (95% confidence interval (CI)= 0.61–0.92). This shows that non-antibiotic interventions significantly reduce the incidence of recurrent UTI compared to antibiotic interventions.
Conclusion. Non-antibiotics interventions such as cranberry extract, D-mannose, NSAIDs, and herbal medicines can prevent recurrent UTI, and the results appear to be better or the same as antibiotic interventions. Meta-analyses should consider small numbers of studies with varying study designs and quality as well as small overall sample sizes.

Keywords: antibiotics, intervention, non-antibiotics, prevention, recurrent urinary tract infection

Introduction

Urinary tract infections (UTIs) are common conditions that clinical practices encounter. One of the most prevalent bacterial illnesses is UTI, which results in over 5 million clinic visits, over 1.5 million emergency room (ER) visits, and around 400,000 hospitalizations annually, costing approximately $2.8 billion in the US alone. Around 50–60% of women will experience UTI at some point in their lives, and 20–30% of them will experience at least one relapse following their initial infection. The risk of UTI in the female population is estimated to be 14 times higher than in the male population [1].

The Enterobacteriaceae family includes the most often found pathogens linked to UTIs: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter spp.*, and *Enterobacter spp.* The extra-intestinal *E. coli* known as uropathogenic *E. coli* (UPEC) is a diverse group that arises from the rectal microbiota. It is responsible for roughly 95% of community-acquired UTIs and 80% of simple UTIs. The current paradigm for managing UTIs combines antibiotic medication with lifestyle modifications [2-3].

The prevalence of recurrent urinary tract infections (rUTIs) is rising by age[MS1] , from 100/100,000 women in the 18–34 age group to 189/100,000 women in the 55–64 age group. In terms of cost and morbidity, rUTIs unquestionably constitutes a substantial burden for both individuals and society. Another significant issue with UTI treatment is the rUTI. Continuous prophylaxis with low-dose antibiotic regimens such as trimethoprim or nitrofurantoin are advised for women who experience UTIs [4]. However, there are a number of adverse effects linked to these drugs, such as headaches, nausea, vaginal burning, diarrhea, and candidiasis, which might worsen overtime. For instance, long-term nitrofurantoin to manage those effects has been linked to liver and lung damage, while the use of trimethoprim-sulfamethoxazole has been linked to a number of significant skin reactions, including blood problems, Stevens-Johnson syndrome, and medication interactions [5].

Furthermore, the widespread emergence of antibiotic-resistant strains and the development of resistance in some bacteria to the most commonly prescribed antibiotics are raising doubts about the wisdom of continuously using daily low-dose antibiotics. These issues can result in rUTIs due to impaired bacterial clearance, frequent empirical antibiotic prescribing, and the transmission of antibiotic-resistant genes and other resistance determinants from transferred genetic elements, which in turn can lead to the increasing emergence of multidrug resistance (MDR) at the community level, complicating the treatment of UTIs [6].

Prolonged antibiotic usage can also lead to modifications in the normal gastrointestinal tract and vaginal microbiome, which affects local metabolite concentrations and pH, and contributes to the urine microenvironment's homeostasis. It has been demonstrated that modifications to the natural microbiome and a drop in vaginal pH have a positive effect on UTI recurrence by inhibiting the growth of microorganisms and making treatment of subsequent UTIs challenging [7].

Research on non-antibiotic rUTI prevention regimens is therefore developing rapidly. Non-antibiotic therapy methods are now crucial since the broad use of antibiotics for various diseases have increased antibiotic resistance. In addition to minimizing antibiotic resistance, reducing the usage of antibiotics will also have fewer negative effects and enhance patients' quality of life [8].

Commonly studied non-antibiotic agents for UTI prevention include cranberries, D-mannose, NSAIDs, and herbal medicine. Non-antibiotic therapy is typically less effective compared to antibiotic therapy, and might cause a mild gastrointestinal (GI) discomfort. However, some agents are promising, with no risk of antibiotic resistance, and generally fewer side effects. Nevertheless, self-management with dietary supplements or lifestyle changes might be more suitable for long-term prevention with fewer side effects, even when the effectiveness may vary [9].

Based on the European Association of Urology (EAU) 2024 guideline on infection, the use of non-antibiotic therapies such as D-mannose and cranberry have been researched and suggested in the guideline, but there is not yet enough evidence to date, to explain in detail their efficacy and effectiveness. This study reviews and investigates the potential impact of non-antibiotic therapies on the prevention of rUTIs in women who have acute UTI symptoms, in comparison to antibiotic interventions, to further strengthen the existing data of non-antibiotic therapy for the prevention of rUTI.

Materials and Method

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. A thorough search of the literature published between 2013 and 2023 was done in the PubMed, Google Scholar, Cochrane, and ScienceDirect databases. The researcher determined the eligibility criteria using the PICO (Population, Intervention, Comparisons, Outcome) model. These criteria include: (i) the population, consisted of adult women; (ii) the intervention, consisted of non-antibiotic interventions, such as probiotics, cranberries, D-mannose, vitamins, and NSAIDs; (iii) the comparison, consisted of placebo or antibiotics; (iv) the outcome, was the incidence of new UTIs.

The keywords and Medical Subject Headings (MeSH) used were urinary tract infection, urinary tract infections, UTI, recurrent UTI, antibiotic, antibiotics, anti-bacterial agents, anti-microbial, versus non-antibiotic agents, probiotics, cranberries, D-mannose, vitamins, NSAIDs, prevention, and treatment. The search was conducted manually and comprehensively by screening references of eligible or potentially suitable studies.

The inclusion criteria include: (i) articles were randomized clinical trials, (ii) the study population was adult women aged 18 years old or older, with or without risk factors for rUTI, (iii) investigated one of the non-antibiotic interventions for UTI

prophylaxis, (iv) compared with antibiotic or placebo interventions for UTI prophylaxis, (v) reported outcomes in the form of relative risk of UTI recurrence, and (vi) full articles were available and written in English. Studies were excluded if they meet one of the following criteria: (i) the study population was children younger than 18 years old, (ii) duplicate publications, (iii) studies published before 2013, (iv) studies published using a non-English language. The data is extracted by identifying the study type, population, intervention, control, and outcome manually. Any discrepancies were resolved through a thorough discussion.

We found a total of 354 potentially eligible publications, including 90 (PubMed), 181 (Google Scholar), 52 (Cochrane), and 31 (ScienceDirect). We eliminated 256 duplicated publications before screening the other 98 articles by the titles and abstracts. Among the 98 studies, 87 did not satisfy the inclusion and exclusion criteria of this study, leaving 11 studies. Furthermore, we excluded five of the 11 studies due to the methodology missing in those articles. Thus, this study analyzes six papers that met the criteria for quantitative analysis. Figure 1 shows a PRISMA flow chart-based literature screening and selection of this study.

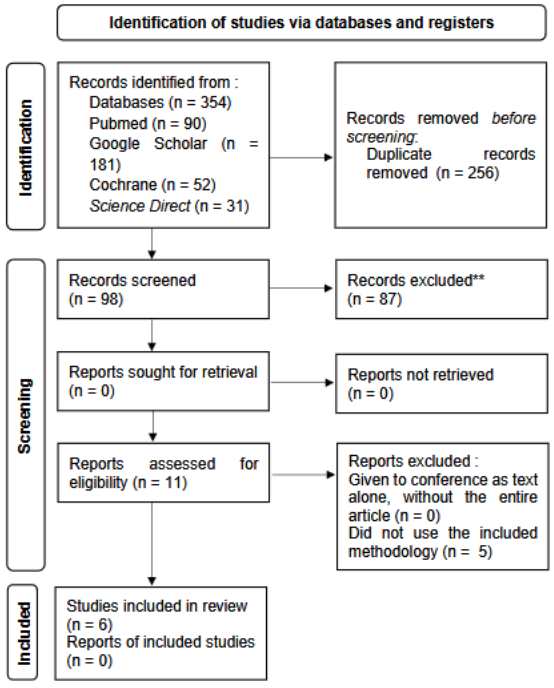

Figure 1. Flowchart diagram of systematic review

Review Manager 5.3 was utilized for quantitative statistical analysis and data synthesis in order to assess the probability of rUTI in the non-biotic intervention and control groups. To assess the impact of dichotomous outcome indicators, relative risk with 95% confidence interval was employed. The I^2, which represents the percentage of overall variation in the statistical estimate, was utilized to assess the heterogeneity of the study. Significant heterogeneity was defined as an I2 index higher than 40%. The result was considered relevant if the quantitative data synthesis finding showed a p value of <0.05.

Result

The six studies used in this study (Table 1) have the same randomized controlled trial (RCT) research design, with all participants were adult females experiencing acute symptoms of UTI without any problems, regardless of whether they had previously had rUTI. The sample sizes for all investigations varied between 30 and 659 samples. The trial employed a range of non-antibiotic therapies, including cranberry extract, D-mannose, herbal capsules, ibuprofen, and sodium diclofenac. The control variables and the duration of the intervention were also different for each study.

Each trial showed a similar result, that the intervention variable had a better or the same effect as the control variable. This contributes to the high heterogeneity of the data, as our meta-analysis yielded significant results (Fig. 2) with a p-value of 0.0006, with the I2 value of 85%. The study design, population type and different types of interventions might also contribute to the high heterogeneity of this study. The utilization of a fixed-effect model in a combined analysis revealed a significantly reduced occurrence of rUTI in women exhibiting non-antibiotic UTI symptoms, as compared to those who received antibiotic intervention. The relative risk (RR) was found to be 0.75 (95% CI= 0.61–0.92). These findings demonstrated that non-antibiotic therapies had a substantial impact in reducing the occurrence of rUTI in comparison to antibiotic therapy. Differences in intervention, control, and observation time might create the risk of research bias. According to four further investigations, it was determined that non-antibiotic therapies exhibited significant efficacy in preventing rUTI and were not found to be inferior to antibiotic intervention.

Table 1. Data extraction of six studies

Authors	Study Type	Population	Intervention (n = 830)	Control (n = 821)	Outcome
Gbinigie et al., 2021 [9]	RCT	Women with acute uncomplicated UTI	Cranberry extract 2 capsules, twice daily for 7 days (n = 15)	Nitrofurantoin 50 mg orally once a day for 3 days (n = 15)	Cranberry capsules effective in preventing recurrent UTIs, same results as antibiotics
Kranjcec et al., 2014 [10]	RCT	Women with UTI symptoms and a history of recurrent UTIs	D-mannose powder 2 g diluted in 200 ml of water once a day for 6 months (n = 103)	Nitrofurantoin 50 mg orally once a day for 6 month (n = 103)	D-mannose is better at preventing recurrent UTIs
Kronenberg et al., 2017 [11]	RCT	Women with acute uncomplicated UTI	Diclofenac 75 mg orally once a day for 3 days (n = 133)	Norfloxacin 400 mg orally, twice daily for 3 days (n = 120)	Norfloxacin is better at preventing recurrent UTIs
Porru et al., 2014 [12]	RCT	Women with UTI symptoms and a history of recurrent UTIs	Oral D-mannose 1 g three times a day, 2 weeks, and then 1 g twice a day for 22 weeks (n = 60)	Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily, for 5 days, followed by a single dose at bedtime for 1 week every month for 23 weeks (n = 60)	D-mannose is better at preventing recurrent UTIs
Vik et al., 2018 [13]	RCT	Women with acute uncomplicated UTI	Ibuprofen 600 mg 3 times daily for 3 days (n = 194) (n = 194)	Pivmecillinam 200 mg 3 times a day for 3 days (n = 189)	Pivmecillinam is better at preventing recurrent UTIs
Wagenlehner et al., 2018 [14]	RCT	Women with uncomplicated acute UTI symptoms	Salut BNO (*Centaurii herba* 18 mg, *Levistici radix* 18 mg, *Rosmarini folium*) 2 capsules 3 times a day for 7 days (n = 325)	Fosfomycin 3 g single dose (n = 334)	Herbal capsules are better at preventing recurrent UTIs

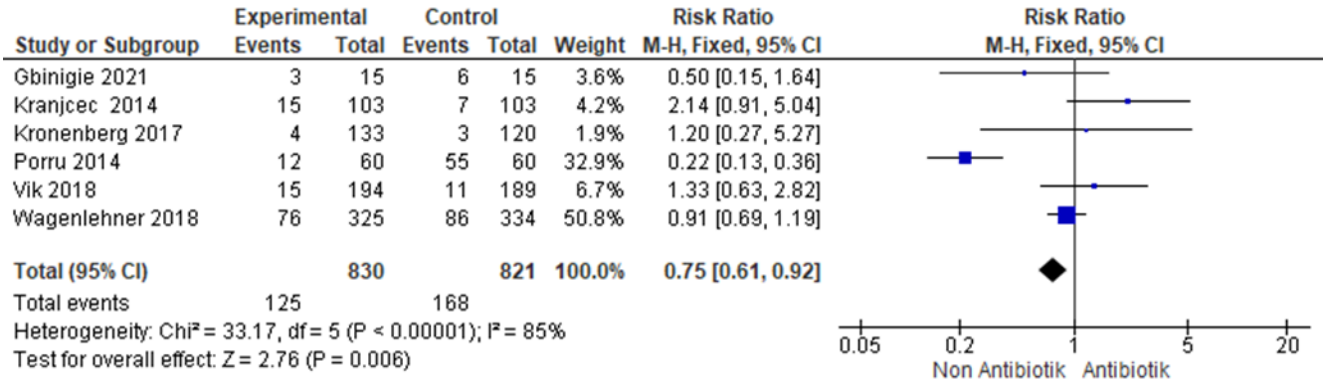

Figure 2. Forest plot of risk of recurrent UTI in non-antibiotic versus antibiotic interventions

Discussion

UTIs are a common problem for women at different ages. Yet, UTIs are not only a problem unique for the patient, but are also a factor of high cost for the health care system. Increasing antimicrobial resistance with its expenditure and health consequences has raised interest in applying different nonantibiotic ways of preventing and treating uncomplicated lower UTIs. Unfortunately, the last 20 years of research on non-antibiotic approaches in UTI have not brought conclusive evidence that antibiotic usage can be replaced completely by non-antibiotic options. Hence, antibiotics still remain a gold standard for UTI treatment and prevention. However, changing the therapeutic strategy by including non-antibiotic measures in the management of UTI could be successful in avoiding antimicrobial resistance at least to some extent [14,20].

According to the updated guidelines of the European Association of Urology (EUA), the prevention of rUTI includes, first of all, counseling of risk factors avoidance, followed by non-antimicrobial measures, then finally antimicrobial prophylaxis. These interventions should be incorporated with an emphasis on that order. With the proper identification of UTI risk factors, such as gender, prior UTIs, vaginal infection, sexual activity, the use of spermicidal agents, trauma/manipulation, diabetes mellitus, obesity, and anatomic abnormalities, together with non-antibiotic interventions, a significant reduction of rUTI could probably be achieved, leaving only a few patients in whom antibiotic prophylaxis needs to be done as last resort [15,21].

In this study, we chose 6 non-biotic therapies, which are, cranberry, D-mannose, NSAIDs (ibuprofen and sodium diclofenac), and Salut BNO (*Centaurii herba*, *Levistici radix*, *Rosmarini folium*). This study is mainly focused on further strengthening and supporting existing research that cranberry and D-mannose may be promising agents in the prophylaxis of recurrent UTI in women. Furthermore, only a few studies describe NSAIDs and Salut BNO, so this study also discusses those two agents as prophylaxis of recurrent UTI in women. The antibiotic therapy used as a comparison variable are nitrofurantoin, norfloxacin, trimethoprim/sulfamethoxazole, pivmecillinam and fosfomycin, as it is recommended in the EAU Guideline 2024 as the prophylactic management of rUTI in women.

There are several agents in the management of rUTI in women beyond those studied in this paper, including probiotics, such as Lactobacillus sp. and estrogen therapy. We did not include them as intervention variables as there are already a lot of literature studies on both agents compared to NSAIDs and herbal therapies, which are still limitedly discussed in the literature. Additionally, the use of probiotics also has disadvantages, including long-term use, inconsistent results depending on the strain of infecting microorganisms, high risk of gastrointestinal side effects. The estrogen therapy also has a high risk of stroke, cancer, heart disease, and is not recommended in premenopausal female patients/patients with hypersensitivity to estrogens.

The utilization of cranberry, as one of the non-antibiotic agents discussed in this study, is typically in the form of juice or pills, both in conjunction with antibiotics and as a standalone treatment to prevention. The mechanism by which it operates entails the inhibition of bacterial adhesion, particularly to uroepithelial cells, with a particular focus on Escherichia coli. The inhibition of adhesion prevents the invasion of germs into the mucosal surface of the urinary system. Flavonoids, particularly proanthocyanidins (PACs), and more specifically the type A PACs, are the primary agents responsible for impeding the attachment of

Escherichia coli to the urinary mucosa [15]. The study conducted by Gbinigie et al. demonstrated the safety and efficacy of cranberry extract in the treatment of acute UTIs, with no notable adverse effects. This finding suggests that cranberry extract has the potential to serve as a valuable health intervention, offering the possibility of substantially reducing antibiotic usage [9]. Maki et al. conducted a study to assess the impact of cranberry juice drinking on the frequency of UTI episodes in women who had recently experienced a UTI. The finding indicates that the cranberry intervention successfully avoided 1 out of every 3.2 instances of clinical UTI [16,22].

Takahashi et al. conducted a randomized, double-blind trial demonstrating that cranberry beverage is more effective than placebo for UTI prevention. Although this effect was only detected in female patients over 50 years of age. The efficacy of cranberry products remains contentious, as they only diminished the risk of UTI in a restricted demography [17]. Conversely, cranberry juice did not significantly diminish UTI risk relative to placebo in a study by Stapleton et al., which involved 176 premenopausal women with a recent UTI history, randomized (120 to cranberry juice and 56 to placebo) and monitored for a median of 168 days, although a trend suggesting a protective effect was noted in this study [18]. The findings indicate that cranberry products could be a viable choice for preventing UTI in healthy, non-pregnant individuals and in patients post-gynecological surgery with catheter placement. Liska et al. in their meta-analysis on cranberries and UTIs indicated that several publications may present conflicting conclusions because recommendations primarily target women with rut Is and encompass outcomes from diverse populations, which may also lead to various results [19].

The symptoms of UTIs are primarily associated with the inflammatory response of the urinary tract, which results from a notable increase in urinary prostaglandin production. The onset and duration of clinical symptoms of UTI appear to be closely linked to prostaglandin levels. NSAIDs can inhibit the biosynthesis of prostaglandins, making them useful in alleviating the symptoms of UTIs. Nevertheless, it remains uncertain if they can serve as a substitute for antibiotics in the treatment and/or prevention of UTIs [23].

In a double-blind, multicenter trial conducted by Gagyor et al., female patients exhibiting UTI symptoms were randomized into two groups: one receiving fosfomycin trometamol (3 g single dose; 243 participants analyzed) and the other receiving ibuprofen (400 mg tid for 3 days; 241 participants analyzed). Participants were selected exclusively from individuals without risk or complicating factors. In this study, two-thirds of the ibuprofen group recovered without the use of antibiotics; however, they exhibited a significantly greater total burden of symptoms. Additionally, the incidence of pyelonephritis was higher in this group, with five cases reported compared to one in the fosfomycin group. The authors propose that symptomatic treatment may be a viable option for women experiencing mild to moderate UTI symptoms [24].

Vik et al. did a randomized, controlled, double-blind, non-inferiority trial with 178 women who had uncomplicated UTIs and compared pivmecillinam (200 mg twice daily) with ibuprofen (600 mg twice daily) over the course of three days. The women were not pregnant. The study indicated that ibuprofen administration had an effect, although it was less effective than pivmecillinam use. The authors concluded that ibuprofen is not advisable as initial treatment for women with uncomplicated UTIs until patients at risk for complications can be identified, as all seven patients who developed pyelonephritis had received ibuprofen [25].

Replacing antibiotics with NSAIDs for the treatment of uncomplicated UTI may be at the cost of prolongation of symptoms and increased risk of pyelonephritis since in uncomplicated UTI, it is preferable to delay the use of antibiotics while closely monitoring the patient rather than completely resigning from antimicrobial treatment. In this strategy it is also important to share a decision-making process with a patient and to know his/her expectations towards the treatment. NSAIDs have been studied only as a treatment option for UTIs, but not for prevention of rUTIs [26].

The urinary tract's mucous membrane is composed of proteins that impede the attachment of germs. D-mannose is a monosaccharide that exhibits high bioavailability and may be efficiently absorbed and eliminated via the urinary system. It possesses the ability to inhibit the attachment of type 1 bacterial fimbriae to the urothelium, hence impeding the pathogenicity of bacteria responsible for urinary tract infections, particularly those caused by Escherichia coli [18]. According to Kranjcec et al., female participants with UTIs were randomly assigned to three groups. The initial cohort was administered a daily dosage of 2 g of D-mannose powder (n = 103), the subsequent cohort was administered a daily dosage of 50 mg of nitrofurantoin (n = 103), and the last cohort did not receive any form of prevention (n = 102) for 6 months. The findings of the study indicate a

significant reduction in the risk of UTI while administering D-mannose and nitrofurantoin. Additionally, the D-mannose group exhibited a decreased incidence of adverse effects [10].

Herbal preparations are potential alternatives to antibiotics for the treatment of UTIs. The BNO 1045, one of the herbal preparations has been shown to preserve the gut microbiota. This is particularly important, given the implications of recent research into urinary microbiota, where asymptomatic bacteriuria appears to play an important protective role against UTI, and could be used as a preventative treatment strategy in recurrent infections. Wagenlehner et al. reported BNO 1045 to be non-inferior to antibiotic regimens in treating UTI (non-AB rate difference: -6.26%; 95% CI -11.99 to -0.53%; p= 0.0014 on 2 sides). BNO 1045 has the potential to reduce antibiotic use in outpatients with UTI [14].

The findings of our meta-analysis indicate that non-biotic therapies exhibited a statistically significant decrease in the occurrence of UTIs in comparison to antibiotic interventions [p= 0.006, I2= 85%, OR : 0.75 (0.61-0.92)]. Based on the results of our forest plot meta-analysis, it was found that antibiotic therapy can significantly prevent rUTI in women. Although this result is significant, we still suggest to also consider certain factors such as gender, history of UTI, vaginal infection, sexual activity, use of spermicidal agents, trauma/manipulation, diabetes mellitus, obesity, and anatomical abnormalities. Non-antibiotic therapy can be used to prevent recurrent UTIs in patients without the above risk factors. If risk factors are present, antibiotic therapy should be used according to the updated EAU guidelines and previous literature. The use of a combination of antibiotic and non-antibiotic therapy may be considered to achieve better patient outcomes and reduce long-term antibiotic use.

Large head-to-head trials comparing the various non antibiotic prophylactic strategies with one another and with the standard antibiotic prophylaxis treatment should be conducted to represent the best clinical decision. At the moment, antibiotic prophylaxis is far more successful than nonantibiotic treatments. However, nonantibiotic prophylaxis can be a suitable substitute to stop UTIs because there is no collateral damage, such as an increase in resistance, and patients prefer natural therapies.[7]

The interpretation of the findings from this meta-analysis necessitates careful consideration and additional deliberation owing to several constraints. The present meta-analysis is characterized by a relatively limited number of studies, specifically six, that examine the impact of non-biotic therapies on the prevention of UTI. This small sample size may compromise the strength and reliability of the findings, thereby diminishing the statistical power of the analysis. In order to conduct a more comprehensive evaluation, it is imperative to conduct large-sample, multicenter studies in the future. Furthermore, a significant degree of heterogeneity was seen among the studies included in the analysis. This heterogeneity can be attributed to several factors such as the specific elastography technique employed, the design of the research, the prevalence of the disease, and several additional covariates that were not documented in the included studies.

Conclusion

Non-antibiotics interventions have a significant effect in preventing recurrent UTI in women with symptoms of acute UTI, with or without a history of recurrent UTI. Overall, non-antibiotics interventions such as cranberry extract, D-mannose, NSAIDs, and herbal medicines can prevent recurrent UTI, and the results appear to be better or the same as antibiotic interventions. Meta-analyses should consider a small number of studies with varying study designs and quality, as well as small overall sample sizes.

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Author Contributions

AMM was responsible for searching and reviewing the literature one by oneafter obtaining the relevant literature, preparing the research manuscript, including the abstract, introduction, research methods, and research citations. AS was responsible for extracting the data and structuring the research results, discussion, and conclusion.

Conflict of interest

The authors declare no conflict of interest.

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