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Consumption of cranberry and probiotics as a natural remedy for urinary tract infections

Dominika Orłowska

Trauma Surgery Hospital of St. Anna, Barska street 16/20, 02-315 Warsaw, Poland dominikarachwal98@gmail.com; ORCID: 0009-0001-9104-0459

Karolina Zalewa

Independent Public Hospital No. 4 in Lublin, Jaczewskiego street 8, 20-954 Lublin, Poland zalewa.karolina@gmail.com; ORCID: 0009-0004-0610-6866

Joanna Olszak

Independent Public Hospital No. 4 in Lublin, Jaczewskiego street 8, 20-954 Lublin, Poland, asia.olszak663@gmail.com; ORCID: 0009-0004-0211-1449

Lidia Bartoszek

National Medical Institute of the Ministry of the Interior and Administration, Wołoska street 137, 02-507 Warsaw, Poland, lidka.bartosz@gmail.com; ORCID: 0009-0000-1656-7325

Wojciech Kapłan

Chair and Department of Psychology, Medical University of Lublin, Chodźki street 7, 20-093 Lublin, Poland, wojtek.kaplan@gmail.com; ORCID: 0000-0003-2270-0318

ABSTRACT

Introduction and Purpose

Urinary tract infections (UTIs) are a prevalent health issue caused primarily by uropathogenic Escherichia coli (UPEC) and other pathogens, affecting millions annually. These infections encompass lower (cystitis) and upper (pyelonephritis) tract manifestations, presenting with symptoms ranging from dysuria to severe complications like sepsis. Traditional antibiotic treatments, while effective, are increasingly challenged by resistance and adverse effects, necessitating exploration of alternative therapies. Cranberry-derived compounds, particularly proanthocyanidins (PACs), are known for their ability to inhibit bacterial adhesion to uroepithelial cells, a critical step in UTI pathogenesis. Clinical studies suggest that cranberry products may reduce UTI incidence, especially in vulnerable populations such as women and catheterized patients. Probiotics, specifically lactobacilli, contribute to urogenital health by competing with uropathogens for epithelial cell binding sites and producing antimicrobial substances. Emerging research highlights the potential synergistic benefits of combining cranberry extracts with probiotics in UTI prevention strategies.

Material and Methods

This review is based on articles from the PubMed database, covering the years 2004-2023, using keywords: urinary tract infections, cranberry, probiotics, E. Coli, antibiotics

Conclusions

Cranberry products and probiotics offer promising non-antibiotic approaches for UTI prevention, targeting fundamental aspects of bacterial pathogenesis. While preliminary studies indicate promising outcomes, rigorous clinical trials are essential to validate these combinations and optimize therapeutic protocols. Further research is warranted to identify specific bioactive compounds within cranberries, standardize probiotic formulations, and establish comprehensive guidelines for their clinical use in UTI management.

Keywords: urinary tract infections, cranberry, probiotics, E. Coli, antibiotics

Introduction

Urinary tract infections (UTIs) are a common and significant public health issue caused by various pathogens, including E. coli, K. pneumoniae, P. mirabilis, E. faecalis, and S. saprophyticus. UTIs can be categorized as uncomplicated or complicated, as well as lower UTIs (cystitis) and upper UTIs (pyelonephritis). Cystitis is more common in females and associated with risk factors such as prior UTI, sexual activity, vaginal infection, diabetes, obesity, and genetic susceptibility. Uncomplicated UTIs occur in healthy individuals without urinary tract anomalies, while complicated UTIs occur in those with factors like urinary obstruction, immunosuppression, renal failure, pregnancy, and the presence of foreign bodies like catheters or calculi [1].

UTIs, including cystitis, are commonly characterized by symptoms such as painful urination (dysuria), urinary frequency, urinary urgency, suprapubic pain, and hematuria (bloody urine). In severe cases, where the pathogens causing cystitis spread through the ureters to the kidneys, patients may also experience fever, nausea, flank pain, and costovertebral angle tenderness. UTIs can result in kidney failure or sepsis, when bacteria invade the bloodstream, and therefore, can be a serious public health problem. Uropathogenic Escherichia coli (UPEC) is the most common causative agent for both uncomplicated and complicated UTIs [2]. Uropathogenic E. coli (UPEC) is responsible for approximately 90% of urinary tract infections in individuals with normal anatomy. UPEC uses P fimbriae (pyelonephritis associated pili) to bind urinary tract urothelial cells and colonize the bladder, and produces alpha- and beta-hemolysins that cause lysis of urinary tract cells [3]. After binding to urinary tract urothelial cells, uropathogenic E. coli (UPEC) often form biofilms that enable colonization and persistence in the urinary tract [4]. Routine use of antibiotics to treat UTI is considered to be very effective, while they can cause emergence of resistance among uropathogens, balance damage in intestinal microbiota and other side effects. In connection with this different alternatives such as the use of antiadhesive components, probiotics or vaccines have been investigated and the need to search new, natural therapies for this pathology is growing [5]. Although the cranberry has been commonly used for UTIs prophylaxis, according to several studies, the efficacy of cranberry supplementation has not yet been proved. Cranberries are rich in phytochemical compounds, such as A-type proanthocyanidins (PACS), anthocyanins, benzoic acid and ursolic acid. Polyphenols contained in cranberries are reported to play the major role in preventing from adhering

uropathogens, particularly Escherichia coli, to uroepithelial cell receptors [4]. The following review is based on recent scientific publications and is intended to summarize all aspects related to the protective effects of cranberry against urinary tract infections. In particular, the anti-adhesive activity of cranberries is discussed, which is considered to be the main mechanism involved in the prevention of UTIs.

Table 1. Risk factors of urinary tract infections.

Uncomplicated UTI	**Complicated UTI**
• Female gender; • Older age; • Prior UTIs; • Sexual activity; • Vaginal infection; • Diabetes; • Obesity; • Genetic susceptibility.	• Urinary tract abnormalities; • Urinary obstruction; • Urinary retention caused by neurological disease; • Immunosuppression; • Renal failure; • Renal transplantation; • Pregnancy; • Nephrolithiasis, urolithiasis; • Indwelling catheters; • Antibiotic exposure.

Urinary tract infections – mechanisms of pathogenesis.

The most common cause of UTI is an increase in the number of faecal microorganisms in the urinary tract, but there are also other risk factors such as direct contact or faecal-oral transmission. Women are more susceptible to this infection due to their anatomy, female urethra is shorter than the male. The imbalance of vaginal microbiota impact on a decrease in the protection of the vaginal mucosa against colonisation by pathogens and as a consequence, their ascending into the urinary system. Reducing the number of commensal lactobacilli creates favourable conditions for the multiplication of pathogens, among others bacteria from the Coli group. Studies have shown that patients suffering from recurrent UTIs were depleted

of Lactobacillis. The homeostasis disorder is associated with postmenopausal period, recurrent infections of the genitourinary system and genetic predispositions [6,7]. The main factor initiating UTI pathogenesis is adherence. Uropathogenic Escherichia coli (UPEC) residing in the gastrointestinal tract, perineum or vagina contaminates periurethral area and adhere to the surface of superficial urotheliocytes using pili and adhesins [1].

Individual bacteria invade umbrella cells and multiply to form biofilm-like intracellular bacterial communities (IBCs). Following internalization, they can evade mechanical and Toll-Like receptor 4 (TLR-4)-mediated immunological clearance mechanisms by the host. The bacteria bind to neighbouring cells to start the next cycle of infection using the filaments that come out of the urothelium cells into the bladder lumen [8].

Microbiology – uropathogenic Escherichia coli.

Many species of bacteria colonize the urinary tract without giving any symptoms. Therefore in many cases the uninfected urinary tract is not sterile in healthy individuals. Gram-negative as well as Gram-positive bacteria and certain fungi cause UTIs but the most common is uropathogenic Escherichia coli (UPEC). Etiologic agents vary according to age, sex, and underlying pathology, but, the most prevalent after UPEC for uncomplicated UTIs Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp [1].

UPEC uses a vast range of virulence factors to colonize the bladder during UTI and overcome the host's immune response. Fimbriae or adhesins, located on the bacterial wall, help UPEC bind to uroepithelial receptors. Depending on environmental changes such as temperature, osmolarity, pH, and nutrient availability, UPEC can modify binding features of adhesins. An increased adherence of UPEC to urothelium was observed in recurrent UTIs. Fimbriae type 1 and type P are the most common adhesins and most frequently take part in pathogenesis of cystitis [5].

Type 1 pili recognizes mannosylated uroplakins in the bladder – FimH-binding transmembrane protein and initiate colonization and invasion into facet cells. This triggers a signal transduction cascade that activates Rho GTPases, to cause actin rearrangement and

internalization of bacteria, which allows to evade host defences and create antibiotic-resistant strains [1,5]. Production of toxins, including α-hemolysin, secreted autotransporter toxin, plasmid-encoded toxin, Shigella enterotoxin-1 and arginine succinyltransferase, cytotoxic necrotizing factor1, cytolysin A, vacuolating autotransporter toxin and iron-chelating factors (siderophores) are other virulence factors that change E.coli into uropathogen. Capsule and lipopolysaccharides located on a bacterial surface can provide antiphagocytosis and antibactericidal complement activity [5].

The understanding of pathogenesis and virulence factors is extremely important in searching more precise molecular diagnosis and the development of alternatives strategies to antibiotic treatment using therapies based on prophylaxis of urinary tract infections [5].

Cranberries – origin.

Cranberries (Vaccinium macrocarpon) are a uniquely American fruit that grow in wetlands. Cultivation of cranberries in the United States dates back to the 19th century when they were exported to Europe. For Native Americans, cranberries were an important source of vitamin C and had medicinal properties, especially for urinary tract infections. [9,10,11].

Cranberry in UTIs Prophylaxis.

Due to the rise in antibiotic resistance and recurrence of urinary tract infections, there has been growing interest in alternative therapeutic approaches based on anti-adhesive activity. As a part of alternative medicine, cranberries in various forms such as fresh or dried fruits, juices, extracts, and tablets are recommended for consumption. Research suggests that cranberry consumption can lower the incidence and recurrence of UTIs, as well as alleviate the severity of symptoms and reduce bacterial adhesion to the urinary tract epithelium [12].

Numerous epidemiological and intervention studies have shown that cranberry products can be effective in preventing urinary tract infections (UTIs). They found that consuming cranberry-containing products reduced the risk of developing UTI by 30% in susceptible populations. Subgroup analysis suggested that cranberry-containing products may be more effective in cranberry juice users, and those using cranberry-containing products more than twice daily. The studies concluded that cranberry intake can prevent UTIs in susceptible populations, particularly for women with recurrent UTIs, children, and patients using indwelling catheters or after elective gynaecologic surgery. However, the exact mechanism behind the protective effects of cranberries against UTIs is still not fully understood. The

study also suggests that cranberry juice might be more favourable than cranberry in capsules or tablets, despite the possibility of adverse effects due to high sugar content [4, 5,12,13].

In recent decades, it was believed that flavonoids such as proanthocyanidins (PACs), were responsible for the preventive effects against UTIs [13]. Low levels of PACs have been detected in urine after cranberry intake. Furthermore, colon microbiota catabolizes PACs to generate bioactive phenolic metabolites that can be further absorbed or excreted in feces and urine. These metabolites include single flavonoids, various conjugates of phenolic acids (e.g., phenylpropionic, phenylacetic, benzoic, and cinnamic acids), and other microbial metabolites such as phenyl-γ-valerolactones, which have been identified in urine collected after cranberry intake. Consequently, these phenolic metabolites may be the compounds responsible for the preventive actions of flavonoids and phenolic acids found in cranberry against UTIs [5].

Furthermore, cranberries contain different phytochemicals, such as quinic, malic, shikimic, and citric acids, which may also result in antibacterial effects as it has been observed in an experimental mouse model of urinary tract infection [14]. Low pH of 2.5 is another important characteristic of cranberry juice. Other suggested active compounds against UTIs is Vitamin C (ascorbic acid) and fructose, which take part in acidification of urine [5].

Antiadhesive effect of cranberry.

The mechanisms underlying the potential preventive effects of cranberry consumption against urinary tract infections (UTIs) are not yet fully established, and several hypotheses have been proposed. Some researchers have suggested that cranberry polyphenols, especially their metabolites produced by gut bacteria, may inhibiting the attachment of uropathogenic Escherichia coli (UPEC) to uroepithelial cells and thus preventing the colonization. One of the studies investigated the antiadhesive activity of cranberry polyphenols and their microbial-derived metabolites against Gram-negative and Gram-positive bacteria in T24 cells. The results showed that A-type procyanidins and cinnamtannin B-1 exhibited antiadhesive activity, while B-type procyanidins did not. Metabolites such as hippuric acid and α hydroxyhippuric acid also showed effective results. Sulfation of cranberry-derived metabolites increased their antiadhesive activity, but methylation decreased it. These findings suggest that cranberry polyphenols and their metabolites have potential as a preventive measure against UTIs [15].

It has been found that the antiadhesive effect of cranberry extract against uropathogenic Escherichia coli (UPEC) cannot be attributed to a single compound or fraction. B-ring substituted flavones and flavonols derived from cranberry have been found to contribute to the antiadhesive activity against Uropathogenic Escherichia coli (UPEC) by inhibiting the interaction between FimH and the bladder epithelium of the host cell. Male volunteers who were treated with cranberry showed a significant interaction with the mannose binding domain of type-1 fimbriae, as indicated by urine samples. This interaction was found to be correlated with the amount of Tamm-Horsfall Protein present in the samples [16].

As part of a biomedical study, urine samples were collected from 16 volunteers (8 male, 8 female) who consumed 900 mg/day of cranberry extract for 7 days. These urine samples were analysed for their potential antiadhesive activity against uropathogenic Escherichia coli (UPEC) using ex vivo experiments. Protein analysis of the urine samples revealed an increase in the levels of Tamm-Horsfall protein (THP, also known as uromodulin) in the samples that exhibited antiadhesive activity. The amount of THP in the urine samples was found to be positively correlated with the inhibition of bacterial adhesion. THP is a mannosylated glycoprotein that interacts with FimH of UPEC, which decreases the interaction with uroplakin, a transmembrane protein of urothelial lining cells that binds to FimH. The data suggests that cranberry's antiadhesive effect is not only due to the direct inhibition of bacterial adhesins but also because it induces THP in the kidney [17].

Table 2. Adherence Inhibition (%) of E. coli ATCC® 53503™ to bladder uroepithelial cells by cranberry phenolic compounds and their metabolites [5].

	Concentration (µM)		
	100	**250**	**500**
Flavon-3-ols			
Cinnamtannin B1	1,05	4,11	13,95*
Procyanidin A2	23,67	30,7	54,5 **
Procyanidin B2	6,79	10,0	-14,7
Simple phenols			
1,2-Dihydroxybenzene (catechol/pyrocatechol)	17,0 *	26,0 *	33,2 **
1,3,5-Trihydroxybenzene (phloroglucinol)	-8,53	-17,6	-8,15
Benzoic acids			
Benzoic acid	16,5 *	23,3 **	32,2 **
3-Hydroxybenzoic acid	11,1	17,0 *	-9,7
4-Hyroxy-3-methoxybenzoic acid (vanillin acid)	18,3 **	24,9 **	29,2 **
Phenylopropionic acids			
3-Phenylopropionic acid	-11,8	14,7	12,2
3-(3-Hydroxyphenyl)-propionic acid	10,2	18,6	30,5 *
3-(3,4-Dihyroxyphenyl)-propionic acid 3-*O*-sulphate sodium salt	6,52	11,22	21,0 *
Hippuric acids			
Hippuric acid	15,6	14,9	25,5
α-Hippuric acid	20,8	23,01	20,0

* Mean significantly different drom zero ($p < 0,05$) using a one-sample t-test.
** Mean significantly different drom zero ($p < 0,01$) using a one-sample t-test.

Alternative mechanisms of cranberry effectiveness against UTIs.

Recent research highlights the critical role of gut microbiota in maintaining homeostasis and regulating health and disease throughout the body [18]. While microbial profiles and metabolites from the gut and other organs may influence urinary microbiota, the connection between these organisms and urogenital health remains incompletely understood. It is now recognized that the urinary tract hosts a complex microbial network that is distinct from gut populations. Disruptions in specific bacterial communities can greatly affect urologic health due to their metabolic activities and other contributions. Unlike the urine of healthy, asymptomatic individuals, an altered microbiome with specific dominant urotypes has been observed in those with functional urinary tract disorders [19].

Given the broad influence of gut microbiota on the body, another hypothesis regarding the mechanisms of cranberry flavonoids and phenolic acids against UTIs is that cranberry components (A-type proanthocyanidins and their metabolites) interact with gut microbiota, modulating its composition and functionality to prevent microbial dysbiosis [20].

The effectiveness of cranberry polyphenols, such as flavonoids and phenolic acids, against UTIs may be affected by a "two-way interaction" between these compounds and the gut microbiota [21]. This means that while the gut microbiome metabolizes cranberry polyphenols, the cranberry compounds and their microbial metabolites also influence the gut microbiota, preventing the intestinal colonization by uropathogens. Similar interactions have been noted with other foods, such as tea and wine polyphenols [5].

In conclusion, the beneficial effects of cranberries against UTIs are modulated by the intestinal microbiota’s ability to metabolize cranberry flavonoids and phenolic acids into bioactive metabolites. This is exemplified by phenyl-γ-valerolactones, one of the most abundant metabolites in the bioactive urine fraction after cranberry consumption, which has shown antiadhesive activity in vitro [22]. Therefore, individual differences in the preventive effects of cranberries against UTIs may be partly due to variations in intestinal microbiota composition among individuals.

Probiotics in UTIs prevention

Probiotics, defined as live microorganisms believed to confer health benefits, represent a promising approach to bolstering the body's natural defenses against infections by enhancing the normal bacterial flora. In the context of women's health, the vagina maintains a delicate balance maintained by Lactobacillus species, which play a crucial role in preventing colonization by pathogenic organisms responsible for urinary tract infections (UTIs). Factors such as sexual intercourse, spermicide use, and menopause contribute to reduced levels of vaginal lactobacilli, thereby increasing susceptibility to UTIs [23].

Lactobacilli exert their protective effects through multiple mechanisms. They compete with uropathogens for adhesion receptors on vaginal epithelial cells, thereby preventing initial binding and colonization. Additionally, lactobacilli produce various antimicrobial substances such as hydrogen peroxide, lactic acid, and bacteriocins. These substances create an acidic environment hostile to bacterial growth and inhibit the formation of bacterial biofilms, which are communities of bacteria protected by a matrix that enhances their resistance to antibiotics and immune defenses [24]

Numerous in vitro studies have demonstrated that different Lactobacillus strains, including L. salivarius, L. plantarum, and L. acidophilus, inhibit the adherence of various uropathogenic bacteria, such as E. coli, Staphylococcus epidermidis, and Enterococcus faecalis, to bladder cells like T24 [25,26]. For instance, Lactobacillus crispatus has been found to excel in blocking uropathogen adherence to vaginal epithelial cells, while other strains like Lactobacillus jensenii demonstrate potent direct inhibition of uropathogen growth. Moreover, studies have highlighted that not all Lactobacillus strains produce the same antimicrobial substances; for example, only certain strains produce hydrogen peroxide or bacteriocins. [27]

Beyond their direct antimicrobial actions, lactobacilli have been implicated in modulating the host immune response. They can activate pathways such as the Toll-like receptor (TLR) pathway, leading to the production of immune mediators like interleukins that help mount a defense against uropathogens. [28] Specific strains, such as Lactobacillus rhamnosus GR-1, have been shown to enhance pathways like nuclear factor-κB (NF-κB), which are crucial in the immune response against uropathogenic bacteria. [29]

Recent advancements have seen the introduction of new products combining cranberry extracts with Lactobacillus probiotics in the market, often without sufficient scientific validation. While some studies have reported positive outcomes from combined cranberry-

probiotic interventions for UTI prevention [30,31], comprehensive research into these combinations is warranted.

Despite promising in vitro results, the clinical efficacy of probiotics in preventing UTIs varies among studies and depends on factors such as the strain of Lactobacillus used and the specific characteristics of the patient population. Further research, particularly in controlled clinical trials, is essential to determine the optimal strains, dosages, and administration protocols for probiotics in UTI prevention and treatment. Understanding these factors will be crucial for harnessing the full therapeutic potential of probiotics in promoting urogenital health and combating UTIs effectively [5,23].

Conclusion

Cranberry consumption has been widely recommended for the prevention of urinary tract infections (UTIs). This review highlights the role of cranberry polyphenols in UTI prevention and treatment, and discusses recent scientific findings. The review notes that while UPEC is a common cause of UTIs, other pathogens such as Klebsiella pneumoniae, Enterococcus, and Staphylococcus also play a significant role. Additionally, complicated UTIs caused by UPEC is a major concern in healthcare. This review concludes that cranberry may be a promising adjuvant therapy for preventing UTIs in susceptible individuals. Cranberry products have been identified as a potential alternative to antibiotics in the treatment of UTIs, supported by evidence from clinical trials. However, the effectiveness of cranberry products may vary depending on individual cases, as well as the type and dosage of the product used. Recent researches have revealed new factors that could contribute to the effectiveness of cranberry polyphenols in preventing urinary tract infections (UTIs). It is not clear which specific cranberry components are responsible for its protective effects against UTIs, and further investigation is needed to identify other potential mechanisms in addition to antiadherence activity.

Author`s contribution:

Conceptualization: Dominika Orłowska, Karolina Zalewa, Joanna Olszak, Lidia Bartoszek.

Methodology: Dominika Orłowska, Karolina Zalewa, Joanna Olszak, Lidia Bartoszek.

Software: Wojciech Kapłan,

Check: Dominika Orłowska, Lidia Bartoszek, Wojciech Kapłan,

Formal analysis: Joanna Olszak, Karolina Zalewa, Wojciech Kapłan,

Investigation: Wojciech Kapłan, Joanna Olszak,

Resources: Joanna Olszak, Karolina Zalewa, Wojciech Kapłan,

Data curation: Dominika Orłowska, Lidia Bartoszek, Wojciech Kapłan

Writing -rough preparation: Dominika Orłowska, Lidia Bartoszek, Joanna Olszak

Writing -review and editing: Dominika Orłowska, Lidia Bartoszek, Karolina Zalewa

Supervision: Joanna Olszak, Dominika Orłowska

Project administration: Joanna Olszak, Karolina Zalewa,Wojciech Kapłan

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