



MYTH OR SCIENCE? CRANBERRIES: TO PEE OR NOT TO PEE?

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Critical Appraisal

Dysuria, polyuria, and urinary urgency. These three symptoms combined should ring a bell with all medical students: they are typically seen in patients with cystitis. Cystitis and other urinary tract infections (UTIs) are common; 40% of all women develop at least one UTI episode in their life [1]. Fortunately, an UTI can be cleared rapidly without therapeutic interference or, if needed, cured by antibiotics. "Problem solved", one could think. But with the increasing development of antimicrobial resistance among micro-organisms, it seems feasible to look for other options to treat persistent UTIs or to prevent them altogether. Cranberries are sometimes already being advised for the prevention of UTIs, but is there truly a proven benefit for its use?

Classification and epidemiology of UTIs

Urinary tract infections (UTIs) are the most common bacterial infections and the most frequent reason for women to consult their general practitioner. UTIs are more prevalent in women than in men. The incidence of cystitis in women is 70 new episodes per 1,000 women every year, whereas in men the incidence is 10 new episodes per 1,000 men every year. This can be explained by examining the anatomical differences in the urinary tract between women and men. The urethra of women is shorter, and the meatus lies in closer proximity to the anus, resulting in a higher risk of bacterial transmission from faeces to the urinary tract. Consequently, most UTIs are caused by colonisation of the bladder by the bacterial contaminant *Escherichia coli*. UTIs can be divided by anatomical location into lower UTIs and upper UTIs. In addition, UTIs can be further categorised into complicated or uncomplicated UTIs. Infections of the bladder, prostate or urethra are characterised as a lower UTI. Infections of the ureter or the kidneys constitute the upper UTIs. A UTI is regarded as uncomplicated only if the patient is a healthy, non-pregnant female with cystitis. All other cases are automatically characterised as complicated UTIs. Isolated cystitis can progress to an upper UTI, like pyelonephritis. Another complication of cystitis is acute prostatitis. The incidence of these two complications is lower than that of cystitis. Pyelonephritis has an incidence of 1 out of 1,000 males and 2 out of 1,000 females every year. The incidence of acute prostatitis is 2 out of 1,000 males every year [2]. The latter can present as an isolated infection, although generally an associated cystitis is found.

Treatment of UTIs

The first step in the first-line treatment of uncomplicated UTI is conservative. It is advised to drink plenty of water to generate an optimal urine flow and use analgesics if necessary [3]. If this does not clear the infection within a week or the patient experiences too much pain, the general practitioner will proceed to the second step of the protocol, i.e. the initiation of antibiotic therapy [4]. Nitrofurantoin 100 mg twice a day for five days in a row is the first choice antibiotic. If ineffective, an one-time oral dose of 3,000 mg fosfomycin can be prescribed. When the UTI is still persistent, a patient might be given trimethoprim 300 mg one time a day for three days. This order of antibiotics is included in the protocol based on the prevalence of *E. coli* resistance to these antibiotics. Nitrofurantoin shows the lowest resistance and is thereby the antibiotic of first choice. As the infection appears to be more persistent and more potent, broad-spectrum antibiotics are prescribed. This should not be done in an earlier stadium in order to limit the development of antibiotic resistance in the population. Moreover, a urine culture including antibiogram should be obtained in any patient not responding to the initial antibiotic therapy. Patients with recurrent cystitis can have an

indication for prophylaxis in the form of cranberry products (drink or tablets) or antibiotics like nitrofurantoin or trimethoprim [5]. Antibiotics are effective in the treatment of UTI infections but have some disadvantages. Using antibiotics as a treatment can not only cause antibiotic resistance but can also cause a disbalance of the microbiome. Antibiotic treatment is also associated with increased oxidative stress which might lead to side effects such as ototoxicity, nephrotoxicity, and tendinopathy [6]. Limiting its use is therefore desirable. Cranberries do not contribute to the development of bacterial resistance. But is there any evidence that cranberry products reduce the incidence of UTI? And would it be a suitable candidate to reduce the use of antibiotics?

Cranberries and cystitis

A systematic review published in 2017, including 7 randomised controlled trials, revealed that cranberries reduce the risk of UTI by 26% in healthy nonpregnant women above 18 years with a history of UTI [7]. The authors concluded that cranberries may be effective in preventing UTI recurrence in generally healthy women. However, the studies used in this systematic review were small, two studies had more than 300 participants. Larger, high-quality studies are needed to confirm this hypothesis. A randomised controlled trial from 2017 examined whether highly standardised cranberry extract oral supplementation is effective as prophylaxis in young healthy boys and girls with recurrent UTIs [1]. Thirty-six subjects aged 12-18 years with recurrent UTI and negative experiences with different antibiotics were included. Exclusion criteria were defined as chronic clinical conditions or risk factors, immunological diseases, concomitant infections of any nature, active (micro- or macroscopic) haematuria, treatment with antibiotics or corticosteroid for any reason in the last 6 months, allergy, or intolerance to cranberries. A urinary culture was performed in all participants, and only those with negative cultures and thus without signs of active infection or bacteriuria were included. The participants were divided into two groups: one group received only the standard preventive management and the other group received the standard preventive management with the addition of oral cranberry extract. Standard preventive management consisted of lifestyle and hygiene instructions. The 120 mg oral cranberry extract was used for 60 days. The number of UTIs in the two months before inclusion was compared with the number of UTIs in the two-month follow-up period. In addition, the number of symptom-free subjects during the registry period was evaluated. The group with standard preventive management showed no decrease in the number of UTIs. The supplemented group, however, showed a noteworthy decrease in the number of UTI and reported fewer symptoms during the registry period (63.1% compared to 23.5% in the control group).

The supplement consisted of 36 mg of proanthocyanins (PACs) which are thought to be the active substance in cranberries. PACs seem to act against pathogens by preventing bacterial adhesion to the uroepithelium and co-aggregation, decreasing biofilm formation and/or reducing inflammation. Fruits are rich in PACs but this is mostly the B-type PACs. Cranberries are rich in A-type PACs which are thought to be most effective in the exertion of its preventive effect within the urinary tract [8]. For example, the *E. coli* is in possession of P-fimbriae that the bacterium uses to bind to the urinary tract epithelium (Figure 1). A-type PACs seem to prevent this binding by decreasing the adhesion forces of the bacteria by shortening the P-fimbriae on the bacterial cell [9].

The results of the randomised controlled trial support the effect of PACs in the prevention of UTIs in subjects who suffer from recurrent UTIs. Unfortunately, the subject group was small and is thereby not the larger high-quality study the authors of the systematic review were looking for. On top of that, the follow-up period was only two months, which is very brief for the follow-up of these chronically recurrent patients.

Conclusions

Cranberries are currently being used as prophylaxis for patients with recurrent UTIs. Although the evidence for the efficacy of cranberries is not enough to conclude the prophylactic effect, it seems that cranberries

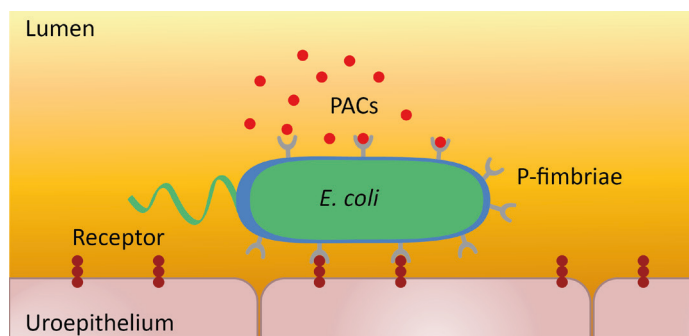


Figure 1: Binding of *E. coli* to the urinary tract. The binding of the P-fimbriae to the urinary tract can be prevented by proanthocyanins (PACs). Without the binding, the bacteria cannot hold onto the urinary tract and will be excreted more easily in the urine. This prevents the colonisation of the bacteria in the urinary tract and thereby preventing urinary tract infections (UTIs).

may play a role in the prevention of UTIs in healthy individuals suffering from recurrent UTIs. More evidence will be needed to confirm the prophylactic effect of cranberries in UTIs, as well as in the more complex patients with relevant comorbidity. Until then, though, we should assume that it works.

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