

Highly standardized cranberry extract supplementation (Anthocran[®]) as prophylaxis in young healthy subjects with recurrent urinary tract infections

A. LEDDA¹, G. BELCARO¹, M. DUGALL¹, A. RIVA², S. TOGNI²,
R. EGGENHOFFNER³, L. GIACOMELLI³

¹Department of Medical, Oral, and Biotechnology Science, Irvine3 Labs, Circulation Sciences, Chieti-Pescara University, Italy

²Indena SpA, Milan, Italy

³Department of Surgical Sciences and Integrated Diagnostics, School of Medicine, Genoa University, Genoa, Italy

Abstract. – **OBJECTIVE:** Several studies have investigated the role of cranberry extract in the prevention of recurrent urinary tract infections (UTIs), on different selected subpopulations at increased risk of UTI. In this registry, we tested the prophylactic effects of an oral supplementation containing a highly standardized cranberry extract (Anthocran[®]) in young subjects with a previous history of recurrent UTIs, over a 2-months follow-up.

PATIENTS AND METHODS: 36 otherwise healthy subjects in juvenile age (between 12 and 18 years of age) suffering by recurrent UTIs were enrolled. Participants received either a standard management (SM) (control group, n=17) or SM associated with an oral daily supplementation (supplementation group, n=19). Oral supplementation consisted in one capsule containing 120 mg of cranberry extract (Anthocran[®]), standardized to 36 mg proanthocyanidins, for 60 days. The effectiveness in the prevention of UTIs was determined by: the number of UTIs evaluated two months before the inclusion in the registry and during the supplementation period; the number of symptom-free subjects during the registry period. Safety considerations and measurement of adherence to treatment were also performed.

RESULTS: The two groups were comparable for age, gender distribution, the days of follow-up and also for the number of UTIs before inclusion. The mean number of UTIs observed during the registry in the supplemented group (0.31 ± 0.2) was significantly lower compared to the control group (2.3 ± 1.3) and to the mean number of UTIs assessed before inclusion (1.74 ± 1.1) (p -value = 0.0001 for both). Moreover, 63.1% of supplemented subjects was symptom-free during the registry period, whereas 23.5% sub-

jects were asymptomatic in the control group (p -value <0.05).

CONCLUSIONS: This registry supplement study provides compelling evidence on the efficacy of an oral supplementation, based on a highly standardized cranberry extract (Anthocran[®]), as prophylaxis in young healthy subjects suffering by recurrent UTIs.

Key Words:

Urinary tract infections, Subjects in juvenile age, Cranberry extract, Proanthocyanidins, Anthocran[®].

Introduction

The term urinary tract infection (UTI) refers to the presence of one or more pathogenic microorganisms exceeding a threshold value in the urinary tract¹. The most common pathogen in UTIs is *Escherichia coli* followed by *Proteus spp.*, *Staphylococcus saprophyticus*, *Klebsiella spp.* and other *Enterobacteriaceae*². Infections are usually localized into the bladder, urethra, kidneys, ureters, or prostate. The main risk factors identified for UTIs are age, previous history of UTI, sexual activity, and diabetes mellitus³. Therefore, specific subpopulations are at increased risk of developing an UTI. UTIs are frequent in childhood and may have significant adverse consequences, such as nephro-urologic abnormalities and consequent renal scarring, especially for the young children with febrile UTIs⁴⁻⁸. Infection of the urinary tract occurs more frequently in boys than in girls below the

age of one year; however, after the age of one year, UTI is more common in girls^{4,9}. Recurrent UTIs (defined as two or more episodes over 6 months or three or more episodes over 1 year) have been found to be associated with a higher risk of developing a new infection, especially in young women^{3,10}. In this light, early initiation of appropriate prevention, prompt and accurate diagnosis and effective treatment of UTIs are crucial in childhood and juvenile age as the risks of ascending UTI or recurrence are significant¹¹. Antibiotics are the most important approach in the prevention and treatment of UTIs. However, the long-term use of antimicrobial prophylaxis is strictly correlated with resistance in uropathogens¹², and with side effects^{13,14}.

Among many non-antimicrobial-based approaches available for the prevention of UTIs^{15,16}, supplementation with cranberries has been gaining specific attention. Cranberries are composed of 88% water and a complex mixture of organic acids¹⁷. Some of these organic substances, such as proanthocyanidins (PACs), flavonols, and hydroxycinnamic acids, seems to act against pathogens by preventing bacterial adhesion and co-aggregation, decreasing biofilm formation and/or reducing inflammation rather than via bactericidal activity^{18,19}. In particular, PACs containing A-type linkages resulted to inhibit the adherence of p-fimbriated *Escherichia coli* to uroepithelium, in *in vitro*, *in vivo* and clinical studies^{20,21}.

In this pilot, registry study, we aim at investigating the prophylactic effects of an oral supplementation containing a highly standardized cranberry extract (Anthocran[®]) in young subjects with a previous history of recurrent UTIs, over a 2-months follow-up.

Patients and Methods

This was a registry, supplement study conducted in 36 young subjects (12-18 years) with recurrent UTIs and previous negative experience or reaction with different antibiotics. Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, preclinical applications. Supplement studies produce supplementary data to compare with data from the best available management plans. These type of studies should be performed with products with a higher level of safety and pharmaceutical standards, and the studies should be at low cost even in emerging markets²³⁻²⁵. Potential

subjects were excluded if they met the following criteria: any chronic clinical condition or risk factors, immunological 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.

An urinary culture was performed in all participants; only subjects showing no bacterial growth were included. Participants or their parents, as appropriate, gave written informed consent before the enrollment in this study.

Participants suffering by recurrent UTIs (n=36) received either a standard management (SM) to control the condition (control group, n=17) or SM associated with an oral daily supplementation (supplementation group, n=19). Oral supplementation consisted in 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 (access to clean toilets when required, accurate washing, drinking and voiding at correct times, treatment of constipation if present)⁷. The occurrence of new UTI episodes (defined as signs/symptoms of UTI, visible presence of blood and need for consultation and specialist's evaluation) over a 2-months follow-up was recorded. Clinical efficacy in the prevention of UTIs was determined according to the following parameters: (i) the number of UTIs in the two months before the inclusion in the registry and during the registry period; (ii) number of symptom-free subjects during the registry period.

Statistical Analysis

All data were analyzed by descriptive statistics. Numerical data comparison between groups was performed by using unpaired two-sample Student's *t*-test or Mann-Whitney U test, as appropriate. Categorical data differences between groups were evaluated by Fisher's exact test. A *p*-value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population are shown in Table I. The two groups were comparable for age, gender distribution, for the days of follow-up and also for the number of UTI episodes occurred before inclusion (Table II). During the registry, no drop-outs were reported. Table II shows the number of UTI episodes in

Table I. Details of subjects enrolled in the study.

	Standard management	Standard management + oral supplementation
Subjects (females)	17(8)	19(11)
Age, years (mean ± SD)	14.3±2.7	15.1±2.4
Follow-up, days (mean)	66.6±3.3	69.3±2

SD: standard deviation

both study groups. In the supplemented group, the mean number (±standard deviation) of UTI episodes observed during the registry (0.31±0.2) significantly decreased compared to the number before inclusion (1.74±1.1; *p*-value = 0.0001).

Conversely, in the SM group, no significant differences were observed in the number of UTIs. Moreover, the cranberry-based oral supplementation plus SM resulted superior at decreasing the mean number of UTIs, in comparison with SM only. In the supplemented group, the mean number of UTI episodes occurred during the study (0.31±0.2) was significantly lower (*p*-value = 0.0001) compared to the UTI number in the control group (2.3±1.3) (Table II). Moreover, 12 out of 19 (63.1%) subjects in the cranberry group did not experience any UTI symptom during the registry period, whereas 4/17 (23.5%) subjects were asymptomatic in the control group (*p*-value <0.05). Enrolled subjects reported that they preferred do not use any antibiotics for UTIs as they had previous reactions to antibiotic treatments.

During the research, no adverse events were observed in both study groups. Compliance to the cranberry-based supplementation was good, with > 91% of the doses correctly used.

Discussion

This is the first study evaluating the prophylactic effect of a cranberry-based supplementation in young otherwise healthy subjects (age range: 12-18 years) suffering from recurrent UTIs. Most of the previous researches focused their analysis on other selected subpopulations at increased risk of UTI development or recurrence, such as children, women, elderly and subjects with catheterization, showing variable results in term of effectiveness of cranberry supplementation^{10,26-28}.

These investigations recorded a high number of dropouts/withdrawals, likely due to the low acceptability of consuming cranberry products,

Table II. Number of UTI episodes in both group.

	Standard management (n=17)	Standard management + oral supplementation (n=19)
Before inclusion	2.1±1.0	1.7±1.1
Registry	2.3±1.3	0.1±0.2 [†]
Follow-up, days (mean)	66.6±3.3	69.3±2

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

particularly juices, over long periods. In particular, studies on children have reported taste of juice as the main reason for discontinuing treatment^{10,26}. Cranberry products, including juice, syrup, capsules, and tablets, need to be characterized, quantified and standardized to ensure enough content of the active ingredient and, basically, studies are difficult to compare. The dosage of cranberry PACs found to be effective in reducing bacteriuria with pyuria and in achieving a bacterial anti-adhesion effect in urine, was 36 mg per day^{29,30}.

In our registry study, an oral daily supplementation consisting of cranberry-based capsules (Anthocran[®]), highly-standardized to 36 mg PACs, was evaluated. It showed favorable results as a prophylactic product in healthy young subjects suffering by recurrent UTIs, particularly in term of reduced number of UTIs, compared to SM only.

Anthocran[®] was well tolerated, resulting in an optimal compliance. Afshar et al³¹ conducted a study in children and young subjects, ranging from 5 to 18 years of age (mean age 9.5), with at least 2 culture-documented UTIs in the previous year. Participants daily received cranberry juice with a high concentration of PACs (37%) for 1 year. The authors observed a 65% reduction in the risk of UTI in the treatment group receiving the cranberry product, in comparison with the placebo group. However, this work included also patients with vesicoureteral reflux (VUR), albeit in low number, that could confound the applicability to the general pediatric/juvenile population.

Noteworthy, cranberry exerts a remarkable anti-inflammatory effect on transitional cells; while antibiotics do not act on residual inflammation (after an infection), cranberry extracts reduce inflammations and symptoms associated to infection remnants in the urinary tract.

Conclusions

This registry, supplement study provides compelling evidence on the efficacy of a highly standardized cranberry extract (Anthocran[®]) oral supplementation as prophylaxis in young healthy subjects suffering by recurrent UTIs and inflammatory consequences.

Acknowledgements

We thank Sara Parodi, PhD, who provided medical writing services, supported by internal funds.

Conflict of interest

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

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