Can Probiotics Reduce Urinary Tract Infections?

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What are Urinary Tract Infections?

Urinary Tract Infections (UTIs) are bacterial infections of any part of the urinary tract causing inflammation. Bacterial infections of the bladder or ureters are commonly known as cystitis. Other specific UTIs include urethritis (inflammation of the urethra) and pyelonephritis (inflammation of the pelvis and parenchyma of the kidney) and are considered more serious. If left untreated, the infection may lead to serious complications such as kidney damage or even death.

Common symptoms of a UTI could include:

- Dysuria – painful urination, often a sharp pain or burning sensation
- Frequent or urgent need to urinate – of often miniscule amounts
- Nocturia – need to urinate at night
- Abnormal urine colour – cloudy
- Foul or strong smelling urine
- Haematuria – blood in the urine
- Pyuria – pus in the urine
- Lower back or abdominal pain
- If spread to the kidneys; fever, chills, nausea and vomiting may occur
- Possible brain confusion, especially in the elderly

Prevalence of UTIs

Although anyone can get a UTI, it is more common in females than males, most likely due to the shorter length of the urethra[1] (so the bacteria do not have as far to travel to enter the bladder) and because of the relatively short distance between the opening of the urethra and the anus[2]. Over half of all women in the UK will experience a UTI in their lifetime and 25% will have recurrent episodes[3, 4]. The incidence of primary UTI is greatest in the first month of life and decreases with age throughout childhood[5]. UTIs are common in children, occurring in 5-10% of children, and recurring in 10-30% of cases, often causing an unpleasant, usually febrile illness[6]. The incidence of UTIs is then reported to increase with age particularly in postmenopausal women[7].

Causes of UTIs

Most UTI pathogens ascend from the colon (end of the gastrointestinal (GI) tract), but a UTI may also be caused by persistent pathogens in the vagina[2, 8]. They travel along the continuous mucosa in the urinary tract, to the bladder and then along the ureters to the kidneys[2]. Occasionally in pyelonephritis, transfer to the urinary tract may be via the bloodstream[2]. *Lactobacillus* organisms that predominate in the vagina of healthy women are known to prevent uropathogens from entering the urinary tract[9] and regular urination is a defence mechanism against ascending infection[1].

The great majority of UTIs are caused by a single bacterial species. More than 80% of UTIs are caused by the Gram-negative bacteria *Escherichia coli (E. coli)*[10, 11, 12]. A number of *E. coli* bacteria strains are resident flora of the intestine[2], known to live harmoniously in small numbers within the GI tract. It may be that it is only when the environment allows the organisms to overgrow that they become opportunistic pathogens[13]. The bacteria need to be able to adhere to the mucosa lining of the bladder, kidney or urethra opening in order to multiply and cause infection by colonisation. The various virulent forms of *E. coli* can adhere to carbohydrate receptors on the surface of uroepithelial cells, due to their possession of special adhesins. These adhesins (proteins that facilitate bacterial adhesion to other cells) are on the end of the hair-like fimbriae that protrude from the surface of the *E. coli*[14]. Preventing this bacterial adhesion is therefore an important strategy in the management of UTIs.

UTI Risk Factors

Possible risk factors that could increase the chance of a UTI include:

- Previous UTIs (when colonisation may not have been fully eliminated by past treatment or the predisposing factors still present)[2, 7]
- Age at first UTI being before the age of 15 years and UTI history apparent in the mother[3]
- Regular sexual intercourse or a change in sexual partner[3, 7]
- Incomplete emptying of the bladder; waiting too long to urinate leading to weakening of the bladder muscle, incontinence and obstruction to urine flow[2]
- Use of contraceptives (oral contraceptive pill, condoms, diaphragm or spermicides)[3, 7]
- Pregnancy and post menopause (this is possibly because the reduction in oestrogen levels affects the vaginal flora by reducing the numbers of lactobacilli)[7]
- Regular use of antibiotics, corticosteroids or immunosuppressants[7]
- Depletion of vaginal lactobacilli[15]
- Catheterisation (may directly introduce bacteria into the bladder and cause damage to the mucosa)[2]
- Decreased host resistance, diabetes mellitus, impaired immunity eg AIDS

Conventional Treatment

The treatment of uncomplicated UTIs has remained unchanged for many years and usually involves a short term course of antibiotics, (preferably guided by the bacteria present in the individual's urinalysis). Antibiotics are very effective, but there is growing concern that their frequent use is leading to resistance to the effect of the medication, in up to 20% of cases for specific antimicrobials[12]. In many cases, recurrences, side effects (diarrhoea, depression, headaches and renal failure) and secondary infections are frequent[16]. Also, the beneficial bacterial flora hosted by the human body, are likely to be damaged by antibiotics, allowing further pathogenic bacteria to selectively overgrow[17].

Repeated infections (more than three in one year) are known as recurrent UTIs (RUTIs). The treatment for a RUTI involves health advice and long term low dose antibiotics to prevent bacteria colonising in the urinary tract. The side effects reported of the long term use of these antibiotics include GI problems, *candida* infections, the development of antibiotic resistant bacteria[18] and possible renal scarring[6].

Other Management Options Available

The infection tends to recur unless the predisposing factors are removed[2]. The following lifestyle suggestions could be considered to reduce the risk of contracting a UTI or a RUTI and to help manage a current infection:

- Avoid vaginal penetration until the infection has cleared
- Wash before and after intimacy and urinate immediately after sexual intercourse to eliminate any new bacteria introduced
- Drink 3 litres of water a day during an acute attack and 2-3 litres thereafter (to help flush the bacteria from the bladder)[1]
- Keep the genital area clean and wipe from front to back
- Avoid retaining urine for long periods of time
- Wear cotton underwear and avoid tight fitting trousers
- Avoid perfumed soaps, vaginal deodorants, lady wipes and tampons[2]

Evidence of Probiotic Benefits

The ability of probiotic interventions in the management of UTIs has long been considered and is now supported by increasing clinical evidence for a growing number of specific strains. There is a close correlation between the loss of the normal genital microbiota, particularly *Lactobacillus* species, and an increased incidence of UTIs[15], therefore suggesting that repletion may be beneficial[19].

A recent review in Canada suggested that the mechanisms whereby certain probiotic lactobacilli improve urogenital health include immune modulation, reduction in pathogen ascension from the rectum, and interference with colonisation and survival of pathogens[20]. A *Lactobacillus plantarum* and *Lactobacillus rhamnosus* were shown in vitro to inhibit the adherence of *E. coli* to the GI tract wall by inducing the production of mucin (a sticky substance coating the epithelial cells known to inhibit the adhesion of pathogens)[21]. A 2011 in vitro study at Reading University also showed two probiotics strains, *Lactobacillus acidophilus* PXN35 and *Lactobacillus plantarum* PXN47, to have good anti-bacterial effects in inhibiting *E. coli* growth[22].

A randomised, double-blind, placebo-controlled trial (RCT) in 2006 showed an oral *Lactobacillus rhamnosus* (1 x 10^9 CFU / 1 billion) and a *Lactobacillus reuteri* (1 x 10^9 CFU / 1 billion) was able to recover vaginal counts of *Lactobacillus* species following antibiotics and infection by 96% compared to 53% in controls[23].

A Finnish study in 2003 involving 139 women with RUTIs and 185 without showed that ingesting fermented milk products containing probiotic bacteria more than three times a week was associated with a decreased risk of RUTIs[24]. A more recent trial in Seattle in 2011 gave 100 young women with RUTIs antimicrobials and then randomised the group to receive either a lactobacilli intravaginal suppository probiotic or a placebo daily for five days, then once weekly for 10 weeks. RUTI occurred in 15% of women receiving the lactobacilli compared with 27% of the placebo group. High-level vaginal colonisation with the lactobacilli strain throughout follow-up was associated with a significant reduction in RUTIs[9].

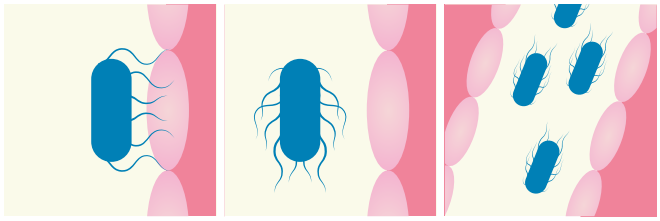
Probiotic therapy has been shown to be safe and in 2001 Reid *et al* proposed that to restore and maintain a normal urogenital flora, oral dosage seems to require around 1 x 10^9 CFU (1 billion) viable bacteria once or twice weekly or over 1 x 10^8 CFU (100 million) daily[25].

The encouraging responses in the above studies lead to the possibility that probiotic supplementation could be beneficial in maintaining urinary tract health and certainly warrant further trials.

Evidence of Cranberry Benefits

The consumption of cranberry juice has long been recommended for the prevention and treatment of UTIs. It was originally believed that the acidic nature of cranberries (hippuric acid content), created an acidic environment in the urine unfavourable to pathogenic growth[26]. It is now understood that cranberries contain specific compounds which prevent the *E. coli* bacteria from adhering to the uroepithelial cells, thereby lessening the chance of infection by multiplication[14].

The specific compounds in cranberries are believed to alter *E. coli* in a number of ways, resulting in reduced adhesion capabilities, such as actively binding to adhesins to inhibit adherence to the receptors on the surface of uroepithelial cells[4]. There is also evidence of reducing adhesin production, changing the shape and length of the bacteria and its fimbriae[27] and reducing its ability to chemically communicate with each other[28].



1. Bacteria adhere to cells with their hair-like fimbriae
2. Cranberry PACs inhibit fimbriae's adhesion capabilities
3. Inhibited bacteria "passing through"

Figure 1: Cranberry PACs Anti-Adhesion

The first compound is the monosaccharide fructose, a constituent of all fruit juices, which has been shown to inhibit type 1 (mannose-sensitive) fimbriated *E. coli* adhesions. A type of condensed tannin called Proanthocyanidin (PAC) is the second compound responsible for the inhibition of P-fimbriated (mannose-resistant) *E. coli* adhesions[2, 29, 30]. It is the P-fimbriated (mannose-resistant) *E. coli* that is usually associated with UTIs[31].

PACs are naturally occurring compounds produced by plants as a defence mechanism. Scientifically, two types of PAC have been identified. The single bond B-type is found in common food sources, such as grapes, chocolate and apples, but has not been shown to have an anti-bacterial effect[32]. Less common is the A-type linkage found in cranberry that is the active component in anti-adhesion studies[4]. Research has indicated that A-linked cranberry PACs are well absorbed in the intestine and remain active in the urinary tract and colon[4, 30].

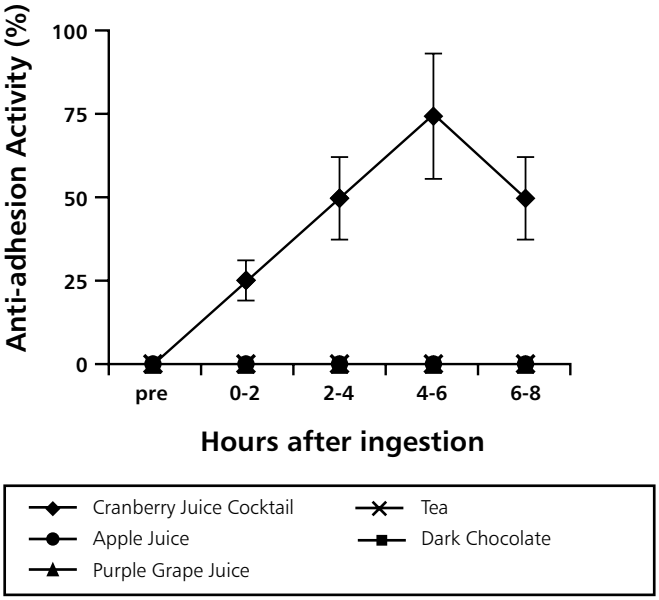


Figure 2: A-type Cranberry PAC Anti-Adhesion Activity (Vs B-type PAC)

Summary of Published Cranberry Data

A number of clinical studies have indicated encouraging evidence of the efficacy of cranberry to prevent UTIs, some of which are highlighted below.

A Cochrane review of all RCT's using cranberry products before 2007 concluded that cranberry products (drinks and capsules), significantly reduced the incidence of UTIs at 12 months compared with the placebo[28].

In light of the development of antibiotic resistant strains there is growing interest in techniques that inhibit bacterial adhesion in UTIs, opposed to the killing of the bacteria. In 2002, Howell *et al* showed that an antibiotic resistant uropathogenic P-fimbriated *E. coli* lost the ability to adhere to bladder cell receptors following incubation in urine of humans who had consumed 240ml of cranberry juice (with 30mg PACs). Prevention of the adhesion was seen in 80% of 39 P-fimbriated *E. coli* and in 79% of the 24 antibiotic resistant strains. Anti-adhesion activity was evident in the urine within two hours and persisted for up to 10 hours[33].

Further studies looking at antibiotic use have strengthened this view. In 2002, Stothers studied 150 women for 12 months. Both cranberry juice (250ml three times a day) and cranberry tablets significantly decreased the number of patients experiencing a UTI (to 20% and 18% respectively) compared to the placebo (to 32%). Total antibiotic consumption was less in both treatment groups compared with placebo, concluding that cranberry tablets provided the most cost-effective prevention for UTI[34]. Then more recently, in 2009, McMurdo *et al* carried out a 6 month trial in 137 elderly women with RUTIs to compare the efficacy in preventing UTI with cranberry capsules or antibiotics. The time to first recurrence of UTI was not significantly different between groups but the antibiotics had more adverse effects and withdrawals[35].

A number of authors have noted that the minimal cranberry PACs A dose with an observed anti-adhesion effect is 36 mg. A significant dose-dependent decrease in *E. coli* adherence to uroepithelial cells was noted in an in-vitro and in-vivo trial in France in 2008 by Lavigne *et al* after the consumption of 36 mg and 108 mg of cranberry PACs A capsules[36]. A more recent RCT by Howell *et al* in 2010 involving 32 volunteers, used capsule dosages standardized to deliver 18 mg, 36 mg or 72 mg of PACs A. The results indicated a significant bacterial anti-adhesion activity in urine samples collected from volunteers that consumed cranberry capsules compared to the placebo. This inhibition was clearly dose-dependent and lasted longer with higher doses. These results highlighted that to achieve bacterial anti-adhesion, 36 mg of cranberry PACs per day is effective (providing most effect up to 6 hours after ingestion), but 72 mg may offer 24 hour protection[37].

The processing of cranberry can impact PAC A composition[38] potentially impacting the bacterial anti-adhesion activity[4]. Thus, proper standardization of PAC A content in cranberry product production is important. Cranberry juice undergoes more processing than cranberry extracts which are more likely to contain more active PAC A with often up to 20 times less sugar, no acidity and no tart taste. Daily ingestion of large volumes of cranberry juice is often challenging, especially for the elderly, making capsules more appealing[39].

In numerous studies, cranberry continues to prove to be a useful tool in the daily management of UTIs. It's delivery in a capsule form, containing at least 36mg of A-type linkage cranberry PACs is suggested as a more stable processing technique and preferable form for consumption.

Evidence of Vitamin A Benefits

Vitamin A has recently obtained a European Food Safety Authority (EFSA) Health Claim Approval stating that it 'contributes to the normal function of the immune system'.

Vitamin A has been known as an anti-infective vitamin since the 1920's[40]. It has been shown to increase the effectiveness of immune response to infection once the GI epithelial barrier has been breached[41]. Vitamin A has also been shown to regulate the growth and differentiation of GI epithelial cells. The GI mucosal barrier, which is an important component of the innate immune system, is considered the first line of immune defence, as it provides a barrier between the external and internal environment, providing protection from external toxins and pathogens. A disturbance in the integrity of the GI epithelium has been found to be one of the main factors involved in increased incidence of infections during vitamin A deficiency[5, 42, 43], therefore suggesting the maintenance of a healthy mucosal barrier is an important strategy in the management of UTIs.

A study in 2009 by Amit-Romach *et al* demonstrated that vitamin A deficiency is associated with an alteration in the GI microflora balance. Levels of *Lactobacillus* were decreased; *E. coli* strains increased and mucin dynamics were significantly changed[42].

In 2005 an RCT was undertaken involving 24 patients with RUTI undergoing antimicrobial therapy for 10 days. Twelve of the patients additionally received a single dose of 200,000 IU vitamin A. This resulted in a significant reduction of infection in the first 6 months from an average of 3.58 to 0.75 times, compared to 2.75 to 2.83 times within the control group. The authors concluded that vitamin A supplementation may have an adjuvant effect on the treatment of RUTI[44].

A review of published studies between January 2007 and June 2008 evaluating interventions to prevent UTI in children, noted that the trials of complementary interventions of vitamin A, probiotics and cranberry generally gave favourable results in comparison to prophylactic antibiotics[6].

More studies are needed in this area but with respect to Vitamin A's supportive effect on the immune system, protection of the epithelial mucosal barrier and positive effects on the microflora balance, vitamin A is emerging as playing an important role in maintaining urinary tract health.

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Natalie qualified as a Nutritional Therapist after studying a three year diploma in Nutritional Therapy at the College of Naturopathic Medicine (CNM) in London and became a fully registered member of The British Association of Nutritional Therapists (BANT) in 2009. Natalie saw clients in a private clinic in London on a part time basis for 2 years, prior to joining Probiotics International Ltd in 2011. Natalie graduated with a degree in Business Studies from the University of Central England in 2000, and spent over 10 years working in food and health related industries, from market research analysis for UK food and drink manufacturers to food preparation and service within the hospitality industry. For 5 years Natalie worked for a UK cancer charity assisting with their awareness program and researching and preparing information articles for the public and health care professionals. Natalie is currently the Technical Advisor for Protexin's Human Health Care range .