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ORIGINAL ARTICLE

Pycnogenol® supplementation prevents inflammation and symptoms in recurrent, non-severe urinary infections

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ABSTRACT

BACKGROUND: The aim of this pilot, registry study was to evaluate the prophylactic effects of oral supplementation with Pycnogenol® (150 mg/day) in subjects with previous history of recurrent (urinary tract infections (UTI) in a 2-month open follow-up.
METHODS: subjects with recurrent-UTIs, defined by: 1) at least three symptomatic UTIs over the past year; 2) two episodes of UTI's in the past six months; 3) symptoms of UTIs with urinalysis without bacterial presence, were included in the study. Pycnogenol® was supplemented at the dose of 150 mg/day for 2 months.
RESULTS: The two groups of subjects (supplement and controls, each including 25 subjects) were demographically and clinically comparable at baseline. No side effects or tolerability problems were observed. The registry evaluated the number of recurrent UTIs in two months; there was a limited decrease in the rate of recurrent UTIs, in comparison with the period before inclusion of 9.93% in the standard management group in comparison with a more important decrease in the Pycnogenol® group (-50.1%; P<0.05). The number of episodes decreased from 3.22±0.4 to 2.9±0.3 in the control group in 2 months *versus* a decrease from 3.1±0.5 to 1.6±0.6 in the Pycnogenol® group. The number of infection-free subjects at the end of the two-month registry study was significantly higher with the supplement (P<0.05) than in controls. Oxidative stress measured as plasma free radicals at inclusion was 388±22 Carr units in the control group and resulted unchanged (not significant) at the end of the study (379±21 Carr units). In the supplement group, there was a significant decrease in oxidative stress from 389±24 to 227±14 Carr units at the end of the study (P<0.05).
CONCLUSIONS: This pilot registry indicates that prophylaxis with Pycnogenol® decreases the occurrence of UTIs both in men and women without side effects and with a good tolerability. The effects of Pycnogenol® in these patients — including the control of oxidative stress — may be very important, particularly when a predominantly inflammatory component (UTI without infection or with a minimal bacterial component due to bacterial fragments) is present and maintains the inflammatory process.

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KEY WORDS: Urinary tract infections; Pycnogenols; *Escherichia coli*; Prevention and control.

Lower urinary tract infections (UTIs) are among the most common bacterial infections. Roughly 50% of women experience UTI during their lifetimes and some 25-30% of women have at least one episode of recurrent urinary infection.[1-3] UTIs in men are also common and often recurrent in subjects with lower urinary tract anomalies and anatomical variations as well as in patients suffering from urinary tract partial or temporary blocks, after catheterization or surgery and in subjects with benign prostatic hypertrophy.

Recurrent UTIs (R-UTI) have been defined as a sequence of three episodes in the previous year or two episodes in the last six months. Recurrent UTIs generally occur in susceptible subjects and are a significant source of patient morbidity and health costs.[5, 6]

R-UTIs can be defined as of mild/moderate intensity when signs/symptoms last less than 3 days, no hospitalization is needed and there are minor signs/symptoms.

The Infectious Disease Society of America (2010) recommends five-day treatment with nitrofurantoin or a sin-

gle dose of fosfomycin trometamol (Monuril) as a first line treatment for acute, uncomplicated cystitis.[6]

Other antibiotics are also used according to local practice, that may vary in different countries and settings.[5, 6] Longer-term antibiotic prophylaxis may also be used in subjects with more complex R-UTIs.

Six to twelve months of antimicrobial prophylaxis has been shown to be effective in reducing the occurrence of R-UTIs in women.[5, 6] However, frequent or long-term use of antibiotics increases costs and side effects and may select adaptive, multi-drug resistant organisms, decreasing the efficacy of antimicrobial treatments, even altering the bacterial population in the intestinal flora. Long-term use of nitrofurantoin has been associated in some patients with anemia, pulmonary toxicity, hepatic disease and neuropathy.[7]

At the moment, there is no well-defined recommendation for a 'standard' prophylactic antibiotic management to prevent R-UTI.[8]

Lower urinary tract infections have a significant concomitant, inflammatory component.

Inflammation may persist after bacteria are not detectable in the urine anymore. The inflamed urothelial cells may cause signs and symptoms and may also attract other bacteria, restarting infections (molecular mimicry).[9]

Recently, standardized supplements have been tested as prophylactic agents to prevent R-UTIs in subjects at risk of developing recurrent lower urinary infections.[10]

Natural extracts (*i.e.* cranberry) have been used for urinary infections and particularly for UTIs in prevention and treatment studies.[10, 11]

It could be possible that the natural components present in Pycnogenol® may inhibit P-fimbriated *E. coli* from adhering to uroepithelial cells. P-fimbriae mediate adherence to uroepithelial cells by the activity of the P adhesin gene (*papG*). The allele III variant has been associated with cystitis.[12]

Pycnogenol® contains high concentrations of polyphenols that appear to be effective in interfering with *E. coli* at intestinal level or by inhibiting adherence of bacteria to mucosal (vaginal) or bladder and uro-epithelial cells in the lower urinary tract (15). In most UTI, *E. coli* is diagnosed as the predominant uropathogen associated with UTI and R-UTIs (particularly in women).[11-14] Evidence of efficacy should be considered only for standard preparations with well-defined doses and absorption rates.[4, 10, 11] The infecting bacteria are typically of intestinal origin and the intestinal tract could be an alternate site in which the active components of Pycnogenol® may interact with *E. coli* decreasing its infectivity.[12, 15]

A recent study[11] has evaluated the efficacy of cranberry preparation in reducing UTI and R-UTI incidence in women in our population. A reduction in the number of UTIs following consumption of cranberry has been observed.

The aim of this pilot, registry study was to evaluate the prophylactic effects of oral supplementation with Pycnogenol® in subjects with previous, recent history of recurrent UTI in a 2-month open follow-up.

Materials and methods

Subjects aged 30-40 years with a recent (<12 months) history of recurrent UTI, were included if: 1) they reported at least three symptomatic UTIs in the past year; or 2) they reported at least two episodes of UTI's in the past six months

Exclusion criteria were diabetes, any other chronic clinical condition or risk conditions, immune-compromising diseases, co-morbidities, antibiotic or corticosteroids treatment for any reason, mycosis, use of chemotherapy within 6 months before inclusion, chronic inflammatory bowel disease and any possible or suspected intolerance or allergy to supplements.

According to common clinical practice[1, 6] subjects with history of UTI receive Monuril (fosfomycin trometamol) for one day (in case of minor symptoms of a single, initial episode and two doses, in two days in case of more severe symptoms or recurrent-UTI).

In case blood was visible in the urine and the urine was not clear, the patients were not included in the registry. A two-day antibiotic (Monuril) before beginning the study[6] was an exclusion criterion (because it was probably associated with more severe UTI). Only subjects who had used one dose, one day of Monuril were included in this registry. Subjects with urinary tract infection using other antibiotic treatments were also excluded to have a homogeneous and comparable registry population.

At 5 days, if a urinary test indicated the absence of blood or a clinically significant bacterial charge (according to the upper limits in Table I)[16] the patients were able to use Pycnogenol® (150 mg/day, equivalent to 3 capsules/day) for 60 consecutive days.

The registry study evaluated the occurrence of new episodes in a two-month follow-up.

A new episode was indicated by signs/symptoms, presence of increased bacterial charge in the urine, visible presence of blood and need for consultation and specialist's evaluation.

All subjects used an associated management. Accurate

TABLE I.—*Upper limits for defining 'normal' urine samples according to the American Family Physician.*[16]

Parameter	Upper limit	Units
Red blood cells (RBC)/erythrocytes	2-3	Per high power field (HPF)
RBC cast	Negative	
White blood cells/leukocytes	Negative-10	Per µL or mm^3
"Blood"/hemoglobin	Negative	Dip-stick scale 0 to 4+
Bacterial cultures	<100,000	Colony-forming units per mL (CFU/mL)

hygiene (without using local disinfectants), improved bladder care (with drinking and voiding at appropriate time, according to needs, *i.e.* without waiting for hours), avoiding use of too much caffeine, spices and alcohol and a careful hydration was suggested. In addition, a program of mild exercise was also associated (20-30 minutes walking daily, avoiding sitting in the same position for hours).

Supplement studies[17-21] are aimed to define the field of activity of pharmaceutical standard (PS) supplements and possible preventive, preferably non-clinical applications. They are planned and organized with the full attention and participation of the evaluation subjects. The best fields of application for supplements are preclinical, borderline applications or the supplementary management of some risk conditions. Supplements, unless there are specific claims, are not generally used for treatment of signs/symptoms or clinical conditions. The aim of supplement studies was to produce supplementary data to be compared to "background" historical data (*i.e.*, based on the best available management for comparable subjects) or to other management plans. In this study, supplements were used according to the following rules:

• the use of the supplement was suggested to the evaluation subjects; the supplement use was not formally prescribed but only suggested as an option, possibly capable of improving the management of the risk condition leading to recurrent-UTI;

• the supplement was only used on top of what was considered at the time the "standard" or best-management/care' available, if available, for that condition, according to relative international guidelines;

• the use of the supplement should not have interfered with any other treatment or preventive measure;

• the period of follow-up is considered variable, according to the needs and availability of the patients or registry subjects. The observation period could be therefore variable, not prefixed. Ideally, the supplement administration should be used as long as needed to see results or changes;

• the type of evaluation for these studies is always a registry;

• in supplement studies there is no defined group allocation, no randomization organized by the investigators;

• subjects decide, based on the initial briefing, the management group they want to join including the control (non-supplement) group.

No placebo is used.

Open label

Patients are informed about the supplement or any treatment and management. A possible placebo effect is also carefully explained and considered.

Data and results are analyzed only after the observation period, ideally, when sufficient evidence is collected or when fund limitations would eventually stop the collection of the observations. The time needed to detect differences among groups is also considered an evaluation target. In this type of studies control groups, if present, are not necessarily parallel.

Characteristics of this registry

This study was a small-scale, independent, pilot, registry study; the evaluation product was not prescribed but recommended. This registry is actually more corresponding to real, practical conditions[22] than most clinical studies that artificially select groups of patients in defined conditions, often not corresponding to an epidemiological reality. This type of supplement studies may be particularly suited for emerging countries and when important sponsorships are not available.

Results and data were evaluated by an external reviewing panel, not in contact with the registry patients.

Sponsors/CRO

Commercial sponsorship from the producers of the tested supplement was not available.

Safety

Safety and tolerability were assessed by weekly contacts and laboratory measurements. Adverse experiences were evaluated throughout the registry. All clinical adverse ex-

periences were classified in terms of intensity: mild, moderate, or severe, also considering duration, seriousness, outcome, and relationship to the study supplement.

Pycnogenol®, a standardized extract from the bark of the French maritime pine (*Pinus pinaster* Aiton), consists of a concentrate of polyphenols, 65-75% of procyanidins.[23]

Several clinical studies have confirmed the beneficial role of Pycnogenol® in reducing the level on inflammation in different ~~several~~ preclinical and clinical conditions[23, 24] and in addition presenting antimicrobial activity.[15]

Clinical efficacy of the supplement was assessed by three main target parameters: 1) comparison of the number of UTIs self-reported episodes (as self-reported dysuria) in the two months before entering the registry and in the two months after inclusion; 2) the number of infection-free subjects at the end of the two-month registry; 3) normal urinalysis at the end of the registry period.[16]

Oxidative stress

Systemic oxidative stress was measured as plasma free radicals as previously described with a drop of blood from one finger.[25] The test has been validated in several clinical studies.[25]

Statistical analysis

Statistical analyses were performed to evaluate clinical efficacy. On the basis of the model study by Burleigh *et al.*,[11] at least two groups of more than 20 subjects would be needed to evaluate differences in the three target parameters after 60 days of prophylaxis with Pycnogenol® supplementation. In this registry, when 25 comparable subjects completed the registry period, the study was closed.

Non-parametric statistics was used to evaluate the differences between the previous observational period (of 2 months) and the registry period in the two groups.

Also, the difference in occurrence of UTI in the two management groups was analyzed using the ANOVA (with Bonferroni correction).[26] A sigma plot software was used.

TABLE II.—*Details of the patients.*

Parameter	Controls Best management	Best management + Pycnogenol®
N. subjects	25	25
Gender, female	13	14
Dropouts	0	0
Mean age, years	37.7±3.3	38.1±3.4
Days of follow-up	64.7±4.3	65.3±4.3
Oxidative stress, Carr units		
Inclusion	388±22	389±24
End of the study	379±21	327±14*

*P<0.05 *vs*. baseline.

Results

Table II shows that the two groups of subjects that completed the study (25 controls and 25 in the Pycnogenol® group) were demographically and clinically comparable at inclusion. There were no dropouts. No side effects or tolerability issues were observed in the Pycnogenol® group.

Table III shows the number of self-reported episodes of infection (as self-reported dysuria) over two months; two months before inclusion and 2 months during follow-up; the number of recurrent UTIs was significantly lower (P<0.05) with Pycnogenol® (from an average of 3.22±0.4 episodes in the two previous months before inclusion to 1.6±0.6 in the two months of supplementation): no significant variations were observed in controls (from 3.22±0.4 to 2.9±0.3). The decrease, compared to the period before inclusion, was 9.93% in the standard management (SM) group compared with a greater decrease in the rate of recurrent infections in the Pycnogenol® group (-50.1%).

The number of infection-free subjects (urines) at the end of the two-month registry (Table III) was significantly higher with the supplement (P<0.05) (23 of 25 subjects) in comparison with 17 of 25 subjects in the control, SM group.

All subjects had symptoms (minor pain, stranguria, repeated need for urination, lower, anterior abdominal pain)

TABLE III.—*Number of self-reported episodes of infection over two months (before and during Pycnogenol administration).*

Parameter	Controls			Pycnogenol®		
	2 months before inclusion	2-month follow-up	P value	2 months before inclusion	2-month follow-up	P value
Mean N. of episodes	3.22±0.4	2.9±0.3	NS	3.21±0.5	1.6±0.6	<0.05
% decrease		-9.93%			-50.15%	<0.05
Completely normal urine, 'infection-free'#	12/25	17/25		13/25	23/25	<0.05
Completely symptom-free	0/25	14/25		0/25	24/25	<0.05

Definition of 'normal' urine (American Family Physician, 2005) as in Table I.[16]

at inclusion. Considering the number of completely symptom-free subjects at the end of the study, after 2 months of management, 24 subjects out of 25 had no symptoms with Pycnogenol® in comparison with 14 out of 25 subjects with the SM ($P<0.05$).

The occurrence of symptoms — all minor/mild — was not parallel to the 'normalization' of the urine.

Oxidative stress (measured as plasma free radicals) at inclusion was 388±22 Carr units in the SM group and resulted unchanged (not significant) at the end of the study (379±21 Carr units).

In the supplement group, there was a significant decrease in oxidative stress from 389±24 carr Units to 327±14 Carr units at the end of the study ($P<0.05$).

Discussion

UTI are a common clinical entity often not arriving at the attention of the practitioner; frequently, minor episodes are self-managed directly by patients with products usable without prescriptions. Epidemiology of UTI indicates a common disease, apparently more frequent or severe in women and less severe or more tolerable in men.[8, 13]

Often, in recurrent UTIs most symptoms are caused by persistent inflammatory processes in the lower urinary tract.

Inflammation may persist due to the presence of bacterial fragments that still induce an inflammatory response and the production of antibodies (molecular mimicry).

A number of components in Pycnogenol® may affect the evolution and genesis of UTI and R-UTI and reduce the inflammation.

Other compounds and components found in Pycnogenol® or metabolites in association with its anti-inflammatory and antioxidant activity could decrease the virulence and diffusion of several bacterial strains including intestinal *E. coli*.[15, 23, 27]

As observed, it is important to consider that lower tract urinary infection may have a preeminent non-bacterial inflammatory component that may respond better to Pycnogenol® than to antibiotic treatments.

The anti-inflammatory effects of Pycnogenol® may be evident almost immediately, significantly reducing the symptoms.

It can be suggested that components in Pycnogenol® may have a special affinity for urothelial cells, reduce inflammation and protect against bacterial adhesion and infections.

Supplementary medicine (namely medicine based on PS supplements) manages many conditions, particularly in borderline, clinical situations, without severe symptoms.

Pycnogenol® tends to decrease management costs and has a high level of safety with an efficacy/risk ratio very favorable.[4]

Conclusions

This pilot registry indicates that 60 days of Pycnogenol® decrease the occurrence of signs/symptoms related to the recurrence of UTIs both in men and women without side effects and with a good tolerability.

The effects of Pycnogenol® in these patients — including the control of oxidative stress — may be very important, particularly when a predominantly inflammatory component is present and continues the inflammatory process.

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