

Supplementation with high titer cranberry extract (Anthocran[®]) for the prevention of recurrent urinary tract infections in elderly men suffering from moderate prostatic hyperplasia: a pilot study

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Abstract. – **OBJECTIVE:** Recently, cranberry extracts have been tested as a nutritional supplementation in the prevention of lower urinary tract symptoms (LUTS) as well as recurrent urinary tract infections (UTIs) in subjects at risk, with mixed results. However, evidence of efficacy should be considered only for well-characterized and standardized products in a more selected study population. Moreover, the efficacy of these interventions in elderly must be further investigated. The aim of this pilot, registry study was to evaluate the prophylactic effects of an oral supplementation containing a highly concentrated and standardized cranberry extract reproducing the natural total profile of cranberry fruits, in elderly men with benign prostatic hyperplasia (BPH), suffering from recurrent UTIs, over a 2-months follow-up.

PATIENTS AND METHODS: 43 men (age > 65 years) enrolled in this study freely decided to receive either a standard management (SM) only (n = 21) or SM associated with an oral supplementation (n = 23). Supplementation consisted in a daily administration of one capsule containing cranberry extract (Anthocran[®]) for 60 consecutive days. The clinical effectiveness in the prevention of UTIs was determined by the number of UTIs in the two months before the inclusion in the registry and during the supplementation period, and the number of symptom-free subjects during the registry period. Safety considerations were also performed.

RESULTS: In the supplemented group, the mean number of UTI episodes reported during the registry (0.8 ± 0.5) significantly decreased compared with inclusion time (3.2 ± 1.3), p -value = 0.0001. No significant changes were observed in control, SM-only group. Importantly,

the cranberry oral supplementation was superior over SM at reducing the mean number of UTIs (p -value = 0.0062).

CONCLUSIONS: These results suggest that cranberry supplementation could be an effective and safe approach, within an SM program, for the prevention of recurrent UTIs in elderly men suffering from BPH avoiding some antibiotic treatments.

Key Words:

Elderly, Benign prostatic hyperplasia, Lower urinary tract symptoms, Urinary tract infections, Cranberry extract, Proanthocyanidins, Anthocran[®].

Introduction

Urinary tract infection (UTI) is the 15th most common condition seen in primary care, diagnosed in 2% of the family medicine visits¹. Particularly, in men the incidence of UTIs remarkably changes with age, increasing from 0.9-2.4 cases per 1000 in men younger than 55 years to 7.7 cases per 1000 in men older than 85 years². Indeed, with aging, men acquire structural and functional abnormalities of the urinary tract that impair normal voiding, the most common being benign prostatic hyperplasia (BPH)². Benign prostatic hyperplasia (BPH) is the progressive enlargement of the prostate gland as a consequence of the non-malignant proliferation of prostatic stromal and epithelial cells³. BPH becomes a clinical entity when associated with bothersome

lower urinary tract symptoms (LUTS)⁴. Epidemiological studies revealed that about 50% of male individuals older than 40 years develop histologic hyperplasia or BPH, among this 30% to 50% show LUTS (which may also be caused by other conditions)⁴. Recurrent UTI is one of the most frequent BPH complications, and it is thought to be caused by the bladder outflow obstruction and subsequent infection of the residual urine, leading to intraprostatic reflux of infected urine and the chronic harboring of bacteria within the prostate and urinary tract⁵.

The goals of treatments have been to alleviate bothersome LUTS that result from prostatic enlargement and to prevent disease progression and complications associated with BPH and LUTS^{6,7}. The established therapeutic strategies for the treatment of male LUTS include α 1-blockers and 5 α -reductase inhibitors. In men with predominant storage LUTS, antimuscarinics, the beta-3-adrenergic agonist mirabegron and synthetic diuretics have been introduced to manage symptoms effectively⁸. Antibiotics are commonly used to eradicate recurrent UTIs secondary to BPH. However, registered pharmacological treatments for LUTS, as well as long-term use of antibiotics, may be responsible for a variety of side effects. Moreover, long-term antibiotic prophylaxis may select adaptive, multi-drug resistant bacteria. In particular, older adults often present renal insufficiency; therefore, the selection of the optimal therapy agent, dose, and duration should be chosen carefully, with adjustment of the common dosage using the estimated glomerular filtration rate. Regrettably, to date specific evidence in this population remains scant.

Recently, cranberry extracts have been tested as a nutritional supplementation in the prevention of LUTS^{9,10} as well as recurrent UTIs¹¹⁻¹³ in subjects at risk, with mixed results. It is important to underline that evidence of efficacy should be considered only for well characterized and standardized products in a more selected study population. Cranberry fruit (*Vaccinium macrocarpon* Ait., Ericaceae), used by Native Americans to treat kidney and urinary ailments, is recognized as a rich source of organic and phenolic acids, flavonols, pentacyclic triterpenoids, anthocyanins and proanthocyanidins (PACs)¹⁴. In particular, the content of A-type proanthocyanidins (PACs) in cranberry fruits are remarkably higher compared to the other berry fruits¹⁴.

The aim of this pilot registry study was to evaluate the prophylactic effects of an oral sup-

plementation containing a highly standardized (25.0-35.0% of PACs) cranberry extract (Anthocran[®]), in elderly subjects (> 65 years) suffering from recurrent UTIs secondary to BPH, over a 2-months follow-up.

Patients and Methods

This was a registry, supplement study conducted in 44 elderly patients (> 65 years) with moderate BPH and suffering from recurrent UTI (at least three symptomatic UTIs in the year before inclusion of two UTIs in the last six months). Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, preclinical applications; they produce supplementary data to compare with these from the best available management plans. These types of researches should be performed with products with a higher level of safety and pharmaceutical standards and the studies should be possible at low cost even in emerging markets¹⁵⁻¹⁷. Subjects were excluded if they met the following criteria: any chronic clinical condition or risk factors, immune-compromising diseases, concomitant infections of any nature, blood in the urines, antibiotic or corticosteroid treatment for any reason in the last 6 months, allergy or intolerance to cranberry.

Informed participants (n = 44) freely decided to receive either a standard management (SM) to control the condition (control group, n = 21) or SM associated with an oral daily supplementation (supplementation group, n = 23).

All patients received fosfomycin for one day. At day 5, a urinary culture was performed; if negative, the subject was suggested to take one capsule containing 120 mg of the highly standardized cranberry extract (Anthocran[®]), corresponding to 36 mg PACs, for 60 consecutive days. Standard management (SM) consisted in lifestyle and hygiene advice (accurate washing, drinking and voiding at correct times, low caffeine, alcohol and spice intake, moderate physical activity). The occurrence of new UTI episodes (defined as signs/symptoms of UTI, the visible presence of blood and need for consultation and specialist's evaluation) over 2-month follow-up was recorded. Clinical effectiveness in the prevention of UTIs was determined according to the following parameters: (1) the number of UTIs in the two months before the inclusion in

the registry and during the supplementation period; (2) number of symptom-free subjects during the registry period. Safety considerations were also performed.

Statistical Analysis

All data were analyzed by descriptive statistical differences were evaluated by the Student *t*-test or the Mann-Whitney U-test, as necessary. A *p*-value < 0.05 was considered statistically significant.

Results

Table I shows the baseline characteristics of the study population. The two groups were comparable for age, BMI and days of follow-up. They also presented a similar number of UTI episodes before inclusion (Table II). No dropouts were recorded during the registry study.

Table II shows the number of UTI episodes in the SM group and the SM + oral supplementation (cranberry extract) group. In the supplemented group, the mean number (\pm standard deviation) of UTI episodes reported during the registry (0.8 ± 0.5) significantly decreased compared to the number before inclusion (3.2 ± 1.3), *p*-value = 0.0001. On the other hand, no significant variations were observed in the control group, which received the SM only. Notably, the oral supplementation containing standardized cranberry extract associated with SM resulted superior than SM in reducing the mean number of UTIs. In fact, the mean number of UTI episodes during the study was significantly lower in the supplemented group (0.8 ± 0.5) in comparison with the control group (2.1 ± 2.1), *p*-value = 0.0062). At the end of the study, we

Table I. Details of subjects enrolled in the study.

	Standard management	Standard management + oral supplementation
Subjects	21	23
Age, years (mean \pm SD)	66.2 \pm 2.3	67.3 \pm 3.2
BMI (mean)	25.4	25.3
Follow-up, days (mean)	63.6	66.2

SD: standard deviation; BMI: body mass index.

Table II. Number of UTI episodes in both group.

	Standard management (n = 21)	Standard management + oral supplementation (n = 23)
Before inclusion	3.14 \pm 1.1	3.2 \pm 1.3
Registry	2.1 \pm 2.1	0.8 \pm 0.5**†

Data are expressed as mean \pm standard deviation; **p*-value < 0.05 (vs. SM group); †*p*-value < 0.05 (vs. before inclusion).

also observed in the group treated with SM+oral supplementation, an increase of 6.5% in asymptomatic subjects, on the control group (96.5% vs. 90%). No adverse events were observed in either group. Compliance to the cranberry-based supplementation was optimal, with > 95% of the doses correctly used.

Discussion

BPH and LUTS are associated with negative impact on patient’s QoL, as well as high personal and social costs. Since the prevalence of LUTS associated with BPH increases with age, the burden to the healthcare system and society may raise due to the aging population¹⁸. Moreover, most episodes, in older patients are minimally symptomatic. Therefore, the frequent under-diagnosis and under-treatment of BPH/LUTS contribute to increasing the risk of complications such as recurrent UTIs, with a further growth of social and economic costs. This increased risk of complications is of particular importance in the elderly, who often present some other comorbidities.

In recent years, there has been an increasing interest in naturally-derived dietary supplements for the prevention of prostate diseases^{13,19-21}. Cranberry-based products are particularly used, since several cranberry components may modulate various cellular pathways in man-including the urinary tract and the prostate. Recent *in vitro*, *in vivo*, and clinical investigations, suggest that A-type PACs isolated from cranberry fruit inhibit P-fimbriated *E. coli* adhesion to uroepithelial cells, the initial step in the development of UTI²²⁻²⁵. Cranberry also showed anti-inflammatory action in chronic bacterial prostatitis²⁶ and anti-tumor activity²⁷⁻²⁹. However, additional research focused on bioavailability, metabolic

fate and additional cancer inhibitory mechanisms of cranberry product are needed, also with specific reference to the older population.

The results of the present supplement registry study adds further evidence to the effectiveness and safety of cranberry extracts in the prevention of recurrent UTIs. In particular, in a selected population consisting of elderly subjects (> 65 years) suffering from moderate BPH, we observed that a standardized cranberry extract supplementation was effective in reducing the number of recurrent UTIs, over a two-months follow-up period. Cranberry is a very safe, no-prescription product and may be useful for self-management in most conditions associated with mild, repeated infections of the urinary tract. Initial interaction studies¹⁵ show no negative interaction with antibiotics or other drugs (i.e. antiplatelets or anticoagulants).

Recent researches^{9,10} investigating the effectiveness of cranberry administration in LUTS showed that cranberries may improve prostate health also reducing the prostate specific antigen (PSA) and improving the LUTS symptom score (known as International Prostate Symptoms Score, IPSS). We could, therefore, speculate that the beneficial effect of the standardized cranberry extract described in this work could also be due to the global improvement of the prostatic condition. These findings should be considered preliminary and larger studies should be planned to study possible specific effects of cranberry on the prostate.

Conclusions

Despite all the limitations implicit in any observational analysis, these results indicate that Anthocran[®] supplementation could represent an effective and safe supplementary management for the prevention of recurrent UTIs in elderly men suffering from BPH. Further studies are needed to evaluate and associate the effect of Anthocran[®] with the severity of UTI/inflammation in a larger cohort of patients. To this end, the investigation of pro-inflammatory markers, such as C-reactive protein (CPR) and prolactin should be pursued.

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Conflict of Interest

AR and ST are employees of Indena S.p.A. LG is a consultant for Indena S.p.A., Milan, Italy. The other Authors declare no conflicts of interest.

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