

Effects of D-Mannose, ElliroseTM and Lactobacillus Plantarum in treatment of urinary tract recurrent infections (rUTIs): A survey of urologists knowledge about its clinical application

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Summary. *Background and aim of the work:* Urinary tract infections (UTIs) and recurrent urinary tract infections (rUTIs) are widespread disease and almost half of all women will experience at least one episode of cystitis during their life. Aim of this study was to review the evidence of literature about the therapeutic and preventive effects of a product containing D-Mannose, ElliroseTM and Lactobacillus Plantarum on patients' symptoms, quality of life and recurrence of UTIs and to investigate the practicing urologists' knowledge about the clinical application of this product. *Materials:* We administrated an investigational survey about clinical use of a phytotherapeutic product made of D-Mannose, ElliroseTM and Lactobacillus Plantarum to 12 residents in Urology at the University of Modena and Reggio Emilia and to 32 urologists working in the provinces of Modena, Reggio Emilia and Parma. *Results:* 61% of physicians have diagnosed rUTIs in 3-6 patients during a month, and 7% of them in more than 6 patients during the same period of time. By these results rUTIs appear as common pathological conditions. 59% prescribed the product at least 1 time a month and 14% prescribed it more than 5 times. 43% administrated the product after out-patient invasive examinations as cystoscopy and urodynamic exam for UTIs prevention. 55% noticed a significant improvement in patient's QoL (Quality of Life) suffering from rUTIs. Furthermore 48% also reported a significant effect for the improvement of urinary symptoms of patients. No gastric or general side effects have been noticed during the administration period. Finally the cost of integrator has been reported affordable for the great majority of patients. *Conclusions:* Many studies in Literature have shown that D-Mannose and H. sabdariffa (ElliroseTM) reduce the risk of development of rUTIs opposing colonization and proliferation of uropathogenic bacteria in urinary tract. Our investigational survey about the administration of a phytotherapeutic product showed that this product is well-known and has a proved positive impact. (www.actabiomedica.it)

Key words: urinary tract recurrent infections (rUTIs), investigational survey, D-Mannose, ElliroseTM and Lactobacillus Plantarum

Background and aim of the work

Urinary tract infections (UTIs) consist in the presence of microbial pathogens in the urinary tract

and represents one of the most common bacterial infections (1).

Clinically UTIs can manifest as urethritis, cystitis or pyelonephritis.

EAU classification of UTIs includes uncomplicated UTIs, complicated UTIs, recurrent UTIs (rUTIs), catheter associated UTIs and urosepsis.

Recurrent UTIs (rUTIs) are UTIs presenting with a frequency of at least three times/year or twice in the last six months.

In this paper we want to evaluate the possible effects of a phytotherapeutic product (D-Mannose, ElliroseTM and Lactobacillus Plantarum) in recurrent UTIs.

Almost half of all women will experience at least one episode of cystitis during their life (1).

Risk factors include sexual intercourses, use of spermicide, a new sexual partner, a mother with an history of UTIs and an history of UTI during childhood (2).

The spectrum of etiological agents includes E. Coli in 70-95% of cases, Staphylococcus Saprophyticus in 5-10% of cases and occasionally other enterobacteriaceae such as Proteus Mirabilis and Klebsiella.

The most important reservoir of uropathogenic E. Coli is the human intestine. Bacteria can be considered normal inhabitants of the gastrointestinal tract where they play an important role in the maintenance of health and in development of diseases (3).

E. Coli and other Bacteria can reach the number of 10¹⁴ in the colon and more than 1000 bacterial species are found in the intestine. In the human intestine E.Coli can become a resident bacteria, survive and persist for many years and finally give rise to bacterial foci, acting like reservoir of UPEC (Uropathogen E. Coli) able to cause UTIs (4).

Urogenital colonization by E.Coli is feasible to a series of predisposing factors, hygiene habits and sexual practices (5).

In most cases female urethra gets infected by fecal material containing uropathogenic bacteria according with the short distance between female urethra and the anus that facilitates contamination (5).

After colonization the next step is adhesion of the bacteria to epithelial cells of urogenital mucosa.

This adhesion is mediated by special hair-like virulence factors of bacteria called fimbriae, particularly type 1 and the P- fimbriae (6).

Intestinal epithelium has several defense mechanisms which include mucociliary clearing, rapid cell

turnover, epithelial cell exfoliation and shedding and finally the urinary flow (7).

However some bacteria have developed mechanisms to bypass host defense mechanisms.

In particular uropathogenic E. Coli expresses special proteins that bind to same host receptors called CEA-related cell adhesion molecules increasing bacteria's stickiness to the infected cells (7). Also blocking epithelial cell exfoliation and shedding Bacteria facilitate the development of rUTIs.

Last step consists in invasion of nearby cells and tissues. Uropathogenic E.Coli can also replicate within the bladder cells and form intracellular Bacteria foci which have been correlated to rUTIs.

Recurrent UTIs consist in recurrences of uncomplicated and/or complicated UTIs with a frequency of at least 3 UTIs /year or 2 UTIs in the last 6 months.

RUTIs include lower tract infections (cystitis) and upper tract infections (Pyelonephritis) and are very common in general population, in particular in women.

About 20-30% of women with a first UTI will have a recurrence and 5% will have chronic recurring infections (8).

Diagnosis should be confirmed by urine culture: a colony count of 10.000 cfu/mL of uropathogens is microbiologically diagnostic in women who present lower urinary tract symptoms as dysuria, frequency, urgency and suprapubic pain with absence of vaginal discharges or irritation.

Risk factors can be considered for young premenopausal women and for post-menopausal and elderly women.

For young women risk factors are sexual intercourses, use of spermicide, a new sexual partner, a mother with a history of UTIs during her childhood and blood antigen secretory status.

For elderly women can be considered as risk factors history of UTIs before menopause, urinary incontinence, atrophic vaginitis, cystocele, increased post-void urine volume, blood group, antigen secretory status, urine catheterization, functional status and deterioration in elderly institutionalised women.

Prevention of rUTIs consists in avoidance of risk factors and prophylaxis with antimicrobial and non antimicrobial measures, unfortunately associated with onset of resistance to the antibiotic.

Non antimicrobial prophylaxis includes administration of probiotics, Cranberry and D-Mannose.

In particular, Lactobacillus probiotics and D-Mannose are included the preparation associated to Ellirose™.

Methods

The product is a phytotherapeutic composed of D-Mannose (1000 mg), Ellirose™ (200 mg) and Lactobacillus Plantarum Lp - 115 (1 mld u.f.c.).

It can be used in non antibiotic prophylaxis of rUTIs and its posology is 2 sachets daily (1 in the morning and 1 in the evening) in presence of urinary symptoms or after an invasive out-patient examination or 1 sachet daily in other clinical situations.

It can be administrated for prolonged time for its generally minimal side-effects.

Its clinical use is based on molecular effects of its components and on their synergistic effects.

In order to understand how this dietary supplement is prescribed, in wich kind of patients and clinical situations, we drafted a quick and concise survey.

We administrated this questionnaire to 12 residents in Urology at the University of Modena and Reggio Emilia and to 32 urologists working in the provinces of Modena, Reggio Emilia and Parma.

The questionnaire was answered by mail or trough direct anonymously compilation.

Investigational survey on a phytotherapeutic product made of D-Mannose, Ellirose™ and Lactobacillus Plantarum

1) How many times have you diagnosed rUTIs during the last month?

- 0-3 times
- 4-7 times
- >8 times

2) Do you trust in alimentary supplements (non pharmacological therapy) for the treatment of urological disorders?

- yes
- no

3) How many times have you prescribed the phytotherapeutic product during the last month?

- 0
- 1-5
- >5

4) For wich urological diseases have you prescribed the phytotherapeutic product?

- None
- rUTIs as non antimicrobial prophylaxis
- others

5) Have you noticed an improvement in the quality of life of patients affected of rUTIs with the phytotherapeutic product as non antimicrobial prophylaxis?

- I do not use
- yes
- no

6) Have you noticed an improvement of urinary symptoms as dysuria, burning, frequency, urgency and suprapubic pain?

- I do not use
- yes
- no

7) Do you administrate the phytotherapeutic product after cistoscopy or invasive urodynamic exam?

- I do not use
- yes
- no

8) Have patients reported occurrence of gastric side effects after assumption of the phytotherapeutic product?

- I do not use
- yes
- no

9) Have patients reported occurrence of other side effects after assumption of the phytotherapeutic product?

- I do not use
- yes
- no

10) Is the cost of the phytotherapeutic product affordable for the majority of patients?

- I do not use
- yes
- no

Results

All the 44 physicians completed the questionnaire in all its parts demonstrating that the phytotherapeutic product made of D-Mannose, ElliroseTM and Lactobacillus Plantarum is a well known product in this area, with a wide diffusion between both young and senior urologists.

The 61% of physicians have diagnosed rUTIs in 3-6 patients during a month, and 7% of them in more than 6 patients during the same period of time. By these result rUTIs appear as common pathological conditions.

16% of physicians surveyed didn't believe in use of dietary supplements for treatment of any medical condition so they refused the use of the product whereas 59% prescribed it at least 1 time a month and 14% prescribed it more than 5 times.

The majority of physicians who administered the phytotherapeutic product prescribed it correctly for rUTIs.

43% administrated the product after out-patient invasive examinations as cistoscopy and urodynamic exam for UTIs prevention.

20% of physicians have not noticed a significant improvement in patient's QoL (Quality of Life) suffering from rUTIs, while the 55% had evidence of clear ameliorations.

Furthermore 48% also reported a significant effect for the improvement of urinary symptoms of patients.

No gastric or general side effects have been noticed during the administration period.

Finally the cost of integrator has reported affordable for the great majority of patients.

Results of investigational survey on a phytotherapeutic product made of D-Mannose, ElliroseTM and Lactobacillus Plantarum

1) How many times have you diagnosed rUTIs during the last month?

- 0-3 times: A 14, 32%
- 4-7 times: B 27 61%
- >8 times: C 3 7%

2) Do you trust in alimentary supplements (non pharmacological therapy) for the treatment of urological disorders?

- yes: A 37, 84%
- no: B 7, 16%

3) How many times have you prescribed phytotherapeutic product during the last month?

- 0: A 12, 27%
- 1-5: B 26, 59%
- >5: C 6, 14%

4) For wich urological diseases have you prescribed phytotherapeutic product?

- None: A 9, 20%
- rUTIs as non antimicrobial prophylaxis: B 33, 75%
- others: C 2, 5%

5) Have you noticed an improvement in the quality of life of patients affected of rUTIs with phytotherapeutic product as non antimicrobial prophylaxis?

- I do not use: A 11, 25%
- yes: B 24, 55%
- no: C 9 20%

6) Have you noticed an improvement of urinary symptoms as dysuria, burning, frequency, urgency and suprapubic pain?

- I do not use: A 11, 25%
- yes: B 21, 48%
- no: C 12, 27%

7) Do you administrate phytotherapeutic product after cistoscopy or invasive urodynamic exam?

- I do not use: A 11, 25%
- yes: B 19, 43% b
- no: C 14, 32%

8) Have patients reported occurrence of gastric side effects after assumption of phytotherapeutic product?

- I do not use: A 11, 25%
- yes: B 0,
- no: C 33, 75%

9) Have patients reported occurrence of other side effects after assumption of phytotherapeutic product?

- I do not use: A 11, 25%
- yes: B 0,
- no: C 33, 75%

10) Is the cost of phytotherapeutic product affordable for the majority of patients?

- I do not use: A 11, 25%
- yes: B 32, 73%
- no: C 1, 2%

From the investigational survey on the phytotherapeutic product can be assumed that it is a dietary supplement widely used by the urologists in our region.

The absence of side effects makes it easily and safety administrable for long period especially for non-antimicrobial prophylaxis in rUTIs without risk of development of any antibiotic resistances.

The number of physicians surveyed is limited but data reported on the amount of prescriptions and on patient feedback indicate that phytotherapeutic product has a positive impact on clinical course of recurrent UTI.

D-Mannose contained has an important role in prevention of rUTIs. It is a sugar with a relevant role in human metabolism, especially in glycosylation of certain proteins.

The supposed mechanism of action is inhibiting bacterial adherence to uroepithelial cells (9).

B. Kranjcec et al. Investigated the role of D-Mannose in prevention of rUTIs in women with history of rUTIs initially treated with antibiotic therapy. These 308 women were randomly allocated in 3 groups. The first group (n=103) received prophylaxis with 2 gr of D-Mannose powder in 200 ml of water daily for 6 months.

The second group (n=103) received 50 mg Nitrofurantoin daily and the third group (n=102) did not received any products.

Overall 98 patients (31,8%) had rUTIs: 15 (14,6%) in the D-Mannose group, 21 (20,4%) in Nitrofurantoin group and 62 (60,8%) in no prophylaxis group.

Patients in first two groups had a significantly lower risk to develop rUTIs compared to patients in no prophylaxis group (RR 0.239 and 0.335, $p < 0.0001$).

Moreover patients in D-Mannose group had a significantly lower risk of side effects compared to patients in Nitrofurantoin group (RR 0.276, $p < 0.0001$) (10).

H. Sabdariffa is a common herbal drink consumed both hot and cold by people around the world and used in traditional medicine for the treatment of hypertension and UTIs.

The infusion is usually called karkade or red tea made from the calyces of the H. Sabdariffa. The red calyces area rich in organic acids as ascorbic acid, minerals, anthocianins, other phenolic components and antioxidants agents.

Issam Alshami et al. in their study wanted to assess the effectiveness of H. Sabdariffa extract in inhibiting the biofilm forming capacity of uropathogenic bacteria.

The antimicrobial activity of the H. Sabdariffa extract was evaluated on 8 different uropathogenic bacteria: 6 Escherichia Coli and 2 Klebsiella Pneumoniae isolates collected from patients with rUTIs. Extract inhibited biofilm production of all the isolates supporting the effective potential of H. Sabdariffa extract to prevent rUTIs (11).

The use of probiotics in prophylaxis is not yet supported by clinical studies showing convincing benefits but the role of Lactobacilli to maintain a normal vaginal flora equilibrium and to interfere with adherence, grown and colonization of uropathogenic bacteria seem suggest a use in prevention of rUTIs (12).

Conclusions

Many studies in Literature have shown that D-Mannose and H. sabdariffa (Ellirose™) reduce the risk of development of rUTIs opposing to colonization and proliferation of uropathogenic bacteria in urinary tract.

Moreover the absence of several side effects during prolonged prophylaxis is really considerable.

Our investigational survey has shown that this phytotherapeutic product is well-known and has a proved positive impact.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 16 May 2019

Accepted: 17 June 2019

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