

Cranberry juice extracts for prophylaxis of recurrent Urinary Tract Infection in women: A mini review

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Abstract: *The most typical bacterial infection found in women is Urinary Tract Infections (UTIs). About half of women experience UTI at least once in their lifetime, and their risk increases with age. Recurrent UTI endures a challenge to heal, as the primary treatment choice is long-term antibiotic prophylaxis, which leads to a greater risk of growing bacterial resistance. Drinking cranberry juice for the prevention of UTIs has been a traditional folk remedy for hundreds of years. Cranberry plant, Vaccinium macrocarpon, belongs to the family Ericaceae are a gathering of dwarf creeping shrubs or trailing vines up to 7 ft long. The fruit is an edible berry that is initially light green, turning bright red when ripe. The mixed content of polyphenols (proanthocyanidins, flavonols, and quercetin) accounts for the cranberry juice tartness, so a cranberry cocktail or rather a cranberry juice blend is preferred in UTI. Cranberry contains various anti-adherent traits that hinder fimbriated E.coli (Escherichia coli) from adhering to the uroepithelial cells of the urinary tract. This review stresses the clinical benefits of cranberries as a precautionary means to manage UTI and also emphasize the need for further research to clinically authenticate its real-world potency to enhance rationality.*

Keywords: *Antibacterial activity, Cranberry, E.coli, Proanthocyanidins, UTI*

1. INTRODUCTION:

In urological practice, a frequent problem encountered is recurrent Urinary Tract Infection (UTI), E.coli being responsible for most. [1] A recurrent UTI is signified by a threshold of 3 UTIs in 12 months. Bacterial reinfection or bacterial persistence serves the leading pathogenesis of recurrent UTI, with the former being the most prevalent. The predisposing factors of recurrent UTI in women are sexual intercourse, spermicidal products use, history of early age UTI, [2] pre-and post-coital voiding patterns, frequency of urination, wiping patterns, etc. Usual contributing factors among adolescent girls cover inadequate water intake, unhygienic practices while menstruation, poor personal hygiene, and toilet habits. [3] Long-term antimicrobial prophylaxis is an effective UTI management method but could result in adverse reactions and antimicrobial resistance. [4],[5] Hence, there is an increased need for alternative therapy towards UTI prophylaxis. The cranberries are non-antibiotic alternatives, which on ingestion associates to forestall urinary tract infections. [6],[7] The fruit's acid is responsible for the speculated beneficial mechanism that generates a

bacteriostatic effect in the urine. But recent studies showed that a group of proanthocyanidins (PACs) with A-type linkages exhibit the bacterial antiadhesion activity against both antibiotics susceptible and resistant strains of P- fimbriated E.coli. [8] Studies also have shown that routine cranberry juice intake is beneficial in UTI patients affected with antibiotic-resistant bacteria.

A. Cranberries

Cranberry plant, *Vaccinium macrocarpon*, belongs to the family Ericaceae. It is native to North America (most commercial farms) and is seen in the acidic swamps of humid forests. [9] Its comprises water, fructose, flavonoids, anthocyanidins, catechins, vitamin C, and triterpenoids, with iridoid glycosides accounting for their taste. The defence mechanism against the microbes requires the presence of tannins like Anthocyanidins and proanthocyanidins. [10] The proanthocyanidins (PACs) present are accountable for their intense red colour, which could also hinder the adherence of P-fimbriated E. coli to the uroepithelial cells. The fructose present in the fruit extract interferes in adhesion of type- 1 fimbriated E.coli to the uroepithelial cells, whereas vitamin C is expected to limit the urinary bacterial growth. [7],[9],[10]

B. Mechanism of action

The main protein structure related to the adhesion phenomenon of uropathogens (E.coli) to the host tissue is adhesin protein. The bacterial fimbriae possess lectins on its surface, which binds to complementary carbohydrates on the host cell's tissue surface, eventually leading to bacterial adhesion, escorted by bacterial pili. [11],[12] The adhesin proteins can either be mannose-resistant or mannose-sensitive. The type-1 pili (mannose-sensitive pili) are the ones that permit bacterial adhesion to the uroepithelial cell surfaces. The fimbriae, isolated from recurrent UTI patients, binds on glycosphingolipids of the renal cell's lipid double membrane, preceding the renal parenchymal invasion. This fimbria is termed the P-fimbriae (pyelonephritis fimbriae) and is the virulent strains of E.coli. [12],[13]

The two components in cranberries identified to restrict E. coli adhesions are fructose and PACs. Fructose inhibits the mannose-sensitive fimbriae adhesins, and proanthocyanidins inhibit the mannose-resistant adhesins of the uropathogenic E. coli bacteria. Though most fruit juices comprise fructose, only cranberries contain the second unique compound named proanthocyanidins. Proanthocyanidins show potent hindrance versus mannose-resistant adhesins formed by urinary isolates of E.coli and modest anti-adherent activity against the fecal isolates of E.coli. The anti-adhesive trait of cranberries may help prevent:

- a) E. coli from adhering to uroepithelium directly
- b) less adherent bacterial strains in the stool. [14],[15]

C. Dosage and Administration

The advised dose of cranberry products to forestall urinary tract infection is poorly defined and varies widely. A 25% pure juice is the most studied formulation for UTIs. Clinical studies suggest that a 50% reduction in the recurrences of UTIs had been noted with an everyday dose of 240-300 ml of cranberry cocktail. A twice-daily dose of cranberries (i.e., 36 mg of PACs) offers additional protection for 24 hours, suggested by a study that examined human urine followed by the cocktail consumption. [16],[17] For dried, concentrated juice extracts, recommended doses range from 600 to >1200 mg/day in two or three divided daily doses.

Cranberries are processed into various forms like juice drinks, sauce products, capsules, and tablets for consumption. Cranberry juice is available as a cocktail drink (25% cranberry juice), is a traditional choice for women seeking to prevent UTI. [11],[12] Dried cranberry extract must be handled with caution since it breaks on exposure to light, heat, etc. The

stabilizing effect of cranberry products could be enhanced with the addition of vitamins C and E. It is also recommended to take cranberries apart from meals, preferably before or two hours after meals. The dehydrated cranberry juice consumption must accompany plenty of water.

The pure juices of cranberry are too acidic and astringent, making them difficult to eat or drink, even with the sweeteners. The high withdrawal rates of cranberries are mainly due to gastrointestinal intolerance, pregnancy, unrelated infection, etc. The taste (sour and bitter) of cranberries, in particular, is a significant factor for stopping the therapy, especially in children. Studies show that patients withdrawal rate ranges from 0 to 55%. Another critical concern regarding withdrawal is its high cost, limiting the general public's acceptance. [17] Mild nausea, headaches, reflux, frequent bowel movements, glucose intolerance, and cutaneous reaction are cranberry's various side effects. Risks of thrombocytopenia, nephrolithiasis, and oxalate stones have also been reported in studies. There are shreds of evidence on interactions between warfarin and cranberry juice. When taken cranberries, patients on warfarin reported having an increase in the international normalized ratio (INR) of prothrombin time values, attributed to the cranberries effect on the CYP450 drug-metabolizing enzyme system. Death due to gastrointestinal and pericardial hemorrhage is also reported. [10],[13],[18]

2. CONCLUSIONS

Many clinical investigations propose the potential benefits of cranberry juice on limiting UTI in the general population. The report's most robust evidence is available for sexually active adult women with prior infection to the urinary tract. Though the fruit seems useful in prophylactic recurrent UTI, it was not explicitly tested. The cranberry cocktail's palatability and the caloric load make it undesirable to some patients, notably in the long run. Capsules of the same could probably be a better-tolerated choice. Therefore, the rapid and colossal emergence of bacterial resistance (due to long-term antibiotic prophylaxis) demands future research to reinforce the cranberry's potent findings against recurrent UTI using large sample sizes.

3. LIST OF ABBREVIATIONS

UTI	:	Urinary Tract Infection
E.coli	:	Escherichia coli
PACs	:	Proanthocyanidins
P-fimbriae	:	Pyelonephritis fimbriae
INR	:	international normalized ratio
CYP450	:	Cytochrome P450 enzyme system

4. CONFLICT OF INTEREST

The author(s) declare no potential conflict of interest.

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7. REFERENCES

- [1] Paul MC, Thomas D, Joseph S, "A STUDY TO EVALUATE THE EFFECTIVENESS OF ANTIBIOTICS IN REDUCING THE RELAPSE OF UTI IN ESBL POSITIVE CASES," Adv J Pharm Life sci Res., vol. 2, pp. 40-49, 2014.

- [2] Howell AB, Fox man B, “Cranberry juice and adhesion of antibiotic resistant uropathogens,” *JAMA.*, vol. 287, pp. 3082-3083, 2002.
- [3] Indhumol TD, Pavithran S, George LK, “Effectiveness Of Structured Teaching Program On Knowledge Regarding Prevention Of Urinary Tract Infection Among Adolescent Girls,” *International Journal of Pharma Medicine and Biological Sciences.*, vol. 3, p.121, 2014.
- [4] Pullanhi U, Khan S, Vinod V, Mohan K, Kumar A, “Outcome of acute urinary tract infections caused by uropathogenic *Escherichia coli* with phenotypically demonstrable virulence factors,” *Annals of African Medicine.*, vol. 18, p.138, 2019.
- [5] Murugan S, Devi PU, John PN, “Antimicrobial susceptibility pattern of biofilm producing *Escherichia coli* of urinary tract infections,” *Current Research in bacteriology.*, vol. 4, pp. 73-8, 2011.
- [6] Svanborg C, Godly G, “Bacterial virulence in urinary tract infection,” *Infect Dis Clin North Am.*, vol. 3, pp. 513-529, 1997.
- [7] Mathers MJ, von Rundstedt F, Brandt AS, König M, Lazica DA, Roth S, “Myth or truth Cranberry juice for prophylaxis and treatment of recurrent urinary tract infection,” *Urologe A.*, vol. 48, pp.1203-1205, 2009.
- [8] Howell AB, “Bioactive compounds in cranberries and their role in prevention of urinary tract infections,” *Molecular nutrition & food research.*, vol. 51, pp.732-737, 2007.
- [9] Gupta K, Chou MY, Howell A, Wobbe C, Grady R, Stapleton AE, “Cranberry products inhibit adherence of p-fimbriated *Escherichia coli* to primary cultured bladder and vaginal epithelial cells,” *The Journal of urology.*, vol. 177, pp.2357-2360, 2007.
- [10] Lee YL, Owens J, Thrupp L, Cesario TC, “Does cranberry juice have antibacterial activity?,” *Jama.*, vol. 283, pp.1691-1691, 2000.
- [11] Valentová K, Stejskal D, Bednář P, Vostálová J, Číhalík Č, Večeřová R, Koukalová D, Kolář M, Reichenbach R, Škňouřil L, Ulrichová J, “Biosafety, antioxidant status, and metabolites in urine after consumption of dried cranberry juice in healthy women: a pilot double-blind placebo-controlled trial,” *Journal of agricultural and food chemistry.*, vol. 55, pp. 3217-3224, 2007.
- [12] Raz R, Chazan B, Dan M, “Cranberry juice and urinary tract infection,” *Clinical infectious diseases.*, vol. 38, pp. 1413-1419, 2004.
- [13] Foo L Y, Lu Y, Howell A B, Vorsa N, “The structure of cranberry proanthocyanidin Which inhibit adherence of uropathogenic P-fimbriated *Escherichia in vitro.*,” *Phytochemistry.*, vol. 54, pp. 173-181, 2000.
- [14] Hisano M, Bruschini H, Nicodemo AC, Srougi M, “Cranberries and lower urinary tract infection prevention,” *Clinics.*, vol. 67, pp. 661-668, 2012.
- [15] Schultz A, “Effect of cranberry juice and ascorbic acid in acidifying the urine in multiple sclerosis subjects,” *J Community Health Nurs.*, vol. 1, pp. 159-169, 1984.
- [16] Reid G, Hsieh J, Potter P, Mighton J, Lam D, Warren D, Stephenson J, “Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients,” *Spinal Cord.*, vol. 39, pp. 26-30, 2001.
- [17] Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B, “Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial,” *Clinical infectious diseases.*, vol. 52, pp. 23-30, 2011
- [18] Suvarna R, Pirmohamed M, Henderson L, “Possible interaction between warfarin and cranberry juice,” *Bmj.*, vol. 327, p. 1454, 2003.