

# Cranberry in children: prevention of recurrent urinary tract infections and review of the literature

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**Abstract:** Urinary tract infections (UTI) are common in childhood. In 30-50% of children with UTI the infections occur recurrently, especially in those with vesicoureteral reflux (VUR), neurogenic bladder (NB), previous cystitis or pyelonephritis and malformative uropathies. To reduce the likelihood of UTI, antibiotic prophylaxis has been regarded as the therapeutic standard for many years. However, the disadvantage of long-term antibiotic therapy is the potential for development of collateral effects and resistant organisms in the host. Such reasons have induced scientists to search for alternative modalities of UTI prevention and have contributed to determining the increasing desire for “naturalness” of the population and preventing excessive medication. The use of cranberry fulfils these needs by potentially replacing or enhancing traditional procedures. The purpose of this study was to assess the effectiveness of cranberry in preventing UTI in pediatric populations. We searched Pubmed, the Cochrane Central Register of Controlled Trials and Internet. Cranberry in patients with previous UTI was evaluated in three studies, cranberry in patients with VUR in three studies and four studies analyzed the efficacy of cranberry in children with NB. In seven of nine studies cranberry had a significant effect in preventing UTI.

## Introduction

Urinary tract infections (UTI) are the most frequent bacterial infections in pediatrics after infections of the respiratory tract: at the age of seven, 8% of females and 2% of males present with at least one episode of UTI. Only in the first three to six months is the incidence in males higher, after which the pathology appears more often in females. Children who have had a UTI run a 10 to 30% risk of recurrence and in 15% of cases may develop high blood pressure (Foxman et al., 2000).

A study carried out in all of Denmark showed that in one thousand patients in pediatric age followed for one year by an area physician there were nineteen episodes of UTI (Kwock et al., 2006). A 2006 study (Wald, 2006) showed that UTI represents the most frequent and serious bacterial infection in the United States since some bacterial infections (*S. pneumoniae* and *H. influenzae*) have been weakened through vaccinations. From the aetiological standpoint the most common bacterium in discussion is *E. coli* (almost 80% of cases) and more rarely other enterobacteria,

especially *Proteus* spp. (mostly in males), *Klebsiella* spp., *Enterococcus* spp., *Citrobacter* spp., *Providencia* spp., *Morganella* spp., *Serratia* spp. and *Salmonella* spp., which, similarly to the strains of *Pseudomonas* spp. with low virulence, may be involved in complicated infections.

In the first months of life, UTI, especially relapsing (infections caused by the same germ) and recurrent (UTI caused by different microorganisms), represent an important clinical element for further investigations and diagnoses of possible urinary tract malformations. Indeed, in children there are factors that favor relapses and/or recurrences of UTI such as malformative uropathies, especially obstructive; vesicoureteral reflux (VUR), previous repeated episodes of cystitis and/or pyelonephritis (three or more episodes per year) even without urinary tract anomalies and the frequently catheterized neurogenic bladder (NB) (Mangiarotti et al., 2000).

Although the literature supplies no univocal indications, in the pediatric age it is common practice to use antibiotic prophylaxis in the treatment of relapsing and recurrent UTI, especially in patients with

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VUR (Fanos & Cataldi, 2004). However, the many side effects of antibiotics, the increasing number of antibiotic-resistant bacteria and the economic impact of the therapy have promoted research on alternative measures to prevent UTI. An important contribution to this research has come from the ever-increasing desire for "natural remedies" among the population as concerns the excessive (or perceived as such) use of drugs in special periods of life, such as pregnancy and infancy (Fanos et al., 2006a).

The use of cranberry (*Vaccinium macrocarpon* Ainton, Ericaceae) juice represents one of the possible solutions that may potentially go hand in hand with traditional procedures or, in some cases, even replace them.

### What do we know about the cranberry?

#### Historical notes

The interest in cranberry juice goes back to the times of the American colonies. The traditional use of the cranberry is associated with Thanksgiving Day starting from 1961 when the pilgrims served it with turkey and lobster (Kemper, 1999). The common name cranberry comes from the colonial name of crane berry, which later became contracted. The withered flower resembles the neck and head of the sandhill crane, which the colonists often saw feeding on this fruit.

It was appreciated by the North American natives owing to its beneficial effects both in the diet (as a sweetener or in the drying of meat and fish) and as a remedy in disinfecting wounds, reducing pain caused by indigestion and in oral and dental hygiene. The Penobscot tribe in Maine used the cranberry for treating kidney stones and other urinary problems (Duthie et al., 2005). In East Europe it was used as an antipyretic and anticancer remedy and, being rich in vitamin C, it was loaded on ships to prevent scurvy. Used as a folk remedy for UTI before the introduction of antibiotics, it continues to be widely used for this purpose (Kemper, 1999); in 1997 it was one of the ten most sold herbal remedies in the United States (Reid & Bruce, 2003). The part used for this purpose is the mature berry, which is extremely bitter so that many preparations are sweetened to improve their taste.

#### Main components and how it acts

The main components of the cranberry are flavonoids (among which the anthocyanins), catechins, triterpenoids, organic acids (butyric, malic, glucuronic, citric and quinic), vitamins (A and C), carbohydrates (especially fructose), mineral salts and tannins such as the proanthocyanidins (PAC) (characteristic of type

A).

This plant has recently been monographed in the ESCOP (ESCOP, 2009) where we find a liquid preparation in compliance with the United States Pharmacopoeia with no less than 2.4% of dextrose, 0.7% of fructose, 0.9% of quinic acid, 0.9% of citric acid and 0.7% of malic acid. The recommended preparation is the concentrated juice extract titrated in proanthocyanidin of type A at 1.2 to 1.4% (or polyphenols at 15%).

For a long time the antiseptic and antibacterial action of the cranberry was attributed to its capacity to acidify the urine owing to its vitamin C content and its capacity to metabolize benzoic acid into hippuric acid with antibacterial properties. More recent pharmacological studies have also revealed that cranberry juice is capable of inhibiting the adhesion of type 1 (activity attributed to fructose) and type P (activity attributed to the proanthocyanidins) fimbriated *E. coli* to the epithelial cells of the bladder wall (Zafriri et al., 1989; Ahuja et al., 1998; Howell et al., 2010). In fact, the pathogenicity of these bacteria is connected to the presence of fimbriae at the extremities of which there are proteinic structures called adhesins which make it possible for the pathogens to adhere to the membrane of uroepithelial cells. The type A proanthocyanidins appear to be those mainly responsible for the antiseptic and antibacterial action. In a study by Howell & Foxman (2002) the antiadhesive activity of the cranberry against type B uropathogen fimbriated *E. coli* was studied *in vitro* by examining PAC A, which has been shown to inhibit adhesion (Howell & Foxman, 2002). PAC, by acting as receptor analogues and adhering to the extremities of the fimbriae, competitively inhibit the adhesion of *E. coli*, thus causing an elongated deformation of the bacterium cell bodies, a reduction in the length and density of the P-fimbriae and finally an inhibition of their synthesis with the total disappearance of the adhesins. The antiadhesive activities of the cranberry help to prevent UTI also indirectly by selecting at the intestinal level less adhesive uropathogenic bacteria. A study in 2005 showed in subjects who regularly drank cranberry juice an increase in urinary salicylates, thus suggesting a possible local anti-inflammatory effect and a further probable mechanism of action (Duthie et al., 2005). The research demonstrated that besides the urinary antiseptic action, the cranberry possesses an antioxidant and radical scavenger (being rich in polyphenols) activity and an antibacterial action against many germs (recently it has been demonstrated as acting against *H. pylori* and *S. mutans*) (Gotteland et al., 2008; Koo et al., 2010).

#### Clinical studies in the adult

There are numerous studies in the literature concerning the use of the cranberry in the adult which provide data that confirm the therapeutic action of this plant in the prevention of UTI.

A double-blind randomized placebo-controlled cross-over trial on twenty healthy volunteers showed a significant dose-dependent reduction of bacterial adhesiveness following the administration of cranberry (Di Martino, 2006).

The Cochrane group has recently demonstrated a significant reduction in UTI in women following the regular assumption of cranberry juice (Jepson & Craig, 2008). The study included consultation of databases, the involvement of companies producing products based on the cranberry and the search for lists of bibliographic references of systematic revisions and important studies. All controlled and randomized studies on cranberry-based products used in the prevention of UTI were examined and studies on patients of both sexes and different ages were included. The authors concluded that there is definite evidence that cranberry juice can be effective in reducing the number of symptomatic urinary tract infections in females after twelve months of treatment. However, certainties are lacking as concerns its pharmaceutical preparation and the most appropriate dosages, and finally there are no clinical studies in support of the fact that the cranberry is just as effective in the pediatric age. The most recent study has demonstrated that besides *E. coli*, the cranberry can significantly reduce the adherence of other common pathogens of the urinary tract, including *P. mirabilis*, *S. aureus*, *K. pneumoniae*, *Enterobacter* and *P. aeruginosa* (Magariños et al., 2008).

#### *Dosage and side effects*

The daily dose recommended in ESCOP Monographs (ESCOP, 2009) is in adults 300 to 750 mL/day of a liquid preparation containing 25 to 100% juice in two to three administrations or 200 to 500 mg/day of dry extract or concentrated juice in two daily administrations. As concerns children between the ages of two and eighteen, 15 mL/kg of juice or equivalent doses are recommended. No limits on use in the pediatric age are reported (some studies included breastfeeding infants a few months after birth).

The cranberry is normally well tolerated. In a study by Kontiokari et al. (2005) in 341 children cranberry juice appeared to have beneficial effects on urinary health and this was not compromised by other unexpected antimicrobial effects (Kontiokari et al., 2005).

A significant increase in the urinary concentration of oxalates (controversial finding) was reported and this suggests caution in patients predisposed for the formation of urinary oxalate stones (Gettman et al., 2005). Against this, the cranberry has a protective effect on the formation of urate stones. A single case of autoimmune thrombocytopenic purpura

was reported in the case of an elderly patient (Davies et al., 2001) and a probable interaction between cranberry and warfarin in anticoagulant therapy (Suvarna et al., 2003) has also been described. The product obviously cannot be administered to patients allergic to cranberry. As concerns the use of cranberry in pregnancy, in Italy this was expressly prohibited by a decree law in 2002 (Official Gazette no.167 of 18 July 2002), concerning the use of products containing biflavonoids. It is to be pointed out that this is an isolated provision, but one that has recently been confirmed by the Supplement to the ESCOP Monographs 2009 (ESCOP, 2009) which states that in pregnancy the administration must be under the control of a physician whenever the dose greatly exceeds the amount found in foodstuffs. The recommendation is extended to the period of breastfeeding. On this subject, the data in a study by Wing et al. (2008) in California on 188 women below the sixteenth week of pregnancy demonstrated that there may be a protective effect in the assumption of cranberry against asymptomatic bacteriuria and UTI in pregnancy (Wing et al., 2008).

As concerns costs, these were analyzed in a controlled clinical study that evaluated the effects of different cranberry-based preparations on UTI in women. One hundred and fifty sexually active women between the ages of 21 and 72 were enrolled; they assumed *per os* 150 mg of dry cranberry extract or 250 mL of cranberry juice or a placebo for one year. The assessment was made on the basis of the number of cystitis episodes and the consumption of antibiotics during the year of the study. At the end of the study it was found that both the dry extract and the juice reduced the number of infections by 20 and 18% respectively. The yearly cost of the therapy was 624 USD for the dry extract and 1400 USD for the juice. The consumption of antibiotics was significantly lower in the two verum groups compared to the placebo group. The study indicates that both the dry extract and the juice of cranberry are effective in UTI, although the dry extract is preferable from the economic standpoint (Stothers, 2002).

#### **The cranberry in the child**

##### *Materials and methods*

Studies on the use of cranberry in the pediatric age are few; however, the literature shows an ever-increasing interest in its use in this delicate age. This is supported by results obtained in adults, by the documented scarcity of side effects, by the ease in administration and the fair and verified compliance by the patients treated.

The purpose of this research was to evaluate the efficacy of cranberry juice in the prevention of UTI

in pediatrics through a review of the entire literature. We searched through Pubmed, Embase, the Cochrane Central Register of Controlled Trials (Central Cochrane Library) and Internet and examined the proceedings of international congresses and the review bibliography. Information was collected on methods, researchers, patients, operations, drugs administered, side effects, compliance with therapy and results. The study, considering the few works now available, included all written publications which were analyzed by type of study (retrospective study, randomised controlled trials etc.) (Table 1).

## Results and Discussion

Recent studies affirm that the use of antibiotic

prophylaxis in children with relapses of UTI is not only ineffective in preventing infection and long-term kidney damage, but is also associated with important side effects. A very recent meta-analysis involving five studies revealed no or little benefit with prophylaxis in the prevention of UTI recurrence (Mattoo, 2010). Also to be considered is the result of a study by Smolkin et al. (2007): one out of two couples does not perform the long-term (e.g. one year) antibiotic prophylaxis prescribed by specialists and 50% of parents cannot explain why they perform antibiotic prophylaxis even though this has been explained to them (Smolkin et al., 2007). It is also of interest to note that in a United States study, about 30% of parents administered cranberry to their children to prevent UTI, but only 25% of them spoke to their physician about this (Super et al., 2005).

**Table 1.** Summary of clinical trials on cranberry products for UTI prophylaxis in children.

| Study             | Year of study | Patients   | Mean age (months)                        | Type of study                                    | Intervention   | Outcome   |
|-------------------|---------------|--|--|--|--|---|
| Bircan et al.     | 2010          | 50 (16M-34F) with NB (32 overactive detrusor/18 hypocompliant bladder) | 84.9±51.4                                | Retrospective study                              | Cranberry 1 capsule/day for 25.94±24.12 months   | A significant reduction in UTI (4.36/year) in overall group   |
| Goj et al.        | 2010          | 63 (24M-39F) with VUR  | 20                                       | Retrospective study                              | Cranberry concentrate 0.5 mL/kg daily; 24 month trial  | A significant reduction in UTI (4.7%) in patients with VUR, including high grade VUR and associated urinary tract malformations |
| Maringhini et al. | 2010          | 79 (23M-56F) with previous UTI   | 62.4                                     | Retrospective study                              | Cranberry concentrate 0.5 mL/kg daily in two doses for a mean of 6.4 months  | UTI average rate during treatment was 0.03/month compared with 0.4/month in the preceding period                                |
| Ferrara et al.    | 2009          | 84F with previous UTI  | 90                                       | Randomized controlled trial                      | Cranberry juice (C.J.) 50 mL daily vs <i>Lactobacillus</i> (L.) GG drink on five days a month/vs controls; six month trial | A significant reduction in UTI: 18.5% for C.J. vs 42.3% for L.GG vs 48.1% for controls  |
| Nishizaki et al.  | 2009          | 31 (18M-13F) with VUR  | 32.5±19.6 (C.J.)<br>18.2±22.9 (Cefaclor) | Randomized controlled trial                      | Cranberry juice (C.J.) 100 mL daily vs Cefaclor 5-10 mg/kg/day; for 17.2±7.90 (C.J.) and 10.2±3.29 (Cefaclor) months       | No significant difference in the risk of having recurrent UTI between the cranberry and cefaclor groups ( $p > 0.05$ )          |
| Fanos et al.      | 2006b         | 20 (4M-16F) with previous UTI  | 85.2±52.3                                | Retrospective study                              | Cranberry 1 capsule/day for 2.8±10 months  | 0.36% UTI/patient/year  |
| Erculiani et al.  | 2004          | 47 (25M-22F) with NB and/or VUR  | Between 24 and 168                       | Retrospective study                              | Cranberry 2 capsule/day for 11.2 months  | Cranberry appears to have beneficial effects in patients with low grade VUR   |
| Schlager et al.   | 1999          | 15 children with NB  | Between 24 and 216                       | Double-blind placebo-controlled cross-over study | 300 mL cranberry concentrate vs placebo, each for three months   | No benefit in preventing UTI or bacteriuria   |
| Foda et al.       | 1995          | 40 children with NB (21 finished)                                      | -  | Randomized single-blind cross-over study         | Cranberry cocktail 15 mL/kg/day vs water, each for six months  | No benefit in preventing UTI or bacteriuria   |



They explained this by saying that since the product was natural it was by definition without side effects and also because they thought physicians knew very little about the subject.

Recent literature offers works with promising results on the use of cranberry in the prevention of UTI in the pediatric age; despite the difficulty of performing a comparative evaluation of the different studies owing to the heterogeneity of the populations, the use of different preparations containing cranberry (concentrated juice, juice, cocktails, capsules and so on) at different dosages, but in any case the data appear encouraging.

Nine studies were included in this review. Some studies were not included in the meta-analyses due to methodological issues or lack of available data. Cranberry in patients with previous UTI was evaluated in three studies, cranberry in patients with VUR in three studies and four studies analyzed the efficacy of cranberry in children with NB (one study assessed both VUR and NB). While Foda (Foda et al., 1995) and Schalager (Schalager et al., 1999) found no effect on the reduction of bacteriuria in children affected by NB treated with cranberry, a subsequent study by Erculiani et al. (2004) on a group of 47 children with the same pathology found favorable results (Erculiani et al., 2004) as in all other works written to date (Table 1). In a preliminary study by one of the authors (Fanos et al., 2006b), twenty children were placed in prophylaxis with a special extract of cranberry having a high content of phenols with vitamin C for the purpose of evaluating the possible use of cranberry in the prevention of UTI in children. During the prophylaxis only three episodes of UTI were found in different patients, for which the cranberry therapy was suspended. In the remaining seventeen patients the treatment was well tolerated and no side effects were reported. Various studies have compared the use of cranberry juice in the prophylaxis of UTI with the administration of a placebo, *Lactobacillus* GG and antibiotic prophylaxis. In a recent work by Ferrara et al. (2009) 84 girls aged from 3 to 14 years with UTI were studied: they were divided into three groups which received three different treatments: G1 (cranberry juice 50 mL/day), G2 (*Lactobacillus* GG 100 mL/5 days per month) and G3 (controls). The first group presented five episodes of UTI (18.5%) against 11 (42.3%) and 18 (48.1%) episodes in groups G2 and G3 respectively (Ferrara et al., 2009). Only one work (Nishizaki et al., 2009) compared the effect of cranberry with that of an antibiotic (Cefaclor) in UTI prophylaxis. This study shows that the effect and efficacy of the two treatments are comparable and without the presence of side effects caused by cranberry juice (Nishizaki et al., 2009). The latest works in 2010 were published in abstract form in the proceedings of the Fifteenth

Congress of the International Pediatric Nephrology Association. They deal with the cranberry treatment of three types of different patients: with VUR (Goj et al., 2010), NB (Bircan et al., 2010) and previous UTI (Maringhini et al., 2010). All three of these works report significantly positive results with the use of cranberry in UTI prevention.

In the site of the United States National Health Institute (ClinicalTrials.gov) we found four studies (three completed and one recruiting) concerning cranberry in children, but no results have been published to date (Uhari, 2009; Godbolt, 2010; Anderson, 2006; Wing, 2006). Some of these authors are studying the interaction between the antibiotic and the cranberry in acute UTI.

In all works examined, the cranberry was well tolerated and there was good compliance both by patients and parents. We must indicate the critical points in this review: the scarcity of data, the heterogeneity of case histories as concerns the population studied, the types of products, their dosage and the duration of treatment.

## Conclusions

Recurrent and relapsing UTI are quite common. Their frequent finding in given age groups, such as infancy, indicate the need to find a therapy that is the least invasive possible and one without side effects. The data in pediatric literature, although few and not definitive, provide encouraging results. The cranberry may be a possible valid alternative to traditional antibiotic prophylaxis, which today is under strong attack. Together with the good tolerability of cranberry there is also good patient and parent compliance as concerns the use of this natural element with proven special characteristics. The potential uses of the cranberry are in cases of: a) documented relapsing and recurrent cystitis once organic causes (e.g. VUR) have been excluded, b) breastfeeding children of three to six months with grade 1 and 2 reflux, normal ultrasonography and with careful, informed and cooperating parents, c) association with the antibiotic in the treatment of acute UTI (in the near future). The results of the studies analyzed may make it possible for pediatricians to take the cranberry into consideration in cases of this kind since its use does not lead to a risk of antimicrobial resistance and to date no side effects have been associated with it in pediatric patients. In any case, further studies are propitious so as to confirm the efficacy and tolerability in the pediatric age.

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