

SCIENTIFIC AND CLINICAL EVIDENCE OF URELL® (well characterized cranberry product) IN URINARY TRACT HEALTH

urell®

- 3 pre-clinical studies
- 4 clinical studies (more than 300 patients!)

ALL PUBLISHED IN GOOD PEER-REVIEWED JOURNALS!

OVERVIEW

A/ MECHANISTIC ANTI-ADHESION STUDIES

- ✚ **Lavigne et al – Path Biol 2007 (1)**
Cranberry and urinary tract infections : study model and review of literature.
- ✚ **Lavigne et al – Clin Microbiol Infect 2008 (2)**
In vitro and in vivo evidence of dose-dependent decrease of uropathogenic *Escherichia coli* virulence after consumption of urell capsules.
- ✚ **Howell et al – BMC Infectious Diseases 2010 (3)**
Dosage effect on uropathogenic *Escherichia coli* anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study.

B/ CLINICAL EVIDENCE

1. Case studies

- ✚ **France – use of urell® in bladder replacement – Scand J Urol Nephrol 2010 (4)**
Effectiveness of a cranberry (*Vaccinium macrocarpon*) preparation in reducing asymptomatic bacteriuria in patients with an ileal enterocystoplasty. (15 patients/ 33 months average)
- ✚ **Spain – urell in reconstructive urological surgery – edited by Dr Luis Gausa (5)**
Study of 25 clinical cases documented by 13 urologists evaluating the interest of urell for prophylactic treatment when antibiotherapy fails.

2. Clinical trials (all randomized, double blind, controlled vs placebo)

- ✚ **Spain – clinical trial in children – Open Access Journal of Clinical Trials 2012 (6)**
Evaluation of urell® syrup vs trimethoprim for the prevention of recurrent UTIs in children (192 children /1 year)
- ✚ **US – clinical pilot in elderly women – letters to the editor – JAGS 2012 (7)**
Pilot Dosing Study of urell® Capsules for Prevention of Bacteriuria plus Pyuria in Female Nursing Home Residents. (80 patients / 1 month)

IN DETAILS

A/ MECHANISTIC ANTI-ADHESION STUDIES

1/ Lavigne et al – Path Biol 2007 (1)

- Model study and review of literature on benefic anti-adherent effects of *V. macrocarpon* cranberry.
- Introduction of *Lavigne* in vitro study (randomized, double blind, cross over study) comparing the urell administration (2 dosis) vs placebo on 8 healthy volunteers (see results & details in Lavigne 2008 Clin Microbiol Infect)

2/ Lavigne et al – Clin Microbiol Infect 2008 (2)

- Double blind, randomized, cross over study on 8 healthy volunteers
- Using one capsule of urell (36 mg PAC/DMAC) or 3 capsules (108mg PAC/DMAC) or a placebo (every participant received 3 capsules per day)
- *ex vivo* assay (T24 cells) using the urine samples collected from the participants
- *Caenorhabditis elegans* (worm) infection assay was performed to study bacterial pathogenicity and virulence

>The results show a significant decrease of bacterial anti-adherence depending on the dose ingested.

> They also showed a significant decrease in virulence of the uropathogenic *E.coli* (reduced ability of *E. coli* strains to kill worms in correlation with the consumption of cranberry capsules)

3/ Howell et al – BMC Infectious Diseases 2010 (3)

- Multicentric study : 32 participants recruited in 4 urology centers.
- Daily dosage used: 18, 36, 72 mg PAC (DMAC) per day
 - ✓ 18 / 36 mg PAC (Spain, France)
 - ✓ 36/ 72mg PAC (Hungary, Japan)

The study clearly shows an dose response awith graduation of the effect :

- 18mg PAC : insufficient anti-adhesion. This dosage is not recommended.
- 36mg PAC : confirmed as the optimum dose for prevention of UTI and long term use
- 72 mg PAC: confirmed as the optimum double dose to be administered during the first 2 days to maximize the anti-adhesive effect in case of symptoms and to extend the effect over 24 hours (50 % potential left after 24 h)

Conclusion:

- Cranberry PAC (*Vaccinium macrocarpon*) has a dose and time dependent effect on the inhibition of bacterial adhesion
- The administration of 36 mg PAC/day appears to offer the best « continuous » 24h protection against *E.coli*
- The dose of 18 mg PAC/day is not recomendaded because insufficient. Dose splitting like taking 2 capsules of 18 mg/day morning and evening has no justification.
- A double dose of 72 mg PAC/day during the first two days brings strong antiadhesive « power » that could help to stop an incipient infection
- The anti-adhesion activity of Urell® is optimum in all volunteers in the 4 countries showing that there is no influence from local diets
- The bacterial resistance does not influence this activity

B/ CLINICAL EVIDENCE

1. Case studies

1/ France – use of urell® in bladder replacement –Scand J Urol Nephrol 2010 (4)

For this open and controlled study, 15 patients (aged 68 ± 9 years) were recruited between 2004 and 2009 at Hôpital Foch, Paris

- Use of 1 capsule of Urell®/ day containing 36 mg PAC measured by DMAC
- Median duration of treatment with cranberry : 32.8 months (13-60 months)
- Result : significant reduction of asymptomatic bacteriuria in 93 % of patients
 - Patients with positive urinary cultures before treatment: 15 (100 %) ; after treatment : 1 (6,6 %)
 - Urinary incontinence before treatment: 9 (60 %) ; after treatment 2 (13,3 %)

2/ Spain – urell® in reconstructive urological surgery - edited by Dr Luis Gausa (5)

Dr Lluís Gausa Gascon, general and reconstructive urology unit. Fundacio Puigvert, Barcelona, Spain.

- 25 clinical cases documented by 13 urologists
- Evaluation of the use of urell® in current clinical practice
- Positive conclusions concerning the use of urell® for prophylactic treatment when antibiotherapy fails.

2. Clinical trials

1/ Spain – clinical trial in children – Open Access Journal of Clinical Trials 2012 (6)

- Site: Hospital Clínico San Cecilio de Granada, Spain.
- A controlled, double blind clinical trial carried out on 192 infants aged between 1 month to 13 years
- Patients followed over a maximum period of 1 year
- The children were randomized in permuted blocks of 10 subjects to receive either cranberry syrup (75) or the antibiotic Trimethoprim (117).
- Results > UTI recurrence rate : 28,4% (urell group) versus 43.2% (TMP group)

The study confirms that in the treatment of recurrent UTI, cranberry syrup is safe and effective for the infant population, and its effectiveness against this condition is equivalent to that of trimethoprim (European Clinical Trials Registry EuOract 2007 -004397 -62). There was observed to be a significant reduction in the risk rate of UTI among patients aged 1-3 years who were given cranberry syrup.

2/ US – clinical pilot in elderly women – letters to the editor – JAGS 2012 (7)

- Pilot dosing study
- Controlled, randomized clinical trial vs placebo
- Duration : 1 month
- 4 arms of 20 patients (placebo, 1, 2 or 3 urell® capsules)

This dosing study of one, two, and three cranberry capsules daily provides some evidence that two capsules are efficacious at reducing bacteriuria plus pyuria, particularly from E.coli, among female nursing home residents over one month. Two capsules should be tested in larger cohorts for prevention of bacteriuria, pyuria, and UTI.

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- (6) Uberos J et al. 2012. Cranberry syrup vs trimethoprim in the prophylaxis of recurrent urinary tract infections among children: a controlled trial *Open Access Journal of Clinical Trials* 2012:4 31–38.
- (7) Juthani-Mehta et al. Pilot randomized controlled dosing study of cranberry capsules for reduction of bacteriuria plus pyuria in female nursing home residents. Letters to the editor. June 2012 – *Journal of the American Geriatrics Society*. Vol 60, n°6.