REVIEW ARTICLE

Role of Cranberry in Urinary Tract Infections

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ABSTRACT

Urinary tract infection (UTI), both symptomatic and asymptomatic, occurs very frequently in the population, especially among patients with diabetes. With the advent of newer medications such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, there is greater focus on this disease. Cranberry products have been used earlier in various forms as a natural remedy for this disease. Certain compounds like flavonoids, distinctive proanthocyanidins with prominent active ingredients like phenolic acid inhibit the adherence of fibrillae of *Escherichia coli* to the urothelial cells lining the urinary bladder. This article takes a brief look at the disease and the role of cranberry as a natural remedy for UTI.

Keywords: Urinary tract infection, cranberry, diabetes mellitus, recurrent UTI treatment

Urinary tract infection (UTI) is very commonly seen in our populations, especially in patients with diabetes. With the advent of newer oral hypoglycemic agents (OHAs) like sodium-glucose co-transporter 2 (SGLT2) inhibitors, the incidence and focus on this disease has increased.[1]

In fact, 12% of men and 50% of women will experience UTI at some point in their lives. Additionally, up to 30% of young women experience recurrent UTIs, which can have a negative impact on their quality of life.[2] Recurrent and persistent UTI has been seen in patient population and the role of natural food substances such as cranberry in UTI has been explored.[3]

Cranberry juice may delay the onset of chronic diseases, lessen their severity and guard against oxidative damage brought on by aging. Cranberry juice is safe for majority of healthy people, but it can interact with several medications.[3]

THE CRANBERRY FRUIT

Cranberry is scientifically known as *Vaccinium macrocarpon*. The name "cranberry" originates from the word "craneberry" and refers to the shape of its flower,[4] which bears a resemblance to head and neck of sand crane. Cranberries belong to the Ericaceae family and typically thrive in wet forests characterized by acidic swamps containing ample peat moss.[5]

Large cranberry, Indian cranberry and American cranberry are all synonyms for cranberry. The following 9 varieties of cranberries are available: Ben Lear, Crimson Queen, Early Black, Franklin, Howes, McFarlin, Pilgrim, Scarlet Knight and Stevens.[6] Cranberries are harvested for use in products throughout September and October.[3]

Native Americans did not grow plants, but they did collect berries and use them in their cuisine. They were the first to employ maple sugar to sweeten cranberry juice.[7]

Cranberry contains 10% carbohydrates and about 80% water by weight along with flavonoids, anthocyanins, catechin, triterpenoids, organic acids and just a little quantity of ascorbic acid. Citric, malic and quinic acids make up the majority of organic acids.[8]

There has been a significant focus on flavonoids, particularly colored anthocyanins and distinctive proanthocyanidins with prominent active ingredients include phenolic acids, benzoates, hydroxycinnamic acids, terpenes and organic acids for their role in inhibiting the adherence of *Escherichia coli* to the urothelial cells of the urinary bladder.[8]

BENEFICIAL PROPERTIES OF CRANBERRIES

Cranberries promote good oral health. They are used in the treatment of bladder and renal problems, urethritis and

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help people lose weight. They also help reduce pulmonary inflammation.[7]

Cranberries contain various antioxidants such as anthocyanins, proanthocyanidins and quercetin that may be beneficial for heart health.[9]

They are one of the best food sources for ursolic acid, which has potential anti-cancer, anti-inflammation and antioxidant properties. It has also been seen to be particular useful in prostate cancer.[10]

Cranberry juice helps in managing UTIs. The proanthocyanidins in cranberries have natural bactericidal effects and may inhibit the adherence of *E. coli* to the inner membrane of bladder and urinary system preventing infection.[11]

Cranberries stop kidney stone production by preventing the build-up of calcium oxalate crystals.[12]

Common cold symptoms can be managed using cranberries and honey.[13] Because of its antioxidant and anti-aging characteristics, applying cranberries as a face pack also aids in protecting the skin against the damaging effects of free radicals.[14]

THE URINARY BLADDER

Although the shape and size of the urinary bladder varies from person to person and is significantly influenced by the amount of urine that it holds, it has a broadly spherical shape.[15] The urinary bladder is situated in the pelvic cavity above the pelvic reproductive organs and in front of rectum.[16] It shares the small pelvic cavity with the uterus, which sits above and behind it, because the urinary bladder is somewhat smaller in females. The enlargement of the urinary bladder is severely limited by the enlarged uterus during pregnancy.[17]

There are various different tissue layers that make up the urinary bladder.[18] The mucosa layer that lines the hollow lumen of the bladder is its deepest layer. The mucosa of other hollow organs is not as flexible as the transitional epithelial tissue that lines the urinary bladder, which can hold a lot of urine.[19]

UTI

Any region of urinary system can become infected, which is known as UTI. The bladder and urethra, which are parts of lower urinary tract, are most commonly infected.[20]

Women are more likely than men to experience a UTI.[21] A bladder specific infection may be uncomfortable and unpleasant. However, if a UTI spreads to the kidneys, major health issues like pyelonephritis and pyoma may occur.[22]

For young boys, older men and women of all ages, UTIs are a significant cause of morbidity. In addition to frequent recurrences, other serious repercussions include pyelonephritis with sepsis, renal injury in young infants, preterm birth and difficulties brought on by constant antimicrobial usage, such as high-level antibiotic resistance and *Clostridium difficile* colitis.[23]

Common Pathogens Causing UTI

Both Gram-positive and Gram-negative bacteria, as well as some fungi, can cause UTIs, which are among the most prevalent bacterial infections.[24]

E. coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis and *Staphylococcus saprophyticus* are the microorganisms most frequently responsible for UTI.[25] Uropathogenic *E. coli* is the most common causative agent for both simple and complex UTIs.[26]

Symptoms of UTI

The symptoms associated with a lower UTI include increased frequency of urination without passing a significant amount of urine, a burning sensation during urination, cloudy urine, a change in the color of urine, a strong odor and pain while urination.[27]

The symptoms indicative of an upper UTI include pain and tenderness in upper back area, accompanied by chills, headache, intermitted fever, feelings of nausea, vomiting and presence of blood in urine.[8]

Pathogenesis of UTI

Uropathogens that live in the gut contaminate the periurethral region and are able to colonize the urethra to cause uncomplicated UTI. The superficial umbrella cells are colonized and invaded as a result of their subsequent passage to the bladder and the expression of pili and adhesins.[25] Extracellular bacteria are removed by host inflammatory responses, including neutrophil infiltration. Some bacteria multiply and develop biofilms in order to avoid the immune system, either by attacking host cells or through structural modifications that make them resistant to neutrophils.[28]

The toxins and proteases secreted by these bacteria cause host cell destruction, releasing vital nutrients that aid in bacterial survival and colonization of the kidneys. This causes host tissue damage and the generation of bacterial toxins. UTIs can eventually result in serious health problems if they are not treated.[29]

These initial steps of periurethral colonization, advancement to the urethra and migration to the bladder also occur in complex UTIs. The bladder must be weakened for the viruses to invade the body though. Catheterization is the most prevalent reason for a weakened bladder. Because catheterization triggers a strong immune response, fibrinogen builds up on the catheter creating perfect habitat for uropathogens that express fibrinogen-binding proteins to attach.[30]

Urinary pH

The pH of urine falls within the range of 6.0 to 7.5, while values between 4.5 and 8.0 are typically not reason for anxiety; 1 being the most acidic and 14 being the most basic on the pH scale.

The urea-splitting bacteria *Proteus*, *Klebsiella* or *Ureaplasma urealyticum* are frequently found in urine with pH of 8.5 or 9. An alkaline urine pH can indicate struvite kidney stones or infection stones.[31]

The nitrate test is considered the most reliable method for detecting the presence of bacteria in urine, as bacteria need time to convert nitrates to nitrites, which takes approximately 6 hours. This is why urologists often request testing of the first urine sample in the morning, especially in males. The nitrate test has a specificity of over 90% meaning it is highly accurate in identifying the presence of bacteria. However, it is worth nothing that certain type of bacteria, such as *Enterococcus*, *Pseudomonas* and *Acinetobacter*, do not convert nitrates despite being implicated in complicated UTIs.[32]

Duration and Time of Action of Bacteria in UTIs

UTI can be influenced by multiple factors, including diabetes, the use of drugs like SGLT2 inhibitors, anatomical considerations such as short ureters, infrequent voiding of urine and a history of recurrent UTIs. Additionally, factors such as particular bacteria causing the infection, the individual's immune response and the efficacy of treatment play significant roles in UTI development and management.[30]

Typically, bacteria enter the urinary tract through the urethra and begin to multiply, leading to infection. The time of infection refers to the period during which bacteria actively replicate and cause symptoms. This period can range from a few hours to a few days, depending on bacterial load and the susceptibility of the individual.

If left untreated, a UTI can persist and potentially spread to the upper urinary tract, such as the kidneys, leading to a more severe infection. In some cases, the bacteria can form biofilms or hide within the urinary tract, making eradication more challenging.[33]

Once appropriate treatment, such as antibiotics, is initiated, the duration of the infection can vary. In many cases, symptoms may start to improve within a few days of treatment. However, it is crucial to complete the full course of antibiotics as prescribed by a health care professional to ensure complete eradication of the bacteria and prevent recurrence. It is important to note that the duration of a UTI can vary from person to person and seeking medical advice is essential for proper diagnosis, treatment and monitoring of the infection.[34]

MECHANISMS OF ACTION OF CRANBERRY

Inhibition of Bacterial Adhesion

Proanthocyanidins have anti-adhesive properties and might help in reducing the probability of bacteria, particularly *E. coli*, attaching to the walls of the urinary tract. They make it more difficult for the bacteria to create an infection by interfering with their ability to bind to the lining of the urinary system.[35]

Acidification of Urine

Consuming cranberry products may cause urine to become more acidic as cranberries are acidic in nature. By creating a less favorable environment for the bacteria to grow, the increased pH may be able to reduce the risk of infection.[36]

Anti-inflammatory Effects

Cranberries contain a number of phytochemicals, including flavonoid and anthocyanins, which have anti-inflammatory properties. These phytochemicals help in lowering urinary tract inflammation, which could assist in preventing UTI symptoms.[37]

Immunological Effects

The high content of antioxidant phenolic compounds in cranberries assists in the natural antioxidant defense system of an individual by preventing formation of reactive oxygen specific. They also stimulate immune cells and promote the production of cytokines by modulating the immune system; cranberry may support the body to fight off UTI more effectively causing bacteria.[38]

SIDE EFFECTS

The potential side effects of consuming high amounts of cranberry juice or supplements, particularly in people prone to these illnesses, include gastrointestinal irritation and increased chances of kidney stones.[39]

DYSURIA AND HEMATURIA

Dysuria and hematuria are two common symptoms of UTIs.

Dysuria: Urination that is difficult and uncomfortable is called dysuria. Typically, the patient presents with lower UTI symptoms like cystitis. Infection can produce inflammation and irritation, which can make urinating feel hot or stinging. Also, an insatiable desire to urinate may be indicative of dysuria.[40]

Hematuria: Blood in urine is termed hematuria, which typically occurs due to UTI and inflammation. The infection can irritate the blood vessels in the urinary system, leading to leakage of blood. The severity of hematuria can vary, ranging from tiny amounts of blood visible only through a microscopic to noticeable amounts that cause the urine to appear pink, red or brown in color.[41]

When these symptoms occur together, especially when accompanied by other UTI-related symptoms like frequent urination, urgency, cloudy urine and lower abdominal pain, strongly indicate the presence of a UTI.[42]

POST-COITAL DYSURIA

Post-coital dysuria refers to the condition where an individual experiences pain or discomfort during or after sexual intercourse, specifically in the urinary tract. It is often characterized by symptoms such as burning or stinging sensation while urinating, increased frequency or urination and general discomfort in the pelvic region following sexual activity.[43]

Post-coital dysuria can have other potential causes such as:

- Irritation or injury to the urethra during vigorous or rough sexual activity, resulting in pain or discomfort during urination.
- Allergic reactions to certain lubricants, latex condoms or other materials used during sexual activity, leading to ureteral irritation or inflammation and subsequent dysuria.
- Vaginal infections like yeast infections or bacterial vaginosis, which can cause inflammation and irritation in genital area resulting in dysuria after intercourse.[44]

DIABETES AND UTI

Individuals with diabetes have a higher risk of developing UTIs compared to those without diabetes. Various factors contributing to this increased risk include immune system dysfunction, elevated blood sugar levels and urinary tract abnormalities. Patients with diabetes may experience more frequent, persistent and severe UTIs. Proper blood sugar control, good personal hygiene and prompt medical attention are essential for managing UTI risk in diabetes.[45]

Frequency of UTI in Diabetes

Frequency of UTIs in individuals with diabetes can vary depending on various factors such as age, sex, duration of diabetes and glycemic control. A prospective study investigated the prevalence of asymptomatic bacteriuria in women with diabetes and the likelihood for asymptomatic bacteriuria in women with diabetes was increased by 1.9-fold.[46]

ASYMPTOMATIC AND SYMPTOMATIC UTIs

UTIs can be classified into two main categories:

- Symptomatic UTIs
- Asymptomatic UTIs

Symptomatic UTIs: Symptomatic UTIs present with symptoms such as constant and pressing urge to urinate, dysuria, a painful or uncomfortable micturition, sensation of incomplete emptying of bladder, pelvic or lower abdominal pain, urine that is cloudy, red or has a strong odor, burning sensation in the urinary tract, tiredness, fever or chills.[47]

Asymptomatic UTIs: Asymptomatic UTI is a condition in which bacteria are present in the urinary tract without causing noticeable symptoms. In such cases, individuals may be unaware that they have an infection unless it is detected through a urine test. Asymptomatic UTIs is more commonly found in certain populations, such as the elderly, individuals with indwelling urinary catheters, or those with compromised immune system.[48] It is important to remember that, despite the absence of overt symptoms, asymptomatic UTIs can still be dangerous if left untreated. The presence of bacteria in the urinary tract increases the risk of problems, such as kidney damage or infection spreading to the kidneys.[49]

CRANBERRY AND UTI

Cranberry products such as cranberry juices or supplements, have been used in the treatment of urinary infections. It is important to note that cranberry products should not be considered a substitute for appropriate medical treatment for UTIs. It is crucial to seek medical attention and follow the prescribed treatment, which usually involves antibiotics.[50]

CONCLUSION

Cranberry products are helpful in patients with symptomatic and asymptomatic UTIs by the action of various phenolic compounds present in this fruit. This is an insight into the occurrence of the disease and mechanisms of action of cranberry. More studies and observations are required to unlock the potential of this fruit and establish its appropriate use in patients suffering from this disease. Further assessment with well-designed randomized controlled clinical trials can further classify the use and benefit of cranberry products in UTIs.

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