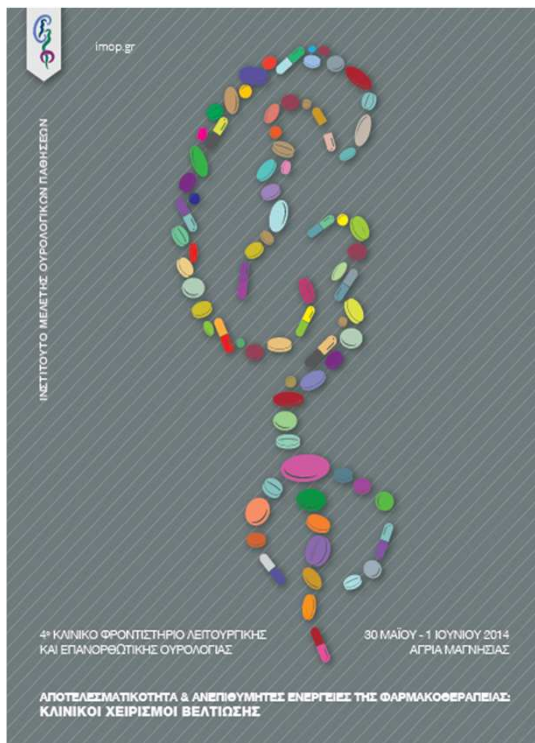




Όλα όσα πρέπει να ξέρετε για το Cranberry

Αθανάσιος Οικονόμου
Ουρολογική Κλινική
Πανεπιστημιακό Νοσοκομείο
Λάρισας



Δήλωση συμφερόντων

Astellas, Allergan

Cranberry

- *Vaccinium macrocarpon*
- Έρπων θάμνος, <30 cm
- Δυτικό τμήμα Β.Αμερικής μέσα σε χερσότοπους, τυρφώνες ή δάση κωνοφόρων



Cranberry

- Ποτό
- Μαγειρική



Cranberry στην ουρολογία



- Προστασία του ουροποιητικού κυρίως στις γυναίκες
- Blatherwick & Long, 1923 οξינוποίηση των ούρων μετά από ευρεία κατανάλωση Cranberries
- Ευρεία χρήση αντιβιοτικών
- Liu et al., 2006 μηχανισμός δράσης cranberry

Ουρολοιμώξεις

- Estimated annual cost of UTI in both men and women is \$US 3.5 billion *
- ♀:♂ 50:1
- Lifetime risk of a single UTI episode in women 50%

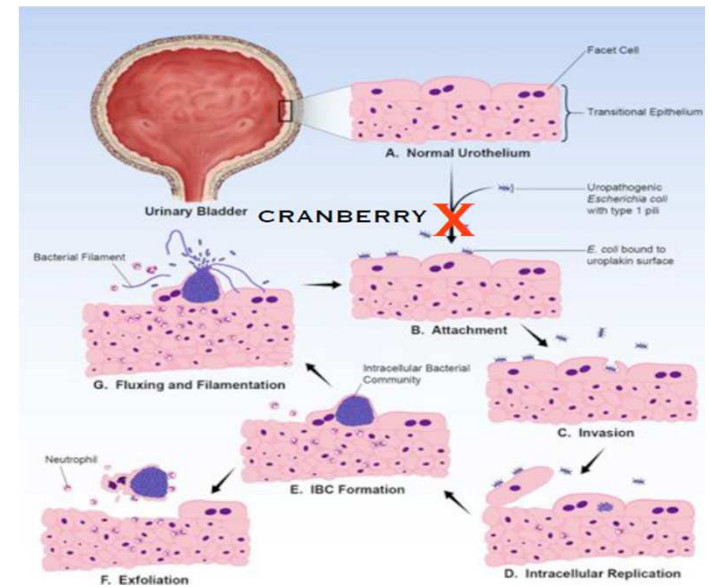
*Griebing,TLJ Urol 2005;174:1281-87 & 1288-94

Μηχανισμός δράσης

Οξινοποίηση των ούρων μέσω της έκκρισης
ιππουρικού οξέος

- Παροδική οξινοποίηση
- 400 ml χυμό cranberry/24ωρο

Μηχανισμός δράσης



Αναστολή της προσκόλλησης των E.coli στο ουροθήλιο

- Φρουκτόζη για E. coli με ινίδια τύπου I
- Α-προανθοκυανιδίνες (A-PACs) για E.coli με ινίδια P (τύπου II)

JOURNAL OF MEDICINAL FOOD

J Med Food 14 (7/8) 2011, 739–745

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DOI: 10.1089/jmf.2010.0154

Oral Consumption of Cranberry Juice Cocktail Inhibits Molecular-Scale Adhesion of Clinical Uropathogenic *Escherichia coli*

Yuanyuan Tao,¹ Paola A. Pinzón-Arango,¹ Amy B. Howell,² and Terri A. Camesano¹

¹*Department of Chemical Engineering, Worcester Polytechnic Institute, Worcester, Massachusetts, USA.*

²*Mariucci Center for Blueberry Cranberry Research, Rutgers University, Chatsworth, New Jersey, USA.*

Inhibition of *Escherichia coli* CFT073 *fliC* Expression and Motility by Cranberry Materials[▽]

Gabriela Hidalgo,[§] Michelle Chan,[§] and Nathalie Tufenkji*

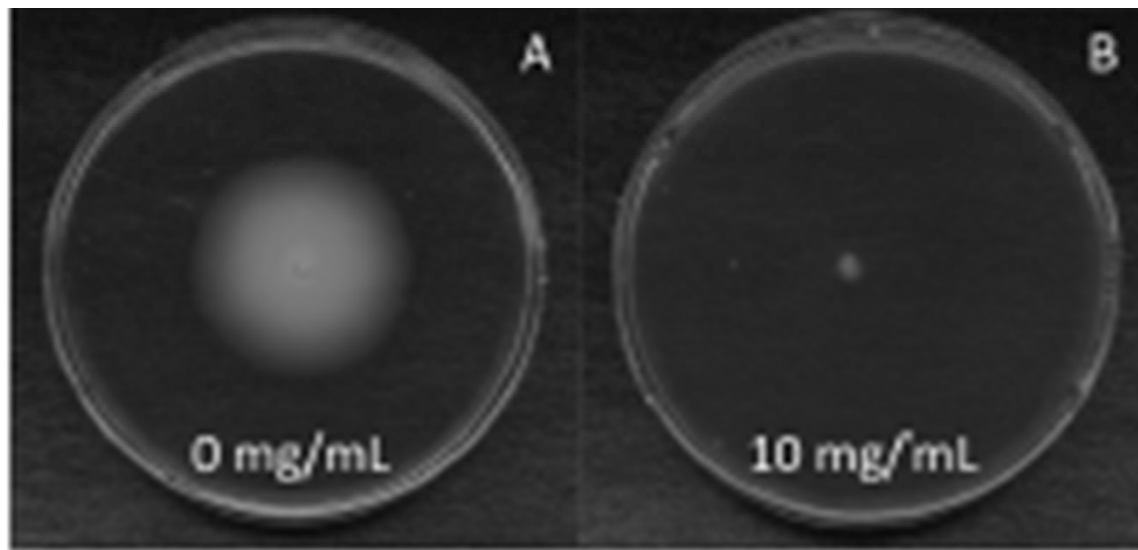
Department of Chemical Engineering, McGill University, 3610 University Street, Montreal, Quebec H3A 2B2, Canada

Received 20 May 2011/Accepted 27 July 2011

- Αναστολή έκφρασης γονιδίου *fliC*
- Απώλεια κινητικότητας του CFT073 *E.coli*

Cranberry impairs selected behaviors essential for virulence in *Proteus mirabilis* HI4320

Jennifer McCall, Gabriela Hidalgo, Bahareh Asadishad, and Nathalie Tufenkji



Can J Microbiol, 59: 2013



RESEARCH ARTICLE

Open Access

Cranberry proanthocyanidins inhibit the adherence properties of *Candida albicans* and cytokine secretion by oral epithelial cells

Mark Feldman¹, Shinichi Tanabe¹, Amy Howell² and Daniel Grenier^{1*}

**Cranberry-derived proanthocyanidins
prevent formation of *Candida albicans*
biofilms in artificial urine through biofilm-
and adherence-specific mechanisms**

[J Antimicrob Chemother.](#) 2014 Feb;69(2):428-36.

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

Amy B Howell¹, Henry Botto², Christophe Combescure³, Anne-Béatrice Blanc-Potard⁴, Lluís Gausa⁵, Tetsuro Matsumoto⁶, Peter Tenke⁷, Albert Sotto⁴ and Jean-Philippe Lavigne*^{4,8}

- Placebo, 18 mg, 36 mg, 72 mg PAC
- Υπερτερεί του εικονικού φαρμάκου
- Δοσοεξαρτώμενη δράση
- Χωρίς σημαντική διαφορά μεταξύ 36 και 72 mg
- Παρατεταμένη δράση (έως 24 ώρες για τα 72 mg)

RESEARCH ARTICLE

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

Amy B Howell¹, Henry Botto², Christophe Combescure³, Anne-Béatrice Blanc-Potard⁴, Lluís Gausa⁵, Tetsuro Matsumoto⁶, Peter Tenke⁷, Albert Sotto⁴ and Jean-Philippe Lavigne*^{4,8}

terial anti-adhesion effect in urine, 36 mg of cranberry PAC equivalents per day is effective, but 72 mg may offer a nyctohemeral protection. The kinetic data indicate that

decreases significantly after 24 h, suggesting that it may be beneficial to consume cranberry in two split doses of 36 mg in the morning and evening. With 72 mg of PAC,

Effects of Cranberry Juice on Pharmacokinetics of β -Lactam Antibiotics following Oral Administration^V

Meng Li,¹ Marilee A. Andrew,^{2,3} Joanne Wang,¹ David H. Salinger,² Paolo Vicini,² Richard W. Grady,⁴ Brian Phillips,⁵ Danny D. Shen,^{1,5,6} and Gail D. Anderson^{6*}

Department of Pharmaceutics,¹ Department of Bioengineering,² and Applied Physics Laboratory,³ University of Washington, Seattle, Washington 98105; Department of Urology, School of Medicine, University of Washington, Seattle, Washington 98195⁴; Pharmacokinetics Laboratory, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington 98109⁵; and Department of Pharmacy, University of Washington, Seattle, Washington 98195⁶

Received 13 June 2008/Returned for modification 16 October 2008/Accepted 19 April 2009

partmental methods and nonlinear mixed-effects compartmental modeling. We conclude that the concurrent use of cranberry juice has no significant effect on the extent of oral absorption or the renal clearance of amoxicillin and cefaclor. However, delays in the absorption of amoxicillin and cefaclor were observed. These results suggest that the use of cranberry juice at usual quantities as prophylaxis for UTI is not likely to alter the pharmacokinetics of these two oral antibiotics.

In vitro vs in vivo



Cranberries for preventing UTIs

Cochrane Database of Systematic Reviews 2009

Jepson RG, Craig JC



- **Systematic review**
 - 10 Studies (1049 participants)
 - Cranberry juice, cranberry capsules
- **Meta-analysis:**
 - Cranberry products significantly reduced incidence of UTIs at 12 months
 - RR 0.66 [0.47-0.92]
 - Effect in women with recurrent UTI > Elderly > indwelling catheters
 - Dropout rate 20-55%



Cranberries for preventing UTIs

Cochrane Database of Systematic Reviews 2009

Jepson RG, Craig JC



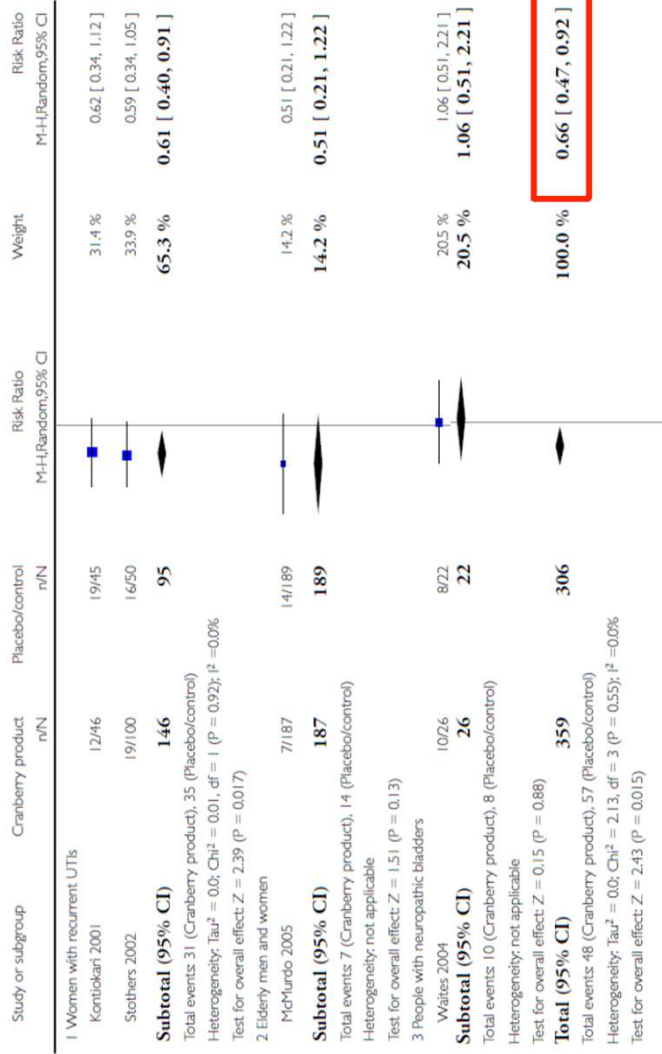
Analysis 1.1. Comparison 1 Cranberry products versus placebo/control, Outcome 1 At least one symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 1 Cranberry products versus placebo/control

Outcome: 1 At least one symptomatic UTI

- Small numbers
- Individually not significant
- Meta-analysis demonstrated significant reduction in recurrence
 - RR = 0.66



Cranberries for preventing UTIs

Cochrane Database of Systematic Reviews 2009

Jepson RG, Craig JC



THE COCHRANE
COLLABORATION®

- Conclusions:

“cranberry products can be effective in reducing UTIs”

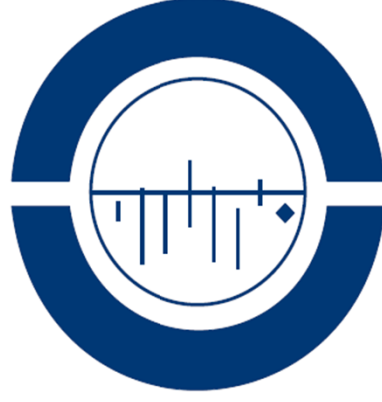
“some evidence to recommend cranberry juice for the prevention of UTIs in women with symptomatic UTIs.”

“not effective in neuropathic bladder”



Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



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COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 10

<http://www.thecochranelibrary.com>

WILEY

Cranberries for preventing urinary tract infections (Review)
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Authors' conclusions

Prior to the current update it appeared there was some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. The addition of 14 further studies suggests that cranberry juice is less effective than previously indicated. Although some of small studies demonstrated a small benefit for women with recurrent UTIs, there were no statistically significant differences when the results of a much larger study were included. Cranberry products were not significantly different to antibiotics for preventing UTIs in three small studies. Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs. Other

Cranberry Juice Fails to Prevent Recurrent Urinary Tract Infection: Results From a Randomized Placebo-Controlled Trial

Cibele Barbosa-Cesnik,¹ Morton B. Brown,² Miatta Buxton,³ Lixin Zhang,¹ Joan DeBusscher,⁴ Betsy Foxman¹

Departments of ¹Epidemiology, Center for Molecular and Clinical Epidemiology of Infectious Diseases, ²Biostatistics, and ³Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, and ⁴Department of Pathology, University of Michigan, Ann Arbor, Michigan

Clinical Infectious Diseases 2011;52(1):23-30

- Double-blind, placebo controlled RCT
- 319 college women with acute UTI
- 8 oz cranberry juice / day
- 6 month follow-up
 - No difference in recurrence rate (20.0% vs 14.0%)



Recurrent Urinary Tract Infection and Urinary *Escherichia coli* in Women Ingesting Cranberry Juice Daily: A Randomized Controlled Trial

- 176 ασθενείς (120 vs 56)
- 6 μήνες

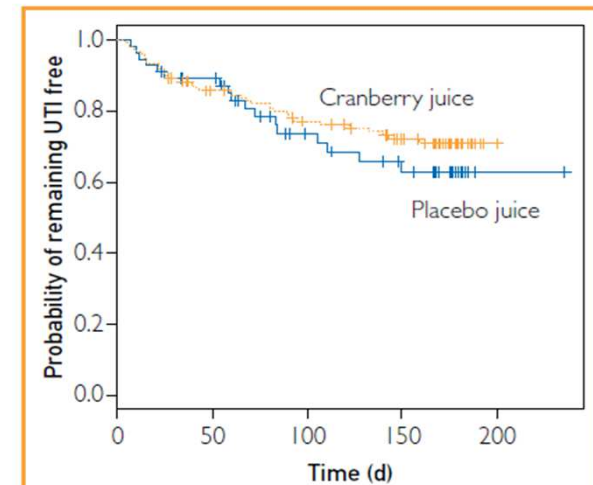


FIGURE 2. Kaplan-Meier curve for time to symptomatic urinary tract infection (UTI) in women ingesting cranberry juice (orange line) vs placebo juice (blue line). No significant difference was found in time to UTI between the groups ($P=.41$; log-rank test).

Conclusion: Cranberry juice did not significantly reduce UTI risk compared with placebo.

Cranberry σε ηλικιωμένους άντρες και γυναίκες

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



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Cranberries for preventing urinary tract infections (Review)
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Overall the data from the studies in older men and women suggest that cranberries are not effective in preventing UTIs. Of the four

Cranberry σε ασθενείς με νευρογενή κύστη

Guidelines on Neuro-Urology

J. Pannek (co-chair), B. Blok (co-chair), D. Castro-Díaz,
G. del Popolo, J. Groen, G. Karsenty, T.M. Kessler, G. Kramer,
M. Stöhrer

Various medical approaches have been tested as UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice for the prevention of UTI could not be demonstrated in randomized controlled trials (12). Methenamine hippurate is not effective in individuals with neuro-urological symptoms (13).

EAU
European
Association
of Urology

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Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



Overall the evidence from six studies suggest there is no benefit of cranberry juice in reducing UTIs in this population group.

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<http://www.thecochranelibrary.com>

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Cranberries for preventing urinary tract infections (Review)
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Cranberry σε ασθενείς με νευρογενή κύστη

Research Paper

MULTIPLE
SCLEROSIS
JOURNAL | MSJ

Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: a multicenter, randomized, placebo-controlled, double-blind trial

Multiple Sclerosis Journal
201X, Vol. XX(X) 1–8
© The Author(s) 2014
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1352458513517592
msj.sagepub.com
 SAGE

Results: The second sequential analyses allowed us to accept the null hypothesis (no difference between cranberry and placebo). There was no difference in time to first symptomatic UTI distribution across 1 year, with an estimated hazard ratio of 0.99, 95% CI [0.61, 1.60] ($p = 0.97$). Secondary endpoints and tolerance did not differ between groups.

Conclusion: Taking cranberry extract versus placebo twice a day did not prevent UTI occurrence in MS patients with urinary disorders. Trial Registration [NCT00280592](https://www.clinicaltrials.gov/ct2/show/study/NCT00280592).

Cranberry σε παιδιά

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



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Cranberries for preventing urinary tract infections (Review)
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The overall evidence suggested that cranberry products are not effective for preventing UTIs in children. Two studies (Ferrara 2009;

Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial

Jarmo Salo,¹ Matti Uhari,² Merja Helminen,³ Matti Korppi,^{3,4} Tea Nieminen,⁵ Tytti Pokka,¹ and Tero Kontiokari²

¹Department of Paediatrics, Oulu University Hospital; ²Department of Paediatrics, University of Oulu; ³Department of Paediatrics, Tampere University Hospital; ⁴Department of Paediatrics, Kuopio University Hospital; and ⁵Department of Paediatrics, Helsinki University Central Hospital, Finland

Conclusions. The intervention did not significantly reduce the number of children who experienced a recurrence of UTI, but it was effective in reducing the actual number of recurrences and related antimicrobial use.

Clinical Study

Urinary Tract Infection Prophylaxis in Children with Neurogenic Bladder with Cranberry Capsules: Randomized Controlled Trial

Hatice Mutlu¹ and Zelah Ekinci²

whereas 0/year during cranberry capsule usage. Decrease in infection rate was significant with cranberry capsule usage ($P = 0.012$). Decrease in the percentage of the pyuria was also recorded as significant ($P = 0.000$). Any adverse events or side effects were not recorded. *Conclusion.* We concluded that cranberry capsules could be an encouraging option for the prevention of recurrent UTI in children with neurogenic bladder caused by myelomeningocele.

Cranberry vs χημειοπροφύλαξη

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



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berry juice. Analysis of the two studies in women showed that cranberry product compared to antibiotic were equally as effective in reducing the risk of repeat UTI in women (Analysis 2.1.1: RR 1.31, 95% CI 0.85 to 2.02) The study in children also showed that the cranberry product were equally as effective in reducing the risk of repeat symptomatic UTI compared to antibiotics (Analysis 2.1.2: RR 0.69, 95% CI 0.32 to 1.51).

Cranberries vs Antibiotics to Prevent Urinary Tract Infections

A Randomized Double-blind Noninferiority Trial in Premenopausal Women

Mariëlle A. J. Beerepoot, MD; Gerben ter Riet, MD, PhD; Sita Nys, PhD; Willem M. van der Wal, MSc; Corianne A. J. M. de Borgie, PhD; Theo M. de Reijke, MD, PhD; Jan M. Prins, MD, PhD; Jeanne Koeijers, MD; Annelies Verbon, MD, PhD; Ellen Stobberingh, PhD; Suzanne E. Geerlings, MD, PhD

ARCH INTERN MED/VOL 171 (NO. 14), JULY 25, 2011

Conclusion: In premenopausal women, TMP-SMX, 480 mg once daily, is more effective than cranberry capsules, 500 mg twice daily, to prevent recurrent UTIs, at the ex-

Cost-Effectiveness of Cranberries vs Antibiotics to Prevent Urinary Tract Infections in Premenopausal Women: A Randomized Clinical Trial

Judith E. Bosmans^{1*}, Mariëlle A. J. Beerepoot², Jan M. Prins², Gerben ter Riet³, Suzanne E. Geerlings²

¹ Department of Health Sciences and EMGO Institute for Health and Care Research, Faculty of Earth and Life Sciences, VU University Amsterdam, Amsterdam, The Netherlands, ² Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Amsterdam, The Netherlands, ³ Department of General Practice, Academic Medical Center, Amsterdam, The Netherlands



Conclusion: In premenopausal women with recurrent UTIs, cranberry prophylaxis is not cost-effective compared to TMP-

Cranberry στην κύηση

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



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Cranberries for preventing urinary tract infections (Review)
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Overall cranberry juice was found not to be effective in reducing UTIs in pregnant women. The two studies in pregnant women

SAFETY AND EFFICACY OF CRANBERRY (*Vaccinium Macrocarpon*) DURING PREGNANCY AND LACTATION

Jean-Jacques Dugoua^{1,2,3}, Dugald Seely^{3,4}, Daniel Perri⁵, Edward Mills^{3,5}, Gideon Koren^{2,6}

- Καμία βλαπτική δράση στο έμβρυο.
- Άγνωστη η επίπτωση στο θηλασμό.
- Μπορεί να είναι θεραπευτική επιλογή στην πρόληψη!

Can J Clin Pharmacol. 2008;15:80-6.



RESEARCH ARTICLE

Open Access

Pregnancy outcome after use of cranberry in pregnancy – the Norwegian mother and child cohort study

Kristine Heitmann^{1*}, Hedvig Nordeng^{2,3} and Lone Holst¹

Conclusions: The findings of this study, revealing no increased risk of malformations nor any of the following pregnancy outcomes; stillbirth/neonatal death, preterm delivery, low birth weight, small for gestational age, low Apgar score and neonatal infections are reassuring. However, maternal vaginal bleeding should be investigated further before any firm conclusion can be drawn. Treatment guidelines on asymptomatic bacteriuria in pregnancy recommend antimicrobial therapy as the first line treatment. According to our data and the outcomes studied, cranberry does not appear to be a harmful adjunctive self-treatment.

Randomised trial of cranberry-lingonberry juice and *Lactobacillus GG* drink for the prevention of urinary tract infections in women

Tero Kontiokari, Kaj Sundqvist, M Nuutinen, T Pokka, M Koskela, M Uhari

recurrence. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, $P = 0.023$, number needed to treat = 5, 95% confidence interval 3 to 34).

Conclusion Regular drinking of cranberry juice but not lactobacillus seems to reduce the recurrence of urinary tract infection.

Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma

Table 3 Description of dysuria discomfort scale: grading extract from Boyarsky score

Degree	Description
0	No symptoms
1	Burning sensation during urination
2	Frequent burning or pain during urination, more than 50% of times
3	Continuous burning sensation or pain during urination

Table 4 Difference in distribution of incidence of dysuria ($P < 0.0001$)

Dysuria	Treated	Control
Degree 0	114 (61.9%)	66 (35.9%)
Degree 1	49 (26.6%)	60 (32.6%)
Degree 2	20 (10.9%)	44 (23.9%)
Degree 3	1 (0.6%)	14 (7.6%)
All	184	184

Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma

Conclusion: Cranberry extracts have been reported to reduce the incidence of LUTIs significantly in women and children. Our data extend these results to patients with prostate cancer undergoing irradiation to the pelvis, who had a significant reduction in LUTIs compared with controls. These results were accompanied by a statistically significant reduction in urinary tract symptoms (dysuria, nocturia, urinary frequency, urgency), suggesting a generally protective effect of cranberry extract on the bladder mucosa.

The effectiveness of dried cranberries (*Vaccinium macrocarpon*) in men with lower urinary tract symptoms

Ales Vidlar¹, Jitka Vostalova^{2*}, Jitka Ulrichova², Vladimir Student¹, David Stejskal³, Richard Reichenbach⁴, Jana Vrbkova⁵, Filip Ruzicka⁶ and Vilim Simanek¹

and urine *ex vivo* anti-adherence activity were determined in all subjects. In contrast to the control group, patients in the cranberry group had statistically significant improvement in International Prostate Symptom Score, QoL, urination parameters including voiding parameters (rate of urine flow, average flow, total volume and post-void residual urine volume), and lower total PSA level on day 180 of the study.

Effect of cranberry juice concentrate on chemically-induced urinary bladder cancers

JEEVAN K. PRASAIN¹, KENNETH JONES¹, RAY MOORE⁴, STEPHEN BARNES^{1,4}, MARGE LEAHY⁵,
ROBIN RODERICK⁵, M. MARGARET JULIANA² and CLINTON J. GRUBBS³

data suggest that components of cranberries may be effective in preventing urinary bladder carcinogenesis.

Ανεπιθύμητες ενέργειες

- Αλλεργική αντίδραση
- Συμπτώματα από ΓΕΣ 10-40%
- Απορρύθμιση Σακχαρώδη Διαβήτη (χυμός)

Ανεπιθύμητες ενέργειες

Αλληλεπίδραση με Βαρφαρίνη?

- Μπορεί να αναστείλει το CYP2C9
- Case reports για αύξηση INR
- 2 RCTs δεν επιβεβαιώνουν αυτό το εύρημα
- Σύσταση για παρακολούθηση INR που λαμβάνουν Βαρφαρίνη και Cranberry

Ανεπιθύμητες ενέργειες

Νεφρολιθίαση?

- Υψηλή περιεκτικότητα σε οξαλικά
- Αντικρουόμενα δεδομένα από τη βιβλιογραφία
 - Αυξημένη απέκκριση στα ούρα οξαλικών, αλλά και Mg και K
Terris MK et al, Urology 2001
 - Ελαττωμένη απέκκριση οξαλικών και φωσφορικών, αυξημένη έκκριση κιτρικών
Mc Harg TA et al, BJU Int 2003

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

tract infection by inhibiting the adhesion of certain bacteria in the urinary tract. The Panel concludes that a cause and effect relationship has not been established between the consumption of CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.

Guidelines on Urological Infections

M. Grabe (chairman), T.E. Bjerklund-Johansen, H. Botto,
M. Çek, K.G. Naber, R.S. Pickard, P. Tenke,
F. Wagenlehner, B. Wullt

3.5.2.4 Prophylaxis with cranberry

Despite the lack of pharmacological data and the small number of weak clinical studies, there is evidence to suggest that cranberry (*Vaccinium macrocarpon*) is useful in reducing the rate of lower UTIs in women (40,41) (LE: 1b, GR: C).

For everyday practice, the daily consumption of cranberry products, giving a minimum of 36 mg/day proanthocyanidin A (the active compound), is recommended (LE: 1b, GR: C). The best approach is to use those compounds that have demonstrated clear bioactivity in urine.

Alternative methods, such as cranberry and probiotic lactobacilli, can contribute but they are not sufficient to prevent recurrent UTI.	51	1b	C
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