

Have you tried these innovative alternatives to antibiotics for UTI prevention?

🔴 With antibiotic resistance on the rise, it helps to know which alternative therapies have data behind them—and for which populations they have been studied

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CASE **Recurrent UTI and antibiotic resistance**
A 53-year-old postmenopausal woman with a history of culture-proven recurrent *Escherichia coli* urinary tract infections (UTIs) presents to the clinic with symptoms of UTI. She was previously treated with a postcoital regimen of trimethoprim/sulfamethoxazole, based on sensitivities identified by culture. A past work-up of her upper and lower urinary

tract was negative. You send a catheterized specimen for culture; again, *E. coli* is identified as the pathogen but proves resistant to her current antibiotic regimen.

What treatment alternatives, aside from antibiotics, are available for this patient—and how might they affect resistance?

Increased antibiotic usage has led to greater bacterial resistance, which is perpetuated by clonal spread. Resistant strains of *E. coli* have been found in household members, suggesting host-host transmission as a mechanism for dissemination. Alternative treatments that reduce the use of antibiotics may minimize bacterial resistance and increase the efficacy of treatment. In the **TABLE** (page 18), we summarize alternative approaches to the treatment of recurrent UTI. We also describe a strategy to alleviate symptoms.

Vaginal estrogen is the only proven alternative to antibiotics for postmenopausal women

A lack of estrogen is a risk factor for UTI and is associated with atrophic mucosa, leading to decreased colonization with lactobacilli, increased vaginal pH, and *E. coli* colonization.

A randomized, double-blind, placebo-controlled trial of intravaginal estriol cream

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Alternatives to antibiotics in the treatment and prevention of recurrent UTI

Category	Type	Examples and doses, if recommended
Vaginal estrogen	Conjugated estrogen cream Estradiol <ul style="list-style-type: none"> • Cream • Ring • Tablet 	Premarin cream, 0.5–2 g vaginally twice weekly <ul style="list-style-type: none"> • Estrace, 2–4 g daily for 1–2 weeks, then 1 g 1–3 times weekly • Estring, 1 ring replaced every 90 days • Vagifem, 1 tablet (10 µg) daily for 2 weeks, then 1 tablet twice weekly
Nutritive agents	Cranberry juice Cranberry tablets Cystopurin Lactobacilli Blueberry products	Not recommended 1 tablet (300 to 400 mg, depending on manufacturer) twice daily Not recommended Vivag, EcoVag, 1 capsule daily by vagina for 5 days, then once weekly for 10 weeks Not recommended
Anti-infective drugs	Methenamine hippurate Methenamine mandelate Methylene blue	Urex or Hiprex, 1 g orally twice daily Mandelamine, 1 g orally 4 times daily Future therapy
Urinary acidifiers	Vitamin C/ascorbic acid	1–3 g orally 3–4 times daily
Herbal remedies	Uva ursi Forskolin	Not recommended for long-term use Not recommended
Behavioral changes		Adequate hydration Postcoital voiding

versus placebo in 93 postmenopausal women found a significant decrease in the rate of UTI among women who used the cream.¹ After 8 months of follow-up, the incidence of UTI was 0.5 vs 5.9 episodes per patient-year ($P < .001$). Interestingly, all pretreatment cultures were negative for lactobacilli. One month after treatment, 61% of women in the estriol group were culture-positive for lactobacilli, compared with 0% of the placebo group.¹

A 2008 Cochrane review of nine studies concluded that vaginal estrogen reduces the number of UTIs in postmenopausal women, with variation based on the type of estrogen and duration of use.²

Adverse effects are mild

Twenty-eight percent of the estriol group in the randomized trial described above

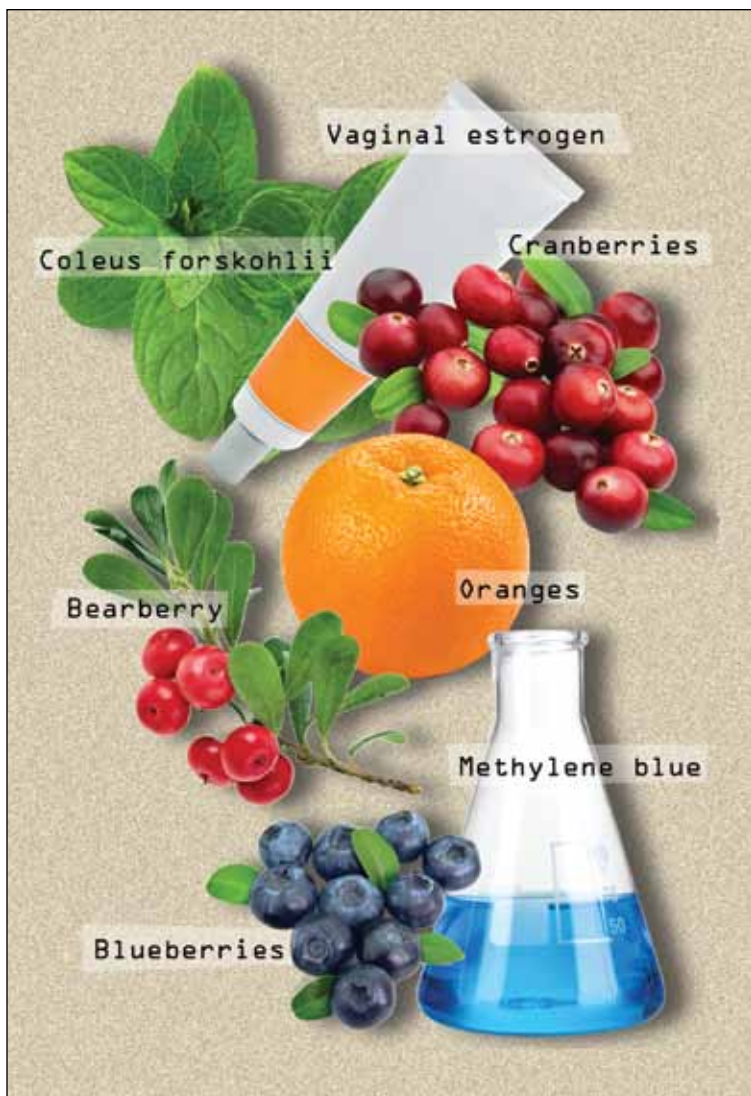
withdrew from treatment, with 20% citing local side effects, including vaginal irritation, burning, or itching—all of which were mild and self-limited.¹ Other possible adverse effects include breast tenderness, vaginal bleeding or spotting, and discharge.²

Clinical recommendations

Given the efficacy of this therapy, we recommend topical estrogen for postmenopausal patients with recurrent UTIs.

Cranberry juice may reduce UTI, but many patients withdraw from treatment

Cranberries belong to the *Vaccinium* species, which contains all flavonoids, including anthocyanins and proanthocyanidins. It was previously thought that the acidification of



urine produced an antibacterial effect, but several trials have documented no change in urine levels of hippuric acid when cranberry products are given, with no acidification of the urine.³ Current theory suggests that cranberries prevent bacteria from adhering to the uroepithelial cells of the walls of the bladder, by blocking expression of *E. coli*'s adhesion molecule, *P. fimbriae*, so that bacteria are unable to penetrate the mucosal surface.^{4,5} The major benefit of cranberry products over antibiotic prophylaxis is that they do not have the potential for resistance.⁴

A 2008 Cochrane review concluded that cranberry juice may reduce symptomatic UTIs, particularly among young, sexually

active women—but there is a high rate of withdrawal from treatment.⁶ The optimal method of administration and dose remain unclear. In contrast, two recent randomized, controlled trials—published after the Cochrane review—found no difference in the rate of recurrent UTI in premenopausal women.^{7,8} Adverse effects in these two trials included constipation, heartburn, loose stools, vaginal itching and dryness, and migraines. Of note, there was no statistical difference in side effects between the cranberry and placebo groups.⁷

Vaccinium tablets may be protective in older women

Cranberry extracts of 500 mg to 1,000 mg daily have been compared with antimicrobial prophylaxis in two randomized, double-blind, controlled trials. The trials demonstrated mixed benefits. Trimethoprim/sulfamethoxazole was associated with a lower rate of UTI in younger women, compared with cranberry extracts alone ($P = .02$), while cranberry extracts were slightly more effective than trimethoprim alone in older women.^{9,10} Cranberry tablets were not associated with bacterial resistance, were cheaper, and were viewed as a more natural option. The interventions were equally well tolerated.

Overall efficacy of cranberry tablets is unclear. Side effects, albeit mild, included gastrointestinal disturbances, vaginal complaints, and rash or urticaria. There was no significant difference in the rate of adverse effects between antimicrobial treatment and cranberry tablets.⁹

Cystopurin has not been studied

Cystopurin is an over-the-counter (OTC) tablet containing cranberry extract and potassium citrate that is taken three times daily (3 g/dose) for 2 days. Interestingly, although a proposed mechanism for the efficacy of vitamin C and cranberry juice has been a reduction of pH, potassium citrate is an alkalinizing agent that is reported to relieve burning and reduce urinary urgency and frequency. No studies have assessed this medication in the treatment of a UTI or its symptoms.

ILLUSTRATION: MARY ELLEN NIATAS

Clinical recommendations

The evidence is mixed on the use of cranberry products to reduce recurrent UTI. However, given the limited side effects associated with these products, we offer cranberry tablets to patients who have recurrent UTIs who are interested in a more natural alternative.

We generally do not recommend cranberry juice because the added fluid volume tends to exacerbate frequency and urgency symptoms.

Lactobacilli suppositories may benefit postmenopausal women

Lactobacilli are fastidious gram-positive rods and are usually the dominant component of the vaginal flora.¹¹ They prevent colonization and infection by more virulent bacteria by competing for adhesion receptors and nutrients as well as producing antimicrobial substances such as hydrogen peroxide and lactic acid. A decrease in lactobacilli leaves the urinary tract susceptible to infectious organisms that may colonize the vaginal mucosa and increase the risk of recurrent UTI.¹²⁻¹⁴

A 2008 review of randomized, controlled trials of oral lactobacilli and UTI was inconclusive, due to inconsistent dosing strategies and small sample sizes.¹⁵ A 2011 randomized, double-blind, placebo-controlled phase 2 trial of Lactin-V, a lactobacilli vaginal suppository, found that it reduced the rate of recurrent UTI. Lactin-V contains a hydrogen-peroxide-producing *Lactobacillus crispatus* developed as a probiotic that was determined to be safe and tolerable as a vaginal suppository in a phase 1 trial.¹⁶ The phase 2 trial enrolled 100 young premenopausal women with a history of recurrent UTI who took either Lactin-V or placebo daily for 5 days, then weekly for 10 weeks. Women in the Lactin-V group who had high levels of *L. crispatus* colonization experienced a significant reduction in the rate of UTI (15% vs 27% in the placebo group), but the effect did not reach statistical significance.¹⁴

Little difference in adverse effects

Adverse effects were reported among 56% of patients who received Lactin-V versus 50% of those given placebo. The most common of these were vaginal discharge, itching, and moderate abdominal discomfort.¹⁴ Although lactobacillus can potentially promote UTI, this phenomenon is rare.¹¹

Regrettably, Lactin-V is not currently available in the United States. However, there are other lactobacilli vaginal suppositories on the market (TABLE, page 18). Given the low risk associated with their use, they should be considered as an alternative for patients who cannot or will not use estrogen.

Clinical recommendations

Probiotics such as lactobacilli are categorized as “dietary supplements”; as such, they are not regulated by the US Food and Drug Administration. We recommend the use of lactobacilli suppositories in postmenopausal women who have a contraindication to (or prefer to avoid) vaginal estrogen.

Skip blueberry products for now

Like cranberries, blueberries belong to the *Vaccinium* species and are thought to interfere with bacterial adhesion to the walls of the bladder. One in vitro trial suggests that blueberries also have antiproliferation effects, although no clinical studies have been performed to date to further investigate safety or efficacy.⁴ Consequently, we do not recommend use of these products.

Methenamine salts may benefit some populations

These anti-infective agents, including methenamine hippurate and methenamine mandelate, often are used to prevent UTI. They are found in combination OTC medications, such as Prosed DS and Urelle. Methenamine salts are bacteriostatic to all urinary tract pathogens due to their production of formaldehyde.^{3,16}

Although methenamine produces varying concentrations of formaldehyde,



Lactobacilli suppositories may benefit postmenopausal women who have a contraindication to (or prefer to avoid) vaginal estrogen

depending on the acidity of the urine, there is no evidence that acidified urine enhances methenamine's effects.¹⁶

Advantages of methenamine include the fact that it produces no changes in gut flora, poses no risk for antimicrobial resistance, and has low toxicity. It also is low in cost.¹⁷

Methenamine is contraindicated in patients with renal insufficiency or severe hepatic disease.

Adverse reactions are generally mild and include gastrointestinal disturbances, skin rashes, dysuria, and microscopic hematuria.¹⁶

Methenamine hippurate

A 2007 Cochrane review, deemed up to date in 2010, analyzed 13 randomized, controlled trials involving 2,032 participants. Subgroup analyses suggested that methenamine hippurate may be of some benefit to patients without renal tract abnormalities; these patients experienced significantly reduced symptoms after short-term treatment of 1 week or less.

Patients with spinal injury do not appear to benefit from treatment, according to a randomized, double-blind, placebo-controlled trial by Lee and colleagues.¹⁸

Methenamine mandelate

This agent is commonly used to prevent recurrent UTI, although there is a paucity of randomized, controlled trials to support its use. One such trial in patients with neurogenic bladder found that methenamine mandelate with acidification was superior to placebo ($P < .02$) for preventing UTI.¹⁹ Beyond this population, however, it's difficult to assess methenamine's efficacy in the prevention of recurrent UTI.

Methylene blue may be useful in the elderly

Methylene blue is a light-activated compound described as "photodynamic antimicrobial chemotherapy" (PACT). Once illuminated, it becomes a bactericide, causing excitation of electrons followed by one of two reactions:

- reduction oxidation

- formation of a labile singlet oxygen and then oxidation.

This makes resistance unlikely.

In an in vitro study, methylene blue was as effective as levofloxacin against *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Enterococcus*, and *Staphylococcus aureus* when illuminated.

Potential benefits of this mode of treatment include local exposure and no drug interactions.

We suggest that methylene blue be placed and illuminated with a special catheter that would target UTI in the elderly population, among whom 52% of UTIs are associated with use of catheters.²⁰ In vivo effects, adverse effects, and cost are not known, which limits current applicability of this compound.

Vitamin C may reduce UTI in pregnancy

The proposed mechanism for the efficacy of vitamin C for the treatment of UTI is the acidification of urine, which is believed to reduce the proliferation of bacteria. However, several studies have shown that vitamin C, at various doses, does not reliably reduce urine pH.^{15,21,22} Nonetheless, 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 ferrous sulfate (200 mg), folic acid (5 mg), and vitamin C (100 mg) daily for 3 months
- The other received ferrous sulfate (200 mg) and folic acid (5 mg) daily for 3 months.

Urine was cultured monthly. The incidence of UTI was significantly lower in the group receiving vitamin C (12.7%), compared with the control group (29.1%) ($P = .03$; odds ratio [OR], 0.35).²³

Uva ursi may have a prophylactic effect

Uva ursi (UVA-E) is one of the most commonly used herbal supplements for



Among pregnant women, the incidence of UTI was significantly lower in the group receiving vitamin C, compared with the control group (12.7% vs 29.1%)

treatment of UTI. The crude extract from Bearberry or *Arctostaphylos uva-ursi* has been shown to act as an antimicrobial by decreasing bacterial adherence.²⁴ In addition, investigators have found the extract to have diuretic and anti-inflammatory properties.^{25,26} However, few studies have explored its efficacy. One randomized, controlled trial that included 57 women (30 allocated to UVA-E and 27 to placebo) found a statistically significant reduction in the rate of recurrence at 1 year among women taking UVA-E, compared with those who did not.²⁷

Note that the women in this trial were given UVA-E for 1 month only. Long-term use of this herb has not been studied and may cause liver damage.

In a mouse model, forskolin reduced urinary-tract *E. coli*

This herb is derived from Indian coleus (*Coleus forskohlii*), a member of the mint family. It has been used primarily for its antiasthmatic, spasmolytic, and antihypertensive effects. It is believed to activate adenylate cyclase, increasing intracellular cyclic AMP (cAMP) concentrations and activating a number of key enzymatic pathways.²⁸

The findings of a recent observational study have spurred the use of forskolin in the treatment of recurrent UTI.²⁹ In the study, conducted on mice, when forskolin was injected into the bladder, intracellular *E. coli* decreased.

It is theorized that the incorporation of bacteria into intracellular vesicles of the bladder prevents exposure to antibiotics. When combined with an antibiotic, forskolin may increase bacterial elimination and thus lower the risk of recurrent infection. However, no randomized trials have evaluated the efficacy of this treatment.

Patients who are already taking antihypertensive medications should be cautious when using this herb, as it may lead to a drop in blood pressure.

Behavior changes are risk-free

One of the natural mechanisms that promotes bacterial elimination and prevents bacterial growth is urination. A recent review article on the subject found several contradictory studies on the effect of fluid intake on the risk of UTI.³⁰ Although there is no definitive evidence that susceptibility to UTI is linked to fluid intake, adequate hydration may reduce the risk of recurrent infection.

Similarly, voiding shortly after sexual intercourse may prevent UTI. One case-control study found a modest protective effect in patients who voided after intercourse.³¹

Clinical recommendations

Given the low risk of these measures, it seems reasonable to recommend postcoital voiding and increased fluid intake to prevent recurrent UTI.

A focus on symptoms

Phenazopyridine, the chemical found in numerous OTC medications, such as Pyridium, AZO, and Uristat, was discovered by Swiss chemist Bernhard Joos in the 1950s. Its mechanism of action is still unclear, but approximately 65% of the oral dose is excreted by the kidneys, where it has a direct topical analgesic effect.^{32,33}

Clinical recommendations

Patients should be warned that phenazopyridine will lead to orange urine discoloration.


The medication is generally well tolerated but should be used with caution in patients with acute renal failure, hemolytic anemia, or methemoglobinemia, as it may exacerbate these conditions.

Last words

Recurrent UTIs are common and impose a significant financial burden on our health-care system. Although there are several antibiotic treatment options and dosing regimens available, increasing antibiotic resistance has made management of recurrent UTIs more difficult. Effective alternative



Phenazopyridine, an ingredient in several OTC medications, may exert a topical analgesic effect in women who have UTI

treatments that reduce the reliance on antibiotics may minimize bacterial resistance and decrease the financial burden of this common condition. 

CASE Resolved

To reduce vaginal *E. coli*, the patient is started on vaginal estrogen cream. She is also advised to purchase cranberry tablets to help prevent future infections. Last, she is counseled about behavioral changes she can make and prescribed a short course of antibiotics to treat her culture-proven infection.

References

- Raz R, Stamm W. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*. 1993;329(11):753-756.
- Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;2:CD005131.
- Mayrer AR, Andriole VT. Urinary tract antiseptics. *Med Clin North Am*. 1982;66(1):199-208.
- Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. *Mol Nutr Food Res*. 2007;51(6):738-745.
- Salvatore S, Salvatore S, Cattoni E, et al. Urinary tract infections in women. *Eur J Obstet Gynecol Reprod Biol*. 2011;156(2):131-136.
- Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2008;1:CD001321.
- Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary *Escherichia coli* in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc*. 2012;87(2):143-150.
- 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. *Clin Infect Dis*. 2011;52(1):23-30.
- Beerepoot MAJ, Reit G, Nys S, et al. Cranberries vs antibiotics to prevent urinary tract infections. *Arch Intern Med*. 2011;171(14):1270-1278.
- McMurdo MET, Argo I, Phillips G, Daly F, Davey P. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. *J Antimicrob Chemother*. 2009;63(2):389-395.
- Barrons R, Tassone D. Use of *Lactobacillus* probiotics for bacterial genitourinary infections in women: a review. *Clinical Therapeutics*. 2008;30(3):453-468.
- Miller JL, Krieger JN. Urinary tract infections: cranberry juice, underwear, and probiotics in the 21st century. *Urol Clin N Am*. 2002;29(3):695-699.
- Osset J, Bartolome R, Garcia E, et al. Assessment of the capacity of *Lactobacillus* to inhibit the growth of uropathogens and block their adhesion to vaginal epithelial cells. *J Infect Dis*. 2001;183(3):485-491.
- Stapleton AE, Au-Yeung M, Hooton TM, et al. Randomized, placebo-controlled phase 2 trial of *Lactobacillus crispatus* probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clin Infect Dis*. 2011;52(10):1212-1217.
- Castello T, Girona L, Gomez MR, Mena Mur A, Garcia L. The possible value of ascorbic acid as a prophylactic agent for urinary tract infection. *Spinal Cord*. 1996;34(10):592-593.
- Gleckman R, Alvarez S, Joubert DW, Matthews SJ. Drug therapy reviews: methenamine mandelate and methenamine hippurate. *Am J Hosp Pharm*. 1979;36(11):1509-1512.
- Vainrub B, Musher DM. Lack of effect of methenamine in suppression of, or prophylaxis against, chronic urinary tract infection. *Antimicrob Agents Chemother*. 1977;12(5):625-629.
- Lee BB, Simpson JM, Craig JC, Bhuta T. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2007;4:CD003265.
- Kevorkian CG, Merritt JL, Ilstrup DM. Methenamine mandelate with acidification: an effective urinary antiseptic in patients with neurogenic bladder. *Mayo Clin Proc*. 1984;59(8):523-529.
- Wainwright M, Stanforth A, Jones R, Loughran C, Meegan K. Photoantimicrobials as a potential local approach to geriatric UTIs. *Lett Appl Microbiol*. 2010;50(5):486-492.
- Bannwart C, Hagmaier V, Straumann E, Hofer H, Buillemier JP, Trutishauser G. Modification of urinary pH through ascorbic acid. *Helv Chir Acta*. 1981;48(3-4):425-428.
- Hetey SK, Kleinberg ML, Parker WD, Johnson EW. Effect of ascorbic acid on urine pH in patients with injured spinal cords. *Am J Hosp Pharm*. 1980;37(2):235-237.
- Ochoa-Brust GJ, Fernandez AR, Villanueva-Ruiz GJ, et al. Daily intake of 100 mg ascorbic acid as urinary tract infection prophylactic agent during pregnancy. *Acta Obstet Gynecol Scand*. 2007;86(7):783-787.
- Turi M, Turi E, Kotjalg S, Mikelsaar M. Influence of aqueous extracts of medicinal plants on surface hydrophobicity of *Escherichia coli* strains of different origin. *APMIS*. 1997;105(12):956-962.
- Beaux D, Fleurentin J, Mortier F. Effect of extracts of *Orthosiphon stamineus* Benth, *Hieracium pilosella* L., *Sambucus nigra* L. and *Arctostaphylos uva-ursi* (L.) Spreng, in rats. *Phytother Res*. 1999;13(3):222-225.
- Kubo M, Ito M, Nakata H, Matsuda H. Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. I. Combined effect of 50% methanolic extract from *Arctostaphylos uva-ursi* (L.) Spreng. (bearberry leaf) and prednisolone on immuno-inflammation [article in Japanese]. *Yakugaku Zasshi*. 1990;110(1):59-67.
- Larsson B, Jonasson A, Fianu S. Prophylactic effect of UVA-E in women with recurrent cystitis: a preliminary report. *Curr Ther Res*. 1993;53(4):441-443.
- Christenson JT, Thulesius D, Nazzal MM. The effect of forskolin on blood flow, platelet metabolism, aggregation and ATP release. *Vasa*. 1995;24(1):56-61.
- Bishop BL, Duncan MJ, Song J, Li G, Zaas D, Abraham SN. Cyclic AMP-regulated exocytosis of *Escherichia coli* from infected bladder epithelial cells. *Nat Med*. 2007;13(5):625-630.
- Beetz R. Mild dehydration: a risk factor of urinary tract infection? *Eur J Clin Nutr*. 2003;57(Suppl 2):S52-58.
- Foxman B, Chi JW. Health behavior and urinary tract infection in college-aged women. *J Clin Epidemiol*. 1990;43(4):329-337.
- Thomas BH, Whitehouse LW, Solomonraj G, Paul CJ. Excretion of phenazopyridine and its metabolites in the urine of humans, rats, mice, and guinea pigs. *J Pharm Sci*. 1990;79(4):321-325.
- Aizawa N, Wyndaele JJ. Effects of phenazopyridine on rat bladder primary afferent activity, and comparison with lidocaine and acetaminophen. *NeuroUrol Urodyn*. 2010;29(8):1445-1550.