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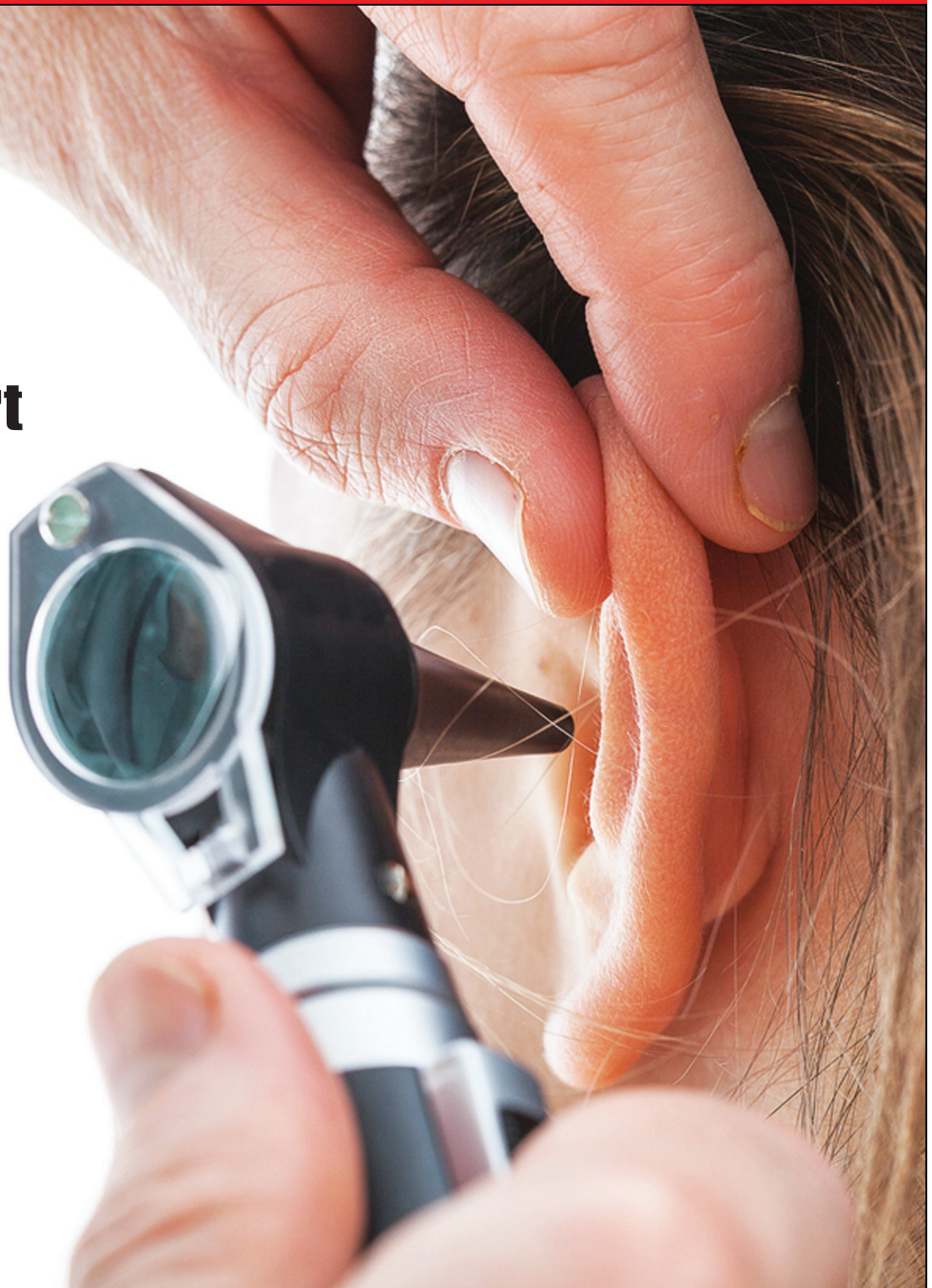
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Nutraceutical and UTIs

SANJAY AGRAWAL

Introduction

Urinary tract infections (UTIs) are amongst the most common community-acquired infectious diseases, with annual costs estimated to be higher than \$1.5 billion in the United States. The impact on public health is significant due to the high recurrence rate and the effect on the patients' quality of life. Most of these patients are women with recurrent bacterial cystitis or acute pyelonephritis, and the causative pathogens can usually be eradicated with a short course of oral antimicrobial therapy. However, the antibiotic treatment can lead to long term impairment of the normal microbiota of the vagina and gastrointestinal tract and to the development of multidrug-resistant microorganisms. This paper explores alternative approaches to treating UTIs, which involve phytotherapy. The paper delves into the use of Cranberry extracts, Chinese herbal medicine, D-Mannose and Probiotics as therapeutic options, and looks at their efficacy in treatment of UTIs.

Aim and Objectives:

To explore alternative approaches for treatment of UTIs that involve phytopharmaceuticals and to compare their efficiency with the currently utilized standard protocol that advises the use of antibiotics.

The mortality rate from UTIs is reported to be as high as 1% in men and 3% in women due

to development of pyelonephritis and urosepsis. After an initial UTI, approximately 20-30% of women with a UTI will have a second UTI within 6 months, and 3% will experience a third UTI during that time. In consequence, women with recurrent UTIs (rUTIs) reported a high indirect cost because of the number of working days lost. There is no well-established recommendation for a 'standard' prophylactic antibiotic management to prevent UTI recurrence. Many women have few signs and symptoms of UTIs without any evidence of bacterial presence. In this sense, the use of phytotherapy to alleviate symptoms related to UTI and to decrease the rate of symptomatic recurrence seems a good alternative and is more commonly used off late.

There are many good reasons for this approach e.g. the low side-effects, low costs and a high level of compliance. It is also important to note the low rate of efficacy of standard preventive measures with subsequent patient disappointment and drop-outs. Traditionally, nutraceuticals and phytotherapy have been used to prevent rUTIs in otherwise healthy women. Although the results from a number of clinical studies have supported their benefits, the efficacy of nutraceuticals and phytotherapy on prevention of rUTIs remains controversial, due to heterogeneity of published studies in terms of methodology and the reported findings such as trial design, inclusion/exclusion criteria, patient characteristics, outcome measures, as well as heterogeneity of the compounds used. The latest Cochrane reviews

on UTI management concluded as follows:

- Chinese herbal medicine alone or in conjunction with antibiotics may be beneficial for treating recurrent UTIs during the acute phase of infection and may reduce the recurrent UTI incidence for at least six months post-treatment.¹
- No significant benefit was demonstrated for probiotics compared with placebo or no treatment, but a benefit cannot be ruled out as the data is sparse, and derived from small studies with poor methodological reporting.¹
- Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and poor evidence for prevention of UTI, cranberry juice cannot currently be recommended for the prevention of UTIs.

International guidelines recommendations

The latest version of European Association of Urology (EAU) guidelines on urological infections states that there are many non-antimicrobial measures for prevention of recurrent UTIs but only a few of them are based on well designed studies which are needed to make evidence-based recommendations. In particular, EAU guidelines highlight that there is no convincing benefit for lactobacillus products or cranberry extracts as prophylaxis of recurrent UTI. The Scottish Intercollegiate Guidelines Network confirmed the recommendations from the EAU guidelines, highlighting that

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cranberry products (juice, tablets, and capsules) are not standardized and the concentrations of active ingredients are not known; hence the concentration may also fluctuate between batches of the same product. There is no evidence to support the effectiveness of cranberry products for treating symptomatic episodes of UTI. The Society of Obstetricians and Gynecologists of Canada's guidelines suggest to inform the patients about the efficacy of cranberry products in reducing recurrent urinary tract infections.

^(IA)² Moreover, they advise against these probiotics and vaccines due to lack of demonstrated efficacy. ^(II-2C)²

Key message

- International guidelines agree that there is no convincing benefit for the use of nutraceuticals and/or phototherapy's prophylaxis of recurrent UTIs.
- New RCTs are needed.

Alternative non-antibiotic measures

Contemporary reviews identify four alternative compounds for non-antibiotic management of recurrent UTIs:

- Cranberry
- Probiotics
- Chinese herbal medicine
- D-mannose

Cranberry extracts

A Cochrane review from 2008 concluded that cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46-0.90) compared with placebo/control in women with recurrent UTIs. In a more recent Cochrane review it was concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTIs in women

with recurrent UTIs. The changed view is based on the inclusion of two additional trials in their meta-analysis. In these two RCTs the effectiveness of cranberry extract was compared with low-dose antibiotic prophylaxis. McMurdo et al. concluded that trimethoprim had a limited advantage over cranberry extract in the prevention of recurrent UTIs in older women. In addition, Beerepoot et al. showed that cranberry capsules are less effective than low-dose (480 mg) trimethoprim/sulfamethoxazole in the prevention of recurrent UTIs in premenopausal women. *Vaccinium macrocarpon*, named also American cranberry, is a rich source of polyphenols that show several in vitro properties, including antibacterial, antiviral, antimutagenic, anticarcinogenic, antitumorigenic, antiangiogenic, anti-inflammatory, and antioxidant effects. Moreover, cranberry extract is a promising therapy due to the fact that it is an anti-adhesive agent against *E. coli* strains and thus prevents the development of antibiotic resistance. On the other hand, it has been demonstrated that uropathogenic bacteria may have an intestinal origin and the intestinal tract could be an alternative site where the active components of cranberry extract may interact with *E. coli* decreasing its infectivity. Several authors demonstrated that some extracts from cranberry decrease the pathogenicity of *Proteus mirabilis* by limiting urothelial cell invasion and improving the mucosal immunity to uropathogens.

Probiotics

Probiotics are defined as “a preparation of, or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a host compartment and by that

exert beneficial health effects in this host”.³ The hypothesis is that probiotics are able to establish a barrier against infectious pathogens ascending the urinary tract, colonizing, and subsequently causing infection.³ The latest Cochrane review showed that probiotics were not superior to placebo in reducing the risk of recurrent symptomatic bacterial UTI. The conclusion was based on 6 studies with (352 participants (RR 0.82, 95% CI 0.60 to 1.12; I²=23%). Hence the data were derived from small studies with poor methodological quality.³ On the other hand the reported evidences could not rule out a reduction or increase in recurrent UTI in women with recurrent UTI who use prophylactic probiotics. One RCT did not provide sufficient evidence to conclude on the effect of probiotics versus antibiotics.³

Chinese herbal medicine

Chinese herbal medicine is a part of Traditional Chinese Medicine and represents complex herbal formulae usually comprising 10 to 15 different herbs.³

Chinese herbal medicine formulae may be standardized or individualized according to specific needs and patients' characteristics. The hypothesis supporting the efficacy of Chinese herbal medicine is based on in vitro research suggesting that some commonly used Chinese herbs may confer significant diuretic, antibiotic, immune enhancing, antipyretic, anti-inflammatory and pain relieving effects. The latest Cochrane review, including 7 RCTs with a total of 542 women, concluded that Chinese herbal medicine alone or in conjunction with antibiotics may be useful in treating recurrent UTIs during the acute phase of an infection and may reduce the incidence of recurrent UTI for at least six

months post-treatment.³ However, this evidence is based on a small number of poor quality studies with severe bias that should be taken into account.

D-mannose

D-mannose is a sugar that has an important role in human metabolism, especially in the glycosylation of certain proteins. The hypothesis is that D-mannose inhibits bacterial adherence to uroepithelial cells. In fact, in vitro and in vivo animal studies demonstrated that D-mannose can inhibit the adhesion of Type 1 fimbriae of the uropathogenic bacteria to uroepithelial cells.⁴

Risk factor assessment as a guide to treatment

Assessment of the risk for recurrence is not only important for predicting the probability of a new recurrence but also for the development of a tailored therapeutic approach on the basis of patient's characteristics. A constipated patient, for example, should be informed about the relationship between the constipation and the risk of new UTI. A nutraceutical or phytotherapeutic approach acting on the bowel function should be preferred. Moreover, a patient who has reported more than 3 episodes of previous UTIs and correlation with sexual intercourses should be treated with nutraceutical products that are able to interfere with the E. coli adhesion to urothelial cell and invasion. Furthermore, a correct non-antibiotic approach should work against one or more of the following infection mechanisms:

- Reduction of the bacterial load in the intestinal reservoir with concomitant correction of the constipation
- Reduction of the spread of E. coli from the perianal zone to the urethra and bladder.

- Reduction of the adhesion and invasion of uropathogens to the urothelial cells.
- Mobilization of the immune system against the intracellular bacterial communities avoiding reactivation and new symptomatic recurrences.

Discussion

There is no ideal nutraceutical or phytotherapeutic compound so far that is able to act in all the aforementioned ways to decrease the risk of recurrence. Even if cranberry extracts seem to be able to act along more than one pathway, there are limitations due to the pharmacokinetic and pharmacological characteristics of this compound. As discussed above, cranberry extracts are able to reduce the adherence of E. coli to the urothelial cells and reduce the adherence of bacterial strains also to the intestinal cells. However, possible reasons for the inefficacy of cranberry extracts found in the cited RCTs should also be taken into account. Firstly, multi-step processing of cranberry production leads to a substantial loss of phytochemicals (through elimination of rich fractions like skin and seeds), which are further damaged by thermal degradation, as well as oxidation by polyphenol oxidase and peroxidase. Moreover, the exact concentration of active metabolites on the action site and the pharmacokinetics of cranberry extracts are unknown. There are other plant extracts that have shown interesting results in the prevention of UTI recurrences. Rafsanjany et al. demonstrated that a mixture of extracts from *Betula* spp. (birch), *Orthosiphonstamineus* (Java tea) and *Urtica* spp. (nettles) is able to reduce the adherence of the pathogen to the host cell. The same results have been obtained by Cai et al. who demonstrated

that a compound with solidago, orthosiphon, birch and cranberry extracts is able to reduce the microbial colonization in patients with indwelling urinary catheters. However, this mixture is not able to cover all mechanisms of infection.

Conclusion

While phytotherapy seems to be a promising option in treating UTIs, there is not enough research done in the area in order for them to be universally recommended and backed by International Organizations. The lack of standardization of these therapeutic options is also a barrier that must be overcome. Cranberry extracts seem to lack uniformity of ingredients and manufacturers must invest in development of a standard formulation. More studies are required in order to clinically validate the efficiency of Chinese herbal medicine, D-Mannose and Probiotics. The current literature available seems to be based on small groups with a heavy bias, and therefore is not reliable. Future studies in this direction must take care to avoid these shortcomings.

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