Review Article

Natural Approaches to Prevention and Treatment of Infections of the Lower Urinary Tract

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Abstract

Infections of the lower urinary tract are common occurrences in young women, during pregnancy, and in peri- and postmenopausal women. Because of the chronic nature of urinary tract infections (UTIs) and the potential for antibiotic resistance, a natural approach to prevention and treatment is desirable. Clinical research suggests the best natural options for long-term prevention include cranberry, mannose, and probiotics. Botanicals that can be effective at the first sign of an infection and for short-term prophylaxis include berberine and uva ursi. Estriol cream and vitamins A and C have also been shown to prevent UTIs, while potassium salts can alkalinize the urine and reduce dysuria. (*Altern Med Rev* 2008;13(3):227-244)

Introduction

Urinary tract infections (UTIs) account for 8.3 million doctor visits yearly in the United States and are the second-most common site for infection. Infections of the lower urinary tract (urethra and bladder) are common among women – affecting as many as one in five women at some time during their lifetime. Although UTIs are not as common in men, they can indicate an obstruction such as a stone or enlarged prostate; thus, they are uncommon in men under age 50.[1] The term UTI in this article refers to infections of the lower urinary tract – the bladder and urethra.

UTIs can chronically recur – 20 percent of women who have one infection will have a recurrence. Of this group, 30 percent will have a third occurrence, and of this group, 80 percent have additional recurrences. In other words, the more infections one has had, the more likely another will occur.[1] Many women with chronic UTIs are on antibiotics more than off, running the risk of developing dysbiosis and antibiotic resistance.

Symptoms

Although UTIs can be asymptomatic, they commonly present with distressing symptoms, including frequent urge to urinate, pain on urination, pressure or pain above the pubic bone in the bladder even when not urinating, difficulty passing urine, and general symptoms of fatigue. In addition to painful urination and pyuria (white blood cells in the urine), men may experience a full sensation in the rectum. Children with UTIs can often be asymptomatic or present with less specific symptoms, such as irritability, incontinence, diarrhea, poor appetite, and fever. Signs include cloudy or milky urine that can be pink or reddish tinged if significant blood is present. A fever, flank pain, nausea, and vomiting are usually signs the infection has reached the kidneys, causing acute pyelonephritis.[1,2]

Risk Factors

Risk factors for UTI include female gender, sexual activity, mode of birth control, menopause, diabetes, catheter use, and urinary tract obstruction (stone, tumor, strictures, or enlarged prostate). Voiding before and after intercourse, use of cotton underwear, and avoidance of feminine hygiene deodorants and scented toilet paper may decrease risk.

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College-age Women

In college-age women, frequent sexual intercourse is a risk factor. In addition, it is not uncommon for a woman to have a UTI after her first sexual encounter ("honeymoon cystitis"). A case-control study compared 43 college-age women with UTIs to college-age controls – 149 women with upper respiratory infections and 227 women receiving routine pelvic exams. Frequency of intercourse and diaphragm use during the previous three weeks were independently associated with increased risk for UTI.[3]

Another study comparing 237 UTI cases in college-age women to 1,404 college-age controls found frequent intercourse, diaphragm/spermicide use, and a new sexual partner increased the risk, while urinating before and after intercourse and vitamin C consumption appeared to decrease the risk.[4] Other studies have also found a strong correlation between sexual activity and diaphragm/spermicide use in both symptomatic[5] and asymptomatic bacteriuric[6] college-age women.

Another study examined college women experiencing a UTI for the first time, comparing 86 cases of UTI with 288 student controls. Intercourse and condom use were associated with increased risk – a single sex act with a condom in the previous two weeks increased the risk by 43 percent. On the other hand, cranberry juice consumption decreased the risk after adjusting for sexual behavior (odds ratio (OR)=0.48).[7]

Pregnancy

It is estimated that eight percent of women experience a UTI during pregnancy;[8] UTIs being the most common bacterial infection in pregnancy.[9] Bacterial vaginosis increases the risk for developing a UTI in both pregnant[10] and nonpregnant[11] women.

A UTI during pregnancy can increase risk of other complications for mother or fetus. A UTI is more likely to spread to the kidneys during pregnancy, due in part to ureteral dilation and resultant hydronephrosis. The ureters dilate in 90 percent of women during pregnancy.[8] In addition, occurrence of a UTI during pregnancy increases the risk for preeclampsia (OR=1.57).[12] Asymptomatic bacteriuria increases the risk for preterm labor and low birth-weight babies.[13]

Peri- and Postmenopausal Women/ Diabetes

A cohort of 1,017 menopausal women were followed for two years, during which time 138 urinary tract infections occurred. Significant risk factors included diabetes treated with insulin (hazard ratio (HR)=3.4) and a history of six or more previous UTIs (HR=6.9). Borderline risk factors included a history of kidney stones (HR=1.9) and asymptomatic bacteriuria at baseline (HR=1.9). Factors that did not affect risk included vaginal dryness, use of cranberry juice, urinary incontinence, sexual activity, post-sex voiding, and vaginal bacterial flora.[14]

The relationship between diabetes and risk for UTI was further examined in a group of postmenopausal women ages 55-75. In this case-control study of 901 women reporting UTIs compared to 913 matched controls, 13.1 percent in the UTI group were diabetic compared to 6.8 percent in the control group.[15] Some of these same researchers followed 218 diabetic women and 799 nondiabetic women (ages 55-75 in both groups) for four years. UTI incidence was 12.2 per 100 person-years in the diabetic group and 6.7 in the nondiabetic group. Incidence of asymptomatic bacteriuria was 6.7 and 3.0 per 100 person-years in diabetics and nondiabetics, respectively.[16]

The Heart and Estrogen/Progestin Replacement Study examined the effect of hormone replacement on cardiovascular health in 2,763 women ages 44-79 with established heart disease. The effect of hormone replacement on other health risks, including UTIs, was also examined. While hormone replacement had no statistically significant effect on UTI risk, the factors that did impact risk included diabetes (treated with insulin (OR=1.81) or oral medication (OR=1.44)), poor health in general (OR=1.34), childbirth (OR=1.38), vaginal dryness (OR=1.30), vaginal itching (OR=1.63), and urge incontinence (OR=1.51). The most significant risk factors were previous urinary tract infections in the past year (OR=7.0) and history of multiple urinary tract infections (OR=18.51).[17]

Etiological Agents

Although the urinary tract is normally a sterile environment, bacteria can migrate to the urethra from the rectum or vagina. Normally, 10^5 organisms per

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Table 1. Botanicals for Prevention and Treatment of UTIs

Treatment	Intervention	Dosage	Results/Population	Strength of Research
Vaccinium macrocarpon (Cranberry)	Cranberry juice cocktail or placebo beverage	300 mL daily for six months	Prevention of UTIs in elderly women	RCT (n=153)
	Low-sugar cranberry juice cocktail w/ aspartame or placebo beverage	300 mL daily until onset of first UTI	Prevention of UTIs in elderly men and women (hx of UTI not a prerequisite)*	RCT (n=376)
	Juice cocktail or placebo beverage	15 mL/kg (children)	No effect in children with neurogenic bladder	Small crossover study (n=15)
	Cranberry juice w/ water or water alone	15 mL twice daily x 4 wk, then crossed over	Decreased bacteriuria during cranberry consumption	Small crossover study (n=38)
	Tablets	400 mg three times daily x 4 wk	No improvement in patients with neurogenic bladder	RCT crossover (n=21)
Cranberry-Lingonberry	Juice concentrate (no added sugar), *Lactobacillus rhamnosus*, or no intervention	50 mL (7.5 g cranberry/1.7 g lingonberry) daily x 6 mo; or 100 mL Lactobacillus drink 5 d/wk	Prevention of UTI in college-age women	Case control (n=150)
Berberine sulfate	Oral administration	400 mg (one dose)	Indirect; men with enterotoxic *E. coli* diarrhea; stopped diarrhea which can indirectly affect migration to urinary tract	RCT (n=63)
		200 mg/kg (one dose)	Prevented cyclophosphamide-induced hemorrhagic cystitis in rats	Animal study
			Direct growth inhibition of *E. coli, Pseudomonas aeruginosa*	*in vitro*
		200 mcg/mL for 18 hr	Inhibition of fimbrial synthesis (anti-adhesion)	*in vitro*
Arctostaphylos uva ursi w/ Taraxacum officinalis	UVA-E: standardized extracts of uva ursi leaf and dandelion herb and root; oral	3 tablets 3x/d for 1 mo; followed 1 yr	Prevention in women	RCT (n=57)

* Unless otherwise indicated, study populations had a history of recurrent UTIs

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mL of urine from a midstream catch are indicative of an infection. Cases, however, can be symptomatic with lower bacterial counts (10^2-10^4/mL).

Most infections are bacterial, the most common etiological agent being gram-negative bacilli. *Escherichia coli* (*E. coli*) accounts for 80 percent of UTIs,[2] while other gram-negative bacilli, including *Klebsiella pneumonia*, *Proteus mirabilis*, and *Enterobacter aerogenes* contribute somewhat less to incidence.[2] Gram-positive cocci account for fewer UTIs than gram-negative bacilli. Among the organisms involved are *Staphylococcus saprophyticus* (responsible for 10-15 percent of UTIs in college-age women), Enterococci, and *Staphylococcus aureus* (most common in individuals with stones or who have been catheterized).[2] Because the majority of UTIs are bacterial in origin, they are most commonly treated conventionally with antibiotics during the acute episode. In addition, it is not uncommon to use antibiotics for long-term prophylaxis for individuals with recurrent infections.

Approximately one-third of women with dysuria and other UTI symptoms have "sterile urine" – with or without pyuria (white blood cells in the urine). In the case of sterile urine and pyuria, the causative agents are often sexually transmitted – *Neisseria gonorrhea* or *Chlamydia trachomatis*. Non-bacterial etiological factors include mycoplasma (*Ureaplasma urealyticum* or *Mycoplasma hominis*), adenovirus, and *Candida albicans* (especially in diabetics or catheterized patients).

Pathogenesis

The female urethra is particularly prone to bacterial infection via migration from the anus or vagina. Normal, nonpathogenic flora of the vagina and urethra include Lactobacilli, Streptococcal sp., Staphylococcal sp., and diphtheroids. The ability of pathogenic bacteria to colonize is associated with altered vaginal and colonic flora, due to other genital infections and use of antibiotics and spermicides. Loss of Lactobacilli, which produce H_2O_2, facilitates colonization of *E. coli*. In addition to Lactobacilli, the urine itself normally prevents infection via antibacterial and flushing mechanisms.[2]

E. coli, the most common pathogen associated with UTIs, has been studied extensively to determine virulence factors. One factor essential to its infective potential is its ability to adhere to epithelial cells of the urinary tract. Both *E. coli* and Proteus attach to uroepithelial cells by proteinaceous appendages called fimbriae.[2] *E. coli* adheres to uroepithelial cells via type 1 pili – long, hairy-surface organelles with a mannose-binding FimH, which is a protein component at the fimbrae end that acts as an adhesive.[18] Bacterial attachment results in a cascade of events involving elaboration of interleukin-6 and -8, which influences leukocyte infiltration.[2]

Figure 1. *Vaccinium macrocarpon*

Botanical Interventions for Lower Urinary Tract Infections

While antibiotics are used to treat and prevent recurrent urinary tract infections, frequent antibiotic use can result in vaginal and intestinal dysbiosis as well as antibiotic resistance. Thus, it is desirable to seek alternative methods of prevention and treatment of simple UTIs. Table 1 summarizes the best-researched botanical interventions.

Vaccinium macrocarpon (Cranberry)

The cranberry (Figure 1) has been used in folk medicine for centuries as a treatment for diseases of the urinary tract. It was once thought to benefit UTIs because hippuric acid in cranberries has the potential to acidify the urine. However, a more complete understanding of the pathogenesis of UTIs has led to a greater understanding of the mechanisms of action of cranberry in prevention and treatment – as an anti-adhesion agent. Cranberries have been found effective in the form of pure juice, sugared cocktail, and capsules and tableted extracts.

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Women of All Ages

In a one-year study of 150 sexually active women (ages 21-72), subjects were assigned to one of three groups: organic cranberry juice plus placebo tablets, cranberry tablets plus placebo juice, or placebo tablets and placebo juice. Juice dose was 250 mL three times daily, while tablets were taken twice daily. Both cranberry juice and tablets resulted in a decrease in antibiotic use compared to placebo and a statistically significant 20- and 18-percent decrease, respectively, in number of subjects experiencing at least one UTI during the year.[19]

Elderly Individuals

In another study, 38 elderly individuals (nine men; 29 women) were assigned to drink 15 mL cranberry juice mixed in water or plain water (same amount of total liquid) twice daily for one month and then crossed over to the other treatment regimen for another month. Because of significant dropout, only seven subjects were available for analysis. The participants experienced less incidence of bacteriuria when consuming cranberry juice compared to water.[20]

In a randomized, double-blind, placebo-controlled trial (RCT), 153 elderly women (mean age 78.5) were given daily beverages consisting of 300 mL cranberry juice cocktail (Ocean Spray Cranberries, Inc.; Lakeville, MA) or a placebo beverage with the same look, taste, and vitamin C content but without cranberry. Urine samples were collected at baseline and at monthly intervals for six months and tested for bacteriuria (defined as 10^5 organisms/mL) and pyuria. The women in the cranberry-drink group experienced significantly less bacteriuria with pyuria (OR=0.42; p=0.004) than the placebo-drink group. Improvements were not a result of change in urine pH since the placebo group had an average urine pH of 5.5 and the cranberry-juice group had an average pH of 6.0.[21]

Another study examined the effect of daily ingestion of 300 mL cranberry juice cocktail (Light Cranberry Juice Cocktail, Ocean Spray; 10 g sugar per serving, but contains sucralose) or matching placebo beverage on UTI incidence in a group of 376 elderly, hospital in-patients of both genders. Twice as many individuals experienced a UTI in the placebo group (14/189) than the cranberry group (7/187) (RR=0.51; p=0.122). Because of the relatively few infections in this large group the result did not reach statistical significance. The effect of cranberry juice consumption was statistically significant, however, when only *E. coli* infections were considered (13 infections in the placebo group compared to four in the cranberry group; RR=0.31; p=0.027).[22]

Patients with Neurogenic Bladder

Biofilm is created by adhesion of bacteria overgrowth to the inner bladder wall. In a pilot study of 15 spinal cord injury patients, who are susceptible to bladder infections due to paralysis and resultant ineffectual bladder emptying and catheterization, one glass of cranberry juice three times daily for seven days significantly reduced the biofilm load. This was associated with a reduction of adhesion of both gram-negative and gram-positive bacteria. On the other hand, one glass of water three times daily for seven days was not associated with a decrease in biofilm load.[23]

Cranberry extract in tablet form has also been tested in patients with neurogenic bladder due to spinal cord injury. In a crossover RCT, 21 subjects were assigned to tablets containing 400 mg cranberry extract three times daily or placebo for four weeks. After a one-week washout period, they were switched to the opposite group for an additional four weeks. Urine was checked weekly for bacteria, white blood cells, and pH. No significant difference in any parameter was noted between the cranberry or placebo periods.[24]

In an RCT with crossover design, 15 children receiving frequent catheterization for neurogenic bladder were assigned to cranberry juice or placebo juice for three months, then crossed over for an additional three months. Urine pH and incidence of bacteriuria and symptomatic infection were assessed weekly. Both the placebo and cranberry juice periods yielded a 75-percent rate of positive cultures (120/160 samples in the cranberry juice group and 114/151 samples in the placebo group). In addition, there was no significant difference in pH between groups (5.5 in the placebo group and 6.0 in the cranberry group). Each group experienced three symptomatic infections.[25]

In another study of pediatric neurogenic bladder, 40 children (21 completed the study) were given 15 mL/kg body weight/day cranberry juice cocktail or water for six months, then switched for another six months. There were no differences between groups in regard to number of infections.[26]

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Meta-Analysis of Cranberry Trials

A meta-analysis of 10 trials using the Cochrane criteria for inclusion summarized the cranberry trials. Of the 10 trials, five were crossover and five were parallel group studies. Cranberry juice was used in seven trials, while tablets were used in four (one trial used both). The conclusion reached is that cranberry significantly reduces the incidence of UTIs over a 12-month period. It seems to be most effective in women with recurrent infections than for the elderly (both genders); individuals with neurogenic bladder do not appear to derive much benefit from cranberry juice.[27]

Combination Treatment: Cranberry-Lingonberry Juice or *Lactobacillus rhamnosus* GG

A combination of cranberry and *Vaccinium vitis-idaea* (lingonberry) juice was compared to a *Lactobacillus rhamnosus* GG beverage or no intervention in 150 women with diagnosed *E. coli* UTIs, recruited from a university health clinic or university hospital staff. The fruit juice group consumed 50 mL cranberry-lingonberry juice (7.5 g cranberry concentrate and 1.7 g lingonberry concentrate; no added sugar) daily for six months, while the other group consumed a 100-mL Lactobacillus drink five days/week; a third group served as a control. The preventive treatment was started after the infection had cleared with antibiotic treatment. During the six months of the trial, there was a 20-percent reduction in UTI incidence in the cranberry group (eight cases; 16%) compared to the Lactobacillus (19 cases; 39%) and control (18 cases; 36%) groups (probiotic prophylaxis is discussed in more detail below).[28]

Mechanism of Action of Cranberry in UTIs

The studies cited above have not found reasonable consumption of cranberry juice or tablets lowers urine pH. Thus, experts no longer adhere solely to the concept of bacteriostatic acids in cranberry providing the mechanism of UTI prevention.[29] Not all studies, however, show no change in pH with cranberry. In a crossover study of eight multiple sclerosis patients, 1,000 mg ascorbic acid and 12 ounces cranberry juice was more effective at lowering urine pH than 1,000 mg ascorbic acid and 12 ounces orange juice.[30]

As early as the 1980s, the concept of cranberry's inhibition of bacterial adherence to the bladder wall was being studied. One investigation examined the effect of cranberry juice on *E. coli* adherence *in vitro*, in an animal model, and in a clinical setting. Cranberry juice inhibited adherence of 75 percent of 77 *E. coli* isolates *in vitro*. Urine from mice given cranberry juice for 14 days demonstrated 80-percent inhibition of *E. coli* to uroepithelial cells. In a clinical setting, 15 of 22 subjects given 15 ounces cranberry juice demonstrated significant anti-adherence activity in urine 1-3 hours after juice consumption.[31]

An RCT compared the effects of four beverages on *E. coli* adhesion in 20 healthy volunteers (10 women and 10 men). Each subject took each beverage in random order with a six-day washout period between test beverages: 750 mL cranberry juice; 250 mL cranberry juice plus 500 mL mineral water; 250 mL placebo plus 500 mL mineral water; and 750 mL placebo. First morning urine was collected and six pathogenic *E. coli* strains introduced. A dose-dependent anti-adhesion effect was noted in the cranberry juice samples.[32]

Another study examined the anti-adhesion effect of dried cranberries compared to raisins in five women with culture-confirmed *E. coli* UTIs. Dried cranberries (42.5 g) resulted in 50-percent inhibition of adhesion in one woman, 25 percent in two women, and no effect in two women. None of the control urine samples or samples after ingestion of 42.5 g raisins demonstrated any effect.[33]

The proanthocyanidins in cranberry are suspected of preventing *E. coli* adhesion, and the fact they contain an A-type linkage is believed to be key to this function. Other plant extracts also contain proanthocyanidins, but contain B-type linkages. An *ex vivo*/*in vitro* study compared the anti-adhesion effect of cranberry proanthocyanidins with A-type linkages to green tea, grape juice, apple juice, and dark chocolate – all containing proanthocyanidins with type-B linkages. Cranberry juice demonstrated inhibition of adhesion at a concentration of 60 mcg/mL. Grape juice required a much greater concentration of 1,200 mcg/mL to show inhibition; neither dark chocolate nor green tea afforded any inhibition.[34]

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Safety During Pregnancy

A literature review on safety of cranberry juice during pregnancy was conducted by the University of Toronto's School of Pharmacy. Included in the literature review was a survey of 400 pregnant women that disclosed no adverse events associated with consumption of cranberry in any form. Given its safety profile, the authors concluded cranberry is a valuable tool for prevention of UTIs during pregnancy.[35]

Cranberry Effect on Oxalate Production

Cranberries are relatively high in oxalic acid, a substance best avoided by individuals with a tendency to form calcium-oxalate kidney stones. In a study of five healthy volunteers, urine was collected for 24 hours and tested for oxalates, calcium, magnesium, phosphorus, potassium, sodium, citrate, urate, creatinine, and pH. Following seven days of cranberry tablet supplementation (at manufacturer's suggested dosage) urine was collected for another 24 hours. Urinary oxalates were significantly increased by an average of 43.4 percent ($p=0.01$). In addition, calcium, phosphate, and sodium ions were increased (other risk factors for stone formation); however, magnesium and potassium, preventive for stone formation, were also increased.[36]

Potential Drug Interactions

Occasional case reports have indicated a possible connection between cranberry juice consumption and enhanced effects of Coumadin (warfarin) – increasing the international normalized ratio (INR); thus increasing bleeding potential.[37] In a study conducted on 12 healthy male volunteers, a single dose of 25 mg warfarin after two weeks of pretreatment with cranberry juice extract (two 500-mg capsules of cranberry concentrate three times daily) significantly increased the INR area under the curve (AUC) by 30 percent, compared to warfarin alone.[38]

Other studies have found no interaction between cranberry and warfarin. A crossover RCT of seven subjects with atrial fibrillation stabilized on warfarin for three months found no significant difference in INR between cranberry juice (250 mL daily) consumption for seven days and baseline or cranberry juice compared to placebo. Each subject was randomly assigned to each regimen for seven days with a seven-day washout period in between.[39]

In a study of healthy volunteers given 200 mL cranberry juice or water three times daily for 10 days, cranberry did not affect the metabolism of drugs given on day 5, including 10 mg warfarin (metabolized by CYP2C9 isoenzyme), 1 mg tizanidine (metabolized by CYP1A2), and 0.5 mg midazolam (metabolized by CYP3A4). Cranberry juice ingestion also did not affect the anticoagulant effect of warfarin.[40] Another study found no effect clinically of cranberry juice consumption on CYP29C isoenzyme activity.[41]

Because of conflicting data on the effect of cranberry consumption on INR in patients on warfarin, close monitoring of patients when initially starting a cranberry juice regimen may be indicated.

Vaccinium myrtillus (Bilberry; Blueberry)

Although *Vaccinium myrtillus* extracts have not been subjected to the same extensive study for UTIs as cranberry, evidence indicates constituents of blueberry juice possess some of the same anti-adhesive effects. Unlike guava, mango, orange, grapefruit, or pineapple, bilberry constituents can bind competitively to the same uroepithelial cells as bacteria.[42,43]

A study examined the effect of cranberry, blueberry, mango, melon, peach, plum, or raspberry on the ability of oral bacteria to aggregate and thus colonize. Although cranberry inhibited bacterial aggregation the most strongly, blueberry juice exhibited weak anti-aggregation effects; the other juices showed no effect.[44]

Berberine

Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine. It is present in many plants, including *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape; *Mahonia aquifolium*), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric). Berberine is found in the root, rhizome, and stem bark of the plants. Berberine extracts and decoctions demonstrate significant antimicrobial activity against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and Chlamydia.

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Direct Antibacterial Effects of Berberine and other Alkaloids

Berberine demonstrates direct antibacterial effects *in vitro*. Berberine extracted from *Berberis aquifolium* demonstrates growth inhibition of several bacteria, including both sensitive and resistant *E. coli*. Bacteria inhibited in this study in order of inhibition were: *Staphylococcus aureus* > *Pseudomonas aeruginosa* (sensitive) > *E. coli* (sensitive) > *Pseudomonas aeruginosa* (resistant) > *E. coli* (resistant) > *Bacillus subtilis*.[45]

Hydrastis canadensis (70% alcoholic extract) and its isolated alkaloids berberine, canadine, and canadaline demonstrate *in vitro* bacteriocidal activity against *E. coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.[46]

Berberine and related alkaloids from *Coptis chinensis* also demonstrate antimicrobial effects against *E. coli*. The inhibitory effect of these constituents in order of potency is: berberine > coptisine > palmatine.[47]

Development of antibiotic resistance continues to be an ongoing concern. Therefore, research continues on herbal extracts that may provide novel antibacterial approaches. A 2008 study identified a novel protein (FtsZ) involved in the first stage of bacterial cell division that is targeted by berberine.[48]

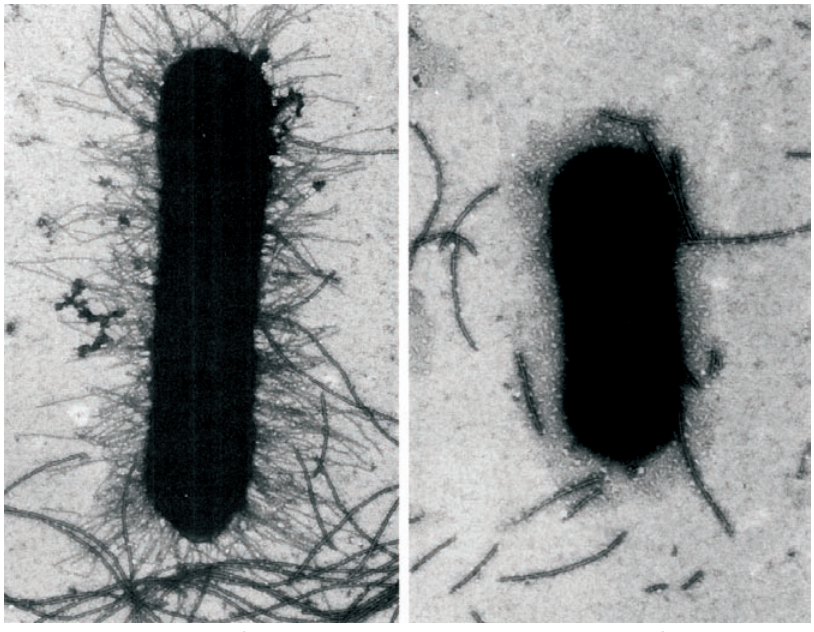
Berberine Prevents *E. coli* Adhesion

In urinary tract infections, the anti-infective activity of berberine is believed to be at least in part due to its ability to prevent adhesion to uroepithelial cells. In one *ex vivo*/*in vitro* study, a urinary pathogenic strain of *E. coli* was isolated from infected patients and cultured. Grown in culture for 18 hours, an electron micrograph showed *E. coli* heavily covered with fimbrial filaments. When *E. coli* was cultured for 18 hours in the presence of 200 mcg/mL berberine sulfate, fimbrial synthesis was completely inhibited (Figure 2). No other bacterial proteins appeared to be affected.[49] Some of these same researchers found berberine sulfate also inhibits the capacity of *Streptococcus pyogenes* to adhere to host cells.[50]

Cyclophosphamide-induced Cystitis

Cyclophosphamides are chemotherapeutic agents used in the treatment of cancer and rheumatoid arthritis and to prevent transplant rejection. Hemorrhagic cystitis, a side effect of these drugs, contributes to significant morbidity and even mortality when high doses are used. A single dose of berberine (200 mg/kg body weight) or two doses of 100 mg/kg body weight completely protected rat bladders from hemorrhagic cystitis induced by cyclophosphamides.[51]

Figure 2. Berberine Sulfate Inhibits Synthesis of *E. coli* Fimbrae[49]



E. coli in absence of berberine *E. coli* in presence of berberine

Indirect Effects of Berberine on UTIs

Because infection of the urinary tract with *E. coli* often results from bacterial migration from the gastrointestinal (GI) tract, treatment of GI-associated *E. coli* can indirectly impact UTI potential. In a clinical study, 63 Bangladeshi men with enterotoxic *E. coli* diarrhea were randomly assigned to one dose of 400 mg berberine sulfate (n=33) or placebo (n=30). During the eight hours following treatment, subjects in the berberine group experienced significant decrease in stool

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volume compared to the placebo group, which persisted throughout the 24-hour observational period (48% decrease; $p<0.05$). In addition, significantly more patients in the berberine group stopped having diarrhea within 24 hours of treatment (42% versus 20%; $p<0.05$).[52] Animal models demonstrate berberine's antisecretory effect on *E. coli*-induced diarrhea in mice, rabbits,[53] and pigs.[54] Successful treatment of intestinal dysbiosis by the antimicrobial and antisecretory effect of berberine may be preventive for urinary tract infections.

Berberine Contraindications

Berberine usage should be avoided in pregnancy due to potential for causing uterine contractions and miscarriage and in jaundiced neonates because of its bilirubin displacement properties.

Arctostaphylos uva ursi (Bearberry)

Biochemistry and Metabolism of Uva ursi

Uva ursi is one of the most commonly used antimicrobial botanicals for UTIs. The antimicrobial constituent is believed to be the aglycone hydroquinone of arbutin, which is released in alkaline urine.[55] For optimum results, the urine pH should be at least 8. Increased urine alkalinity can often be achieved by a high vegetable diet; however, in some cases consumption of 6-8 g sodium bicarbonate in water daily may be necessary.[56]

A study of 16 healthy volunteers found a dried-leaf extract of uva ursi resulted in significant urinary arbutin (64.8% of arbutin consumed in tablet form and 66.7% of arbutin in an aqueous solution).[57]

Mechanisms of Action

Uva ursi impacts urinary tract infections by virtue of its antimicrobial effect. Two studies available in German[58] and Polish[59] and discussed by other authors[59,60] examined the urine from patients given extracts of uva ursi or isolated arbutin. Activity was demonstrated against "*E. coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and 70 other urinary tract bacteria."[60] According to Werbach,[61] "Frohne found the crude extract of uva ursi to be of more benefit as an antimicrobial than arbutin."

The antimicrobial effect appears to be in part due to the capacity of aqueous uva ursi extracts to change microbial cell surface characteristics. In a study of 40 *E. coli* strains extracted from urine of patients with pyelonephritis or calves and pigs with diarrhea, uva ursi or St. John's wort significantly increased the hydrophobicity of the microbial cell surface, decreasing the ability of bacteria to adhere to the host.[62]

Uva ursi also appears to have diuretic and anti-inflammatory effects. An animal study found uva ursi significantly increased urine output without affecting sodium or potassium excretion.[63] In another animal model, uva ursi extracts and arbutin isolate demonstrated inhibition of inflammation, both alone and as an additive effect with prednisolone.[64]

Clinical Evidence

Although uva ursi is commonly used successfully for UTI treatment, no studies have been conducted to confirm its efficacy. However, one clinical study indicates its effectiveness for UTI prevention. In an RCT, 57 women (ages 32-63) with chronic UTIs (at least three infections during the preceding year) were assigned to UVA-E extract (n=30) or placebo (n=27) for one month, then followed for one year. UVA-E consists of standardized extracts of uva ursi leaf and dandelion root and leaf (the latter providing diuretic effects). A statistically significant difference in occurrence of infection was noted at the end of one year – 5 of 27 in the placebo group compared to 0 of 30 in the uva ursi/dandelion group.[65] Uva ursi is best used at the first sign of an infection or for short-term prophylaxis. Note in the above study the women took uva ursi for only one month, despite the fact they were followed for one year.

Other Herbs

Barosma betulina (buchu) has a long history of use in urinary tract infections. In addition to its diuretic effect,[66] *in vitro* evidence suggests it has an antimicrobial effect against certain urinary pathogens.[67] It has been used traditionally for catarrhal cystitis and urethritis.[68]

In an *in vitro* study, essential oil extracted from *Salvia officinalis* inhibited several urinary pathogens extracted from urine samples provided by individuals with UTIs. Salvia demonstrated 100-percent inhibition of Klebsiella and Enterobacter species, 96-percent inhibition of *E. coli*, 83-percent inhibition of *Proteus mirabilis*, and 75-percent inhibition of *Morganella morganii*.[69]

While not directly impacting urinary tract infections, herbs such as *Sabal serrulata* (saw palmetto)

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Table 2. Herbs Used in Traditional Folk Medicine for Treatment of UTIs

Herb: Latin name (common name)	Properties	Specific Indications
Agrimonia eupatoria (agrimony)	Astringent; diuretic[68]	
Althea officinalis (marshmallow)	Mucilaginous	Soothe irritated uroepithelium[56]
Apium graveolens (celery seed)	Diuretic[56]	
Arctium lappa (burdock)	Antimicrobial; diuretic	*E. coli*[68]
Elymus repens (couchgrass)	Antimicrobial; diuretic	Urethritis and cystitis with inflammation[68]
Hydrangea aborescens (hydrangea)	Antilithic; diuretic	Cystitis with stone irritation[68]
Juniperus communis (juniper)	Diuretic/aquaretic[56]	
Mentha piperita (peppermint)	Antispasmodic[71]	
Taraxacum officinalis (dandelion) leaf	Diuretic[56]	
Ulmus fulva (slippery elm)	Mucilaginous	Soothe irritated uroepithelium[56]
Zea mays (corn silk)	Diuretic/aquaretic[56]	

and *Urtica dioica* (stinging nettle) can be preventive of UTIs in older men by improving urinary flow and ameliorating other lower urinary tract symptoms associated with benign prostatic hyperplasia.[70]

Many other herbs have been used successfully for treatment of UTIs but lack scientific research. Table 2 lists several of these herbs.

Nutrient Interventions for Lower Urinary Tract Infections

Vitamin C

Ascorbic acid was tested for its effect on UTI prevention during pregnancy. In a single-blind trial, 110 pregnant women were divided into two groups (55 in each group): one group received 200 mg ferrous sulfate, 5 mg folic acid, and 100 mg vitamin C daily, while a second group received only 200 mg ferrous sulfate and 5 mg folic acid daily for three months; urine was cultured monthly. Occurrence of UTIs was significantly lower in the group receiving vitamin C (12.7%) than the group without vitamin C (29.1%) (p=0.03; OR=0.35).[72]

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Vitamin A

In an RCT the effectiveness of vitamin A for prevention of UTIs was tested in 24 children, 12 in the vitamin A group and 12 in the placebo group (average age 7.6 years in the treatment group; 8.0 in the placebo group). During a UTI, those in the treatment group received 200,000 IU vitamin A in addition to 10 days of antimicrobial therapy, while the placebo group received just antimicrobial therapy in addition to placebo. Both groups were followed for one year and continued on "antimicrobial prophylaxis." Table 3 illustrates the infection rates in the treatment versus placebo groups. The difference before and after treatment in the vitamin A group was statistically significant.[73]

D-Mannose

D-mannose is a simple sugar that prevents adherence of certain bacterial strains to uroepithelial cells of the bladder. *In vitro* research has identified a mannose-specific lectin on the surface of adherent strains of *E. coli*.[76] Other *in vitro* research has elucidated the adherence mechanism. D-mannose is apparently the primary bladder cell receptor site for uropathogenic *E. coli*. The first step in adhesion involves the mannose-sensitive binding of FimH (adhesin at the tip of type 1 pili of *E. coli*, for example) to bladder epithelium.[77] One *in vitro* study found aromatic alpha-glycosides of mannose to be more effective inhibitors of *E. coli* adherence than alpha-methyl-mannoside.[78]

Table 3. Infection Rates: Vitamin A versus Placebo

	Six months prior to study	First six months of study	Second six months of study
Treatment group	3.58±0.42	0.75±0.21	1.75±0.30
Control group	2.75±0.27	2.83±0.42	2.66±0.35

Citrate Salts

Potassium or sodium citrate salts can be effective means of alkalinizing the urine. Alkaline urine can provide significant benefit for UTI symptoms, particularly dysuria. In a study of 205 women with UTIs, 48 hours of sodium citrate significantly improved symptoms in 80 percent of women who presented with bacteriuria. Failure to respond can signify significant bacteriuria.[74]

Alkalinizing the urine can also provide a more effective environment for certain botanicals, including uva ursi and berberine, to function.

Citrate salts can also be of benefit for urinary candidiasis, a condition associated with indwelling catheters. In a study of hospitalized patients with catheter-associated urinary Candida infection, 16 of 18 experienced significant increase in urinary pH and disappearance of Candida after oral potassium-sodium-hydrogen-citrate for two days to one month (average seven days).[75]

In a mouse model, alpha-D-mannose not only blocked adhesion of *E. coli* but also prevented invasion into bladder cells and subsequent formation of biofilm.[18] D-mannose inhibited adherence of 25 of 66 (42%) *E. coli* strains isolated from vaginal or buccal epithelial cells from women with recurrent UTIs.[79] In a study of urinary tract epithelial cells collected from voided urine from healthy women, a 2.5-percent concentration of D-mannose, D-mannitol, or alpha-methyl-D-mannoside completely inhibited *E. coli* adherence. The same concentration of D-lyxose, D-arabinose, D-fructose, and D-glyceraldehyde only partially inhibited adherence. Also, only partial inhibition was achieved by lower concentrations (0.1-1.0 percent) of mannose, mannitol, and mannoside.[80]

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Dietary Interventions

In a Finnish case-control study, 139 women in a university setting (students or faculty) who presented to the university clinic with acute UTI were compared to 185 controls who had not had a UTI for at least five years. A dietary questionnaire was completed by all participants. Fresh fruit juice consumption resulted in protection from UTIs (OR=0.66 per 2 dL of juice); a preference for berry juice in the Vaccinium family improved the odds even more (OR=0.28). Fermented dairy products containing probiotics were also protective with consumption ≥3 times weekly compared to <1 time weekly yielding an OR of 0.21. Consumption of coffee, tea, non-fermented milk products, and soft drinks had no significant effect on UTI frequency.[81]

In an epidemiological study at the University of California at Berkeley, urine was cultured from 99 women with acute UTIs. Bacterial drug resistance was determined as well as subjects' dietary habits. Women with *E. coli* UTI resistant to ≥2 antibiotics were significantly more likely to have eaten poultry ≥4 days per week (OR=3.7). Specific antibiotic resistance was also examined. Women with ampicillin-resistant *E. coli* were 3.5 times as likely to have eaten chicken, while pork consumption ≥1-3 times weekly was associated with ampicillin- and cephalosporin-resistant *E. coli* (OR=3.2). Frequent alcohol consumption (≥1-3 days/week) was also associated with UTIs resistant to ampicillin and cephalosporin. The authors speculated on the possibility of meat acting as a reservoir for *E. coli*. Foods that did not yield an increased risk for an antimicrobial-resistant infection included organic meats, organic produce, fish, raw meat, and alfalfa sprouts. Situations that did not appear to increase risk included location of meals (home, cafeteria, etc.), childcare providers, pet owners, frequency of sexual intercourse, and recent history of diarrhea.[82]

Probiotics for UTI Prevention

A number of probiotics have been studied for effectiveness in prevention of recurrent UTIs. Because *E. coli*, the primary pathogen involved in UTIs, travels from the intestines and/or vagina to inhabit the normally sterile urinary tract, improving the gut or vaginal flora can impact the urinary tract.

Mechanisms of Action of Probiotics for UTIs

An *in vitro* study examined 15 Lactobacillus species to determine the ability to inhibit growth and block uropathogenic bacterial adherence to vaginal epithelial cells. *Lactobacillus crispatus* was the species that demonstrated the strongest capacity to block bacterial adhesion. Of the pathogenic bacteria tested, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were most susceptible to blockage, while *Staphylococcus aureus* and *Proteus mirabilis* were most resistant. The various Lactobacillus species showed similar inhibitory effects; Pseudomonas was the most readily inhibited, while Enterococcus species E15 was the least inhibited.[83]

Since previous research indicated *Lactobacillus crispatus* was the species most likely to block bacterial adherence, it was tested for the ability to adhere to vaginal epithelium, a necessary step in the capacity to prevent pathogenic bacterial overgrowth. Vaginal epithelial cells from 51 women with a history of recurrent UTIs and 51 women without UTI history, combined *in vitro* with *L. crispatus*, were found to be very adherent to Lactobacillus. Interestingly, the adherence was stronger in women with chronic UTI history (50.5 organisms/cell) than in women without chronic UTIs (39.4 organisms/cell).[84]

Another *in vitro* study examined the antagonistic effect of five Lactobacillus strains against six pathogenic bacteria, including some uropathogens. While a pyelonephritic *E. coli* strain was sensitive to *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb12, and *Bifidobacterium longus* 46, no lower urinary tract cystitis *E. coli* were affected significantly.[85]

Animal Studies

A safety study of *Lactobacillus crispatus* vaginal suppositories was conducted on macaque monkeys, which are used extensively as a human vaginal physiology model. A one-time application was well tolerated with no changes on colposcopy and resulted in colonization of beneficial flora in three of eight monkeys.[86]

A Lactobacillus species specific to the murine model, *Lactobacillus murinus*, was able to partially inhibit growth of *Proteus mirabilis* (a common uropathogen in catheterized individuals) in mouse bladder and kidneys. When used as treatment for already existing infection, it decreased bacterial counts in the bladder but not the kidneys.[87]

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Clinical Studies

Lactobacillus Vaginal Suppositories for Prevention of UTI

Several clinical studies with varying outcomes have examined the effect of probiotic suppositories for prevention of UTIs. In a small pilot study, nine women (mean age 57.2) with recurrent UTIs (≥2 in the past year) used a *Lactobacillus crispatus* vaginal suppository every other night for one year. Infection rates were decreased from 5.0±1.6 in the year prior to treatment to 1.3±1.2 during the year of treatment (p=0.0007).[88]

In a somewhat larger study, 41 women with acute UTIs were treated with antibiotics (norfloxacin or trimethoprim/sulfamethoxazole) for three days, although recurrence occurred in 29 and 41 percent of patients in the norfloxacin and trimethoprim/sulfamethoxazole groups, respectively. Individuals were randomized to Lactobacillus suppositories (*L. rhamnosus* GR-1 and *L. fermentum* B-24) or placebo suppositories (sterilized skim milk) twice weekly for two weeks, then once at the end of each of the next two months. Recurrence was 21 percent in the Lactobacillus group compared to 47 percent in the placebo group.[89] The same group of researchers conducted a follow-up study comparing the effects of suppositories containing the same Lactobacillus species as the previous study with suppositories containing Lactobacillus growth factor (to enhance growth of already existing Lactobacilli). Fifty-five women (mean age 34; ≥4 UTIs in past 12 months) were randomly selected to Lactobacillus or growth factor suppositories once weekly for 12 months. At the end of 12 months both groups exhibited a 73-percent lower incidence of UTIs than in the 12 months prior to study onset (1.6/patient and 1.3/patient in the Lactobacillus and growth factor groups, respectively).[90]

Not all studies of the use of probiotic suppositories for UTI prevention have yielded positive results. In an RCT, 47 women (mean age 37; ≥3 UTIs in the previous 12 months) were assigned to Lactobacillus (*L. rhamnosus* or *L. casei* (4 cases)) or placebo suppositories – twice weekly for 26 weeks. No significant difference was noted on monthly UTI incidence between treatment and placebo groups (0.21 and 0.15, respectively).[91]

In another RCT, 30 women (ages 18-35) with a median UTI incidence of three in the previous year were randomized to receive *L. crispatus* suppositories or placebo suppositories once daily for five days and followed for six months. Four women (in one place the authors said two women) in the treatment group and one in the placebo arm reported one or more incidents of cystitis. No severe negative effects were reported, although seven women in the treatment group and none in the placebo group experienced asymptomatic pyuria. The authors reported the study was "not designed or statistically powered to evaluate the effect of *L. crispatus* CTV-05 on the rate of UTI recurrence."[92]

Oral Probiotics for UTI Prevention

In order for oral probiotic supplementation to benefit UTI risk, the bacteria must be able to colonize the intestinal tract and/or the urovaginal region. In a study of 10 women, *L. rhamnosus* GR-1 and *L. fermentum* RC-14 given twice daily for 14 days resulted in bacterial recovery from vaginal tissue within one week of commencing supplementation.[93]

Oral probiotic supplementation has been shown to benefit pediatric populations. In a multi-center RTC in 12 neonatal intensive care units, 585 preterm newborns were randomized to oral *Lactobacillus rhamnosus* GG (n=295) or placebo (n=290) once daily until discharge (average 47.3 and 48.2 days, respectively). Incidence of UTIs in the Lactobacillus group was 3.4 percent compared to 5.8 percent in the placebo group – clinically, but apparently not statistically, significant.[94]

In a case report, a six-year-old girl with no urinary tract anatomical abnormalities experienced three consecutive UTIs – once a month for three months. She was treated with increasingly potent antibiotic regimens and each episode was more serious – the last two spreading to her kidneys. After the third episode and antibiotic treatment, urine was negative for *E. coli* but feces was positive for a uropathogenic strain of *E. coli*. At that point the patient was given *L. acidophilus* DDS-1 twice daily for one month, followed by once daily for five months. After two months, the stool was negative for the pathogenic strain of *E. coli*. During probiotic treatment the girl had no UTI recurrence. However, probiotics were then discontinued and she experienced a UTI within two weeks – caused by *Klebsiella pneumoniae*.[95]

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Table 4. Nutrients, Probiotics, and Other Natural Approaches to Prevention of UTIs

Treatment	Form/Route of Administration	Dosage/Length of Study	Results of Treatment: Population	Strength of Research
Vitamin C	Oral ascorbic acid w/ or w/o ferrous sulfate & folic acid	100 mg ascorbate daily for 3 mo (w/ or w/o 200 mg ferrous sulfate & 5 mg folic acid)	Prevention of UTIs in pregnant women	Single-blind trial (n=110; 55 in each group)
Vitamin A	Antimicrobial therapy w/ oral vitamin A or placebo during infection	One 200,000 IU dose vitamin A or placebo during infection	Prevention of UTIs in children	Small RCT (n=24)
D-Mannose	Direct bladder inoculation via catheterization of heptyl-α-D-mannose (HM)	Incubation of *E. coli* with 5mM HM	Prevention of adherence of *E. coli* to mouse bladder epithelium	Animal study
	Uroepithelial cells from healthy women extracted from voided urine	Incubated with 2.5% concentration of D-mannose, D-mannitol, or α-methyl-D-mannoside	Complete inhibition of *E. coli* adherence to cells from healthy women	*ex vivo / in vitro*
Probiotics	*Lactobacillus crispatus*; vaginal suppository	Insertion every other night for 1 yr	Prevention of UTI (mean age 57.2)	Small pilot study (n=9)
	L. rhamnosus and *L. fermentum* or placebo; vaginal suppository	Insertion twice weekly for 2 wk; then once at the end of each of the next 2 mo	Prevention of UTIs	RCT (n=41)
	L. rhamnosus and *L. fermentum* or Lactobacillus growth factor; vaginal suppository	Insertion once weekly for 12 mo	Prevention of UTIs (mean age 34)	RCT (n=55)
	Lactobacillus rhamnosus GG or placebo; oral	Once daily from birth until discharge (average 47.5 days)	Prevention of UTIs in preterm infants	Multi-center RCT (n=585)
	Saccharomyces boulardii; oral	Once daily for 5 days	Decrease of *E. coli* colonization in stool of children (ages 3-16 yr)	Small pilot study (n=24)
Estriol	Estriol or placebo intravaginal cream	Cream applied once nightly for 2 wk; then twice weekly for 8 mo	Prevention of UTI, increase in Lactobacillus in postmenopausal women	RCT (n=93; 60 completed)

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Children are particularly susceptible to UTIs caused by bacterial migration from the intestinal tract. In a study of children and teenagers (14 boys, 10 girls; ages 3-16) supplementation of the probiotic yeast *Saccharomyces boulardii* resulted in a significant decrease in *E. coli* colonies in the stool. *S. boulardii* once daily for five days resulted in a decrease from an average of 384,625 colonies (measured in g/mL of stool) prior to treatment to an average of 6,283 after treatment.[96]

Estriol for UTI Prevention

Hormone waning in postmenopausal women results in thinning of the vaginal and urethral mucosa, disruption of the normal vaginal flora, and increased risk for UTIs. In fact, 10-15 percent of women over age 60 suffer from recurrent UTIs. In an RCT, 93 postmenopausal women with recurrent UTIs were randomized to receive intravaginal estriol cream (n=50/36 completed) or placebo cream (n=43/24 completed). The cream (0.5 mg estriol or placebo) was inserted once nightly for two weeks followed by twice weekly for eight months. The incidence of UTI in the estriol group was significantly lower than the placebo group (0.5 episodes per patient year in the estriol group compared to 5.9 episodes in the placebo group). Lactobacilli, which had been absent in all vaginal cultures at the beginning of the trial, reappeared in 61 percent of the estriol group but none of the placebo group.[97]

Conclusion

Simple, uncomplicated infections of the lower urinary tract are common occurrences, particularly in sexually active young women, during pregnancy, and in peri- and postmenopausal women. The conventional approach, after urine dipstick or culture, is to treat with antibiotics at the first sign of an infection. In addition, women with chronically recurring infections are often prescribed long-term antibiotic treatment, contributing to gut and vaginal dysbiosis and antibiotic resistance.

Numerous clinical studies indicate several natural substances may provide effective prophylaxis in the case of recurrent infection. Nutrients and botanicals that have demonstrated the greatest effectiveness include cranberry, berberine, and probiotics. Other interventions with some positive clinical evidence but requiring further study include uva ursi, vitamins C and A, mannose, and estriol cream. In addition, numerous botanicals lacking in clinical research have a long history of successful use in the treatment of UTIs. Table 4 summarizes nutrients and other non-botanical approaches to prevention and treatment of UTIs.

While most clinical research has examined the effect of natural substances for prevention of UTIs, the mechanisms of action (primarily anti-adherence) and clinical experience of health care practitioners demonstrate effectiveness when used acutely, particularly at the first sign of infection. Botanicals and botanical extracts that can be particularly effective for acute use, but not intended for long-term use, include berberine and uva ursi; whereas, cranberry, mannose, probiotics, and estriol are suitable for long-term prevention.

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