The Director General

Maisons-Alfort, 18 March 2011

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the assessment of the potential effects of cranberry on community-acquired urinary tract infections

1. REVIEW OF THE REQUEST

On 15 September 2010, the French Agency for Food, Environmental and Occupational Health & Safety issued an internal request for an assessment of the potential effects of cranberry on community-acquired urinary tract infections.
This assessment was conducted jointly with the French Health Products Safety Agency (AFSSAPS).

2. BACKGROUND

The cranberry (*Vaccinium macrocarpon*) is a member of the Ericaceae family. It has been cultivated since the early 19th century, mainly in the United States and Canada.
Native Americans traditionally used cranberries for a variety of culinary and medicinal purposes, including as a poultice on wounds, for preventing and treating urinary tract infections and for treating various disorders of the digestive system, liver, kidney and blood. They were also used by sailors in New England during their long sea voyages to prevent scurvy. From the mid-19th century, German physicians helped to spread throughout the world knowledge on the medicinal use of cranberry for the treatment of urinary tract infections. This practice was abandoned after the Second World War with the development of antibiotics. However, since the 1960s, there has been renewed interest in the purported properties of cranberries, mainly for treating urinary tract infections (Bruyere, 2006).

Between 2003 and 2008, the French Food Safety Agency (AFSSA) assessed various cranberry products for which numerous claims had been made suggesting a direct link between consumption of cranberry and prevention of urinary tract infections (AFSSA, 2003b; AFSSA, 2003a; AFSSA, 2004; AFSSA, 2006). AFSSA considered as acceptable the claim "Helps to reduce the adherence of certain *E. coli* bacteria to the urinary tract walls" on the basis of studies conducted with several cranberry products providing 36 mg of cranberry proanthocyanidins (PACs) (AFSSA, 2003a).
In 2008, AFSSAPS issued guidelines entitled *"Diagnostic et antibiothérapie des infections urinaires bactériennes communautaires chez l'adulte"* ["Diagnosis and antibiotic treatment of community-acquired bacterial urinary tract infections in adults"] (AFSSAPS, 2008) mainly indicating:
"*Non-antibiotic prophylaxis treatment for recurrent cystitis*
Cranberry:
There is evidence of the efficacy of certain preparations (Vaccinium macrocarpon, Large Cranberry or American Cranberry, providing 36 mg/d of proanthocyanidins) against E. Coli. However, the data are not sufficient to recommend its use, especially since the composition of the available preparations varies greatly."
This document also points out several non-medicinal measures to reduce the risk of recurrent urinary tract infections, including an adequate fluid intake (at least 1.5 L/d).

In 2009, the European Food Safety Authority (EFSA) assessed the claim "Helps reduce the risk of urinary tract infection in women by inhibiting the adherence of certain bacteria in the urinary tract" (EFSA, 2009) related to a cranberry juice containing 80 mg of PAC per 250 mL serving and to dried

cranberries containing 80 mg of PAC per 40 g serving. This claim targeted healthy women aged over 16 years. EFSA concluded that the data were insufficient to establish a cause and effect relationship between consumption of the products and a reduction in the risk of urinary tract infection in women due to inhibition of the adherence of certain bacteria on the urinary tract wall. In this opinion, EFSA noted that *in vitro* data show that consumption of cranberry does have an anti-adherence effect on the bacteria contained in urine. It stressed however that these *in vitro* studies did not establish the validity of such an anti-adherence effect for predicting the occurrence of a similar, clinically relevant effect within the urinary tract.

Press articles and advertisements state that consumption of cranberry products can help prevent urinary tract infections, with some improperly referring to an ANSES opinion. To clarify the context for using the claim validated in 2004 (AFSSA, 2003a), ANSES issued an internal request to reassess the potential effects of cranberry on urinary tract infections.

3. EXPERT APPRAISAL METHOD

The collective expert appraisal was conducted by the Expert Committee (CES) on "Human Nutrition", which met on 16 December 2010 and 27 January 2011.

This internal request was addressed jointly with AFSSAPS, through its Working Group on "Anti-infectives" which met on 8 November 2010.

The following scientific questions were investigated:

1. What anti-adherence effect is shown by the *in vitro* and *ex vivo* studies?
2. What conclusion can be drawn from the clinical trials for therapeutic and prophylactic purposes, on the effect of consumption of cranberry on urinary tract infections?
3. Is cranberry safe to use?

4. DISCUSSION

ANSES's rationale is based on the opinion of the CES on "Human Nutrition" whose points are dealt with below. It takes into account the conclusions of the AFSSAPS Working Group on "Anti-infectives".

The term "urinary tract infections" (UTIs) covers a heterogeneous group of infections of either the anatomical parts of the urinary tract or its annexes. These infections occur more frequently in women than in men, with 40 to 50% of women having at least one UTI during their lifetime (AFSSAPS, 2008).

Adherence of bacteria to the uroepithelium is the first step in the pathogenesis of UTIs and is followed by bacterial multiplication and colonisation of the urinary tract. Adherence mainly allows bacteria to move up through the urethra into the bladder, avoiding elimination by urine flow. The uropathogenicity of the bacteria is therefore related to their capacity to adhere to tissue, through a specific interaction phenomenon between the bacterial membranes and the corresponding hydrocarbon receptors on the surface of the uroepithelial cells. Recognition molecules called adhesins are carried by the bacteria. These adhesins are either found on filamentous structures called *fimbriae,* or directly carried by the bacterium and are called amorphines. *Escherichia coli (E. coli)* is the pathogen most frequently responsible for UTIs in women aged from 15 to 65 years (80% of samples). In *E. coli,* there are different types of *fimbriae* which adhere to different receptors. These are primarily:

- type 1 *fimbriae,* found in all pathogenic and non-pathogenic strains, which have the D-mannose receptor;
- P *fimbriae,* specifically found in pathogenic strains, which bind to polysaccharide receptors (α-Gal(1-4)β-Gal).

P *fimbriae* are found with a high prevalence (70%) in *E. coli* responsible for pyelonephritis in children; prevalence rates are respectively below 30 and 20% in cystitis and urinary colonisation. The prevalence of P *fimbriae* is lower in strains of *E. coli* isolated from pyelonephritis patients with urinary tract abnormality (Nielubowicz & Mobley, 2010).

4.1. Anti-adherence effect of cranberry

4.1.1. Activities of cranberry measured *in vitro* and *ex vivo*

Many studies have been conducted on cranberry's effects and mechanisms on the adherence properties of bacteria, using a wide variety of models and protocols. The bacteria whose adherence is tested generally come from urine samples of patients with symptomatic UTIs. The adherence of the bacteria is measured on cells exfoliated from uroepithelium collected in the urine, or on humanT24 uroepithelial cell cultures, the validated model for studying the adherence of *E. coli* pathogens (Miyazaki *et al.*, 2002). Furthermore, there is a wide range of protocols used. The effect can be observed:

- after incubation of bacteria with urine collected after consumption of cranberry *(ex vivo* studies*)* or with cranberry juice or extracts *(in vitro* studies),
- after incubation of uroepithelial cells with the tested product,
- after incubation of bacteria already attached to uroepithelial cells.

The adherence index is calculated using the average number of bacteria attached per cell. The *in vitro* and *ex vivo* studies taken into account in this assessment are summarised in the tables in Annex 1.

In 1984, Sobota was the first to suggest that consumption of cranberry juice and cranberry juice cocktail inhibited bacterial adherence to uroepithelial cells in urine (Sobota, 1984). Adherence of *E. coli* strains isolated from the urine of patients with a UTI was significantly reduced (more than 75% reduction in 60% of clinical isolates) on uroepithelial cells that had previously been incubated with cranberry cocktail. In addition, the urine of 15 out of 22 subjects showed significant anti-adherence activity one to three hours after drinking about 450 mL of cranberry cocktail.

Schmidt and Sobota (1988) showed that incubation of exfoliated uroepithelial cells with cranberry juice cocktail *in vitro* inhibited the adherence to uroepithelial cells of *E. coli, Proteus* and *Pseudomonas* clinical isolates obtained from urine. This effect was not observed with non-urine isolates. This study also showed an anti-adherence effect in contact with urine collected after consumption of 350 mL of cranberry juice cocktail and in contact with exfoliated epithelial cells in urine collected after consumption of 350 mL of cranberry juice cocktail.

In a double-blind, randomised, placebo-controlled, crossover trial, 20 healthy volunteers were given randomly in cross-over, in addition to their normal diet, a single dose of 250 mL of placebo + 500 mL of mineral water, 750 mL of placebo, 250 mL of cranberry juice + 500 mL of mineral water, or 750 mL of cranberry juice (Di Martino *et al.*, 2006). The drinks were administered during the evening meal at intervals of at least 6 days. Adherence of six strains of uropathogenic *E. coli,* including three with P *fimbriae,* on cultured uroepithelial cells was tested in contact with urine collected from the 20 subjects. A dose-dependent reduction in the adherence of all strains was observed in contact with the urine collected after consumption of cranberry juice. Moreover, in contact with urine collected after consumption of the placebo, the three P-fimbriated strains exhibited better adherence to epithelial cells than the three strains not expressing P *fimbriae*. This difference was not significant after consumption of cranberry juice. These results suggest that urine collected after consumption of cranberry juice contains a substance which has a specific action on P-fimbriated bacteria.

In a randomised cross-over study, 12 women without UTIs followed four successive regimes for a week: 2 times 500 mL/day of reconstituted cranberry juice (1), 2 times 500 mL/d of water (control), 500 mL of water and 500 mL of cranberry juice (2), 1600 mg of cranberry extract and 2 times 500 mL/d of water (3). In contact with the urine collected 4 h and 1 week after drink regimes 1 and 3, adherence to uroepithelial cells of a uropathogenic P-fimbriated *E. coli* strain was significantly reduced compared to the control. Such an effect was not observed with urine collected after regime 2 (Jass & Reid, 2009).

Two multicentric, randomised, double-blind placebo-controlled studies showed a dose-dependent anti-adherence effect on uropathogenic strains of *E. coli* on human T24 uroepithelial cells. In the first, the effect was observed on contact with urine from 32 healthy volunteers who ingested cranberry powder containing 18, 36 or 72 mg of PAC (Howell *et al.*, 2010). In the second, the effect was observed in eight healthy volunteers who consumed dietary supplements containing 36 or 108 mg of cranberry PAC (Lavigne *et al.*, 2008).

Zafriri *et al.* (1989) reported an inhibitory effect in urine collected after consumption of cranberry juice cocktail or cranberry juice on adherence of *E. coli* expressing type 1 *fimbriae* and P *fimbriae,* but not on adherence of *E. coli* expressing CFA/I *fimbriae*. In addition, an anti-adherence effect on *E. coli* expressing type 1 *fimbriae,* and not on other *E. coli* strains, was also observed for orange and pineapple juice. According to the authors, the shared effect on type 1 *fimbriae* may be related to the presence of fructose in all three fruits. Only cranberry may also contain an inhibitor of the adherence of uropathogenic P-fimbriated *E. coli*.

The *in vitro* and *ex vivo* studies conducted with cranberry products (juice, juice cocktail or extracts) or with urine from subjects who consumed these products show an inhibition of the adherence of the P-fimbriated *E. coli* bacteria to uroepithelial cells.

4.1.2. Activities of cranberry components measured *in vitro*

Cranberry PACs, due to their high molecular weight, are very poorly absorbed from the intestinal lumen (Scalbert *et al.*, 2000; Scalbert & Knasmuller, 2008).

The anti-adhesive biological activity of PACs seems to be related to the oligomeric fraction of epicatechin having a double (A-type) interflavanoid linkage, which was highlighted by mass spectrometry analysis (Foo *et al.*, 2000a). Several types of PACs have been isolated from cranberry and characterised by chromatography (Foo *et al.*, 2000a; Foo *et al.*, 2000b). The anti-adherence activity of a uropathogenic P fimbriated *E. coli* on cell surfaces containing receptors of P *fimbriae* similar to those of cells from the urinary tract wall was measured for each molecule. Among the PACs identified, three were found to be active, one was slightly active and two were inactive. The three active PACs all had a double A-type interflavanoid linkage.

One study compared the anti-adherence activity *in vitro* of PACs with A-type linkages from cranberry to that of PACs with B-type linkages isolated from grape, apple, green tea and chocolate (Howell *et al.*, 2005). The A-type PACs from cranberry and the B-type PACs from grape inhibited bacterial adherence respectively by 60 and 1200 µg/mL and the other B-type PACs, isolated from apple, green tea and chocolate, showed no activity. These results suggest that the presence of a type-A linkage in the PAC molecules is predictive of anti-adherence properties.

The partial inhibition of adherence of P-fimbriated *E. coli* to urinary and vaginal epithelial cells has been shown in contact with a cranberry extract containing 9 mg/g of PAC and in contact with cranberry PACs (Gupta *et al.*, 2007). The cranberry extract reduced the average adherence rate from 18.6 to 1.8 bacteria per cell in the vaginal epithelium. The reduction observed with the PACs on bladder cells was on average from 6.9 to 1.6 bacteria per cell for a PAC concentration of 50 µg/mL, with the effect being linear for concentrations between 5 and 75 µg/mL.

The activity of cranberry PACs may be related to changes in surface properties of P *fimbriae* and bacterial polysaccharides. The adherence strength of P-fimbriated *E. coli,* in the presence of cranberry juice, cocktail or PAC, was studied in an *in vitro* model (surface coated with silicon nitride) (Liu *et al.*, 2006; Pinzon-Arango *et al.*, 2009). The three products studied decreased the bacteria's adherence strength by modifying their surface properties (*fimbriae* and lipopolysaccharides) with a dose-dependent and reversible effect.

Furthermore, Ahuja *et al.* (1998) have shown that cranberry juice (concentrated to 25% in the culture medium at pH 7) reversibly inhibits P-*fimbriae* expression in *E. coli.* PACs also seem to have an antagonistic action on the linkage between the ligand located on the P *fimbriae* and its uroepithelial receptor (Liu *et al.*, 2008). Finally, a study showed that the morphology of *E. coli* is changed in cultures in the presence of cranberry juice. Analysis of gene expression shows downregulation of flagella and motor proteins, and decreased expression of P *fimbriae* (Johnson *et al.*, 2008).

This inhibitory action is however not complete, since the bacterial adherence is reduced by a factor of 3 to 4 and varies *in vitro* depending on the PAC concentration (Gupta *et al.*, 2007). It disappears when exposure to cranberry extracts or PAC is interrupted (Liu *et al.*, 2006; Pinzon-Arango *et al.*, 2009). *Ex vivo,* the effect is greater in contact with urine from subjects who consumed 72 mg of PAC compared to 18 or 36 mg (Howell *et al.*, 2010), or after consumption of 108 mg of PAC compared to 36 mg (Lavigne *et al.*, 2008). The action was maximal at 6 h and disappeared after 24 h (Gupta *et al.*, 2007; Howell *et al.*, 2010).

All of these data show an *in vitro* bacterial anti-adherence effect on uroepithelial cells of the A-type PACs found in cranberry. This action is specific to *E. coli* bacteria expressing type P *fimbriae*.

4.2. Review of clinical studies relating to the effect of cranberry on UTIs

4.2.1. Curative effect

The literature review conducted as part of this assessment did not identify any clinical study showing the effect of cranberry as a therapeutic treatment for urinary tract infections.

4.2.2. Preventive effect

Several clinical studies have been conducted to assess the effect of consumption of cranberry on reducing the risk of recurrent UTIs. These studies and their key results are summarised in the table in Annex 2.

a) Review conducted by the Cochrane Centre

In 2007, a review was conducted of the available data evaluating the efficacy of consumption of cranberry juice, juice cocktail or extract for a period of at least one month (Jepson & Craig, 2008). Ten randomised controlled studies were selected, that were conducted on groups of between 15 and 376 subjects. These studies involved different population groups: with a history of UTIs (Walker *et al.*, 1997; Kontiokari *et al.*, 2001; Stothers, 2002), elderly people (Avorn *et al.*, 1994; Haverkorn & Mandigers, 1994; McMurdo *et al.*, 2005), or with a neurogenic bladder[1] (Foda *et al.*, 1995; Schlager *et al.*, 1999; Linsenmeyer *et al.*, 2004; Waites *et al.*, 2004). In all the studies, the main outcome was recurrence of symptomatic or asymptomatic UTIs.

Seven studies evaluated the effect of juice consumption, with intakes ranging from 30 mL/d (Haverkorn & Mandigers, 1994) to 300 mL/d (Avorn *et al.*, 1994; McMurdo *et al.*, 2005) in adults and between 15 mL/kg/d (Foda *et al.*, 1995) and 300 mL/d (Schlager *et al.*, 1999) in children. None of the authors substantiated the amount administered to the participants, and only the article by McMurdo *et al.* (2005) specified the amount of PAC in the juice consumed (11 µg/g dry mass).

In four studies assessing the effect of consumption of cranberry extracts, participants received tablets containing 400 mg of cranberry in dried form (Walker *et al.*, 1997; Linsenmeyer *et al.*, 2004), or containing 2 g of cranberry juice concentrate (Waites *et al.*, 2004), or containing 1:30 parts of cranberry juice concentrate (Stothers, 2002).

b) Meta-analysis from the review by the Cochrane Centre

Jepson and Craig (2008) conducted a Cochrane meta-analysis based on four of the studies examined in their review (Kontiokari *et al.*, 2001; Stothers, 2002; Waites *et al.*, 2004; McMurdo *et al.*, 2005), on a total of 665 subjects (Jepson & Craig, 2008). The other studies were not taken into account because of methodological weaknesses or lack of data.

The study by Kontiokari *et al.* (2001) was conducted in 150 women with a mean age of 30 years and a history of *E. coli* UTIs in the previous year, who were randomly assigned to three groups. The first group received 50 mL/d of a drink containing 7.5 g of cranberry juice concentrate for 6 months, the second group received 100 mL/day of a drink containing *Lactobacillus GG* 5 days/week for 1 year, the third group (control) did not undergo any intervention. The authors reported that at 6 months, 16% of the cranberry group (8/50 subjects), 39% of the *Lactobacillus GG* group (19/50 subjects) and 36% of the control group (18/50 subjects) had at least one UTI. The differences between the cranberry group and the control group were statistically significant and involved a 20% decrease in the relative risk of appearance of UTI in the cranberry group compared with the control group.

Stothers (2002) studied the effect of consumption of cranberry in the form of food supplements and/or drink for one year in 150 women with a mean age of 42 years, who had at least two symptomatic UTIs in the previous year. Subjects were randomly divided into three groups, the first consuming 750 mL/d of a placebo drink + a dietary supplement containing cranberry extract (1), the second consuming 750 mL/day of cranberry juice + a dietary supplement placebo (2), the third consuming 750 mL/d of a placebo drink + a dietary supplement placebo (control). The authors

[1] urinary disorder caused by a malfunction or damage to the nervous system

reported a significant decrease in the number of subjects with at least one UTI in groups 1 (18%) and 2 (20%) compared with the control group (32%), and a significant decrease in the average number of UTIs per group (0.72 in the control group, 0.39 in group 1 and 0.3 in group 2). Moreover, the durations of antibiotic treatments were reduced in groups 1 and 2 compared to the control.

In the study by Waites *et al.* (2004), 74 subjects with neurogenic bladder consumed either 2 g/d of cranberry extract, or 2 g/d of a dietary supplement placebo for 6 months, in a randomised double-blind design. The authors observed no significant difference between the two groups regarding the frequency of symptomatic and asymptomatic UTIs.

In a randomised, double-blind placebo-controlled study, 376 hospitalised subjects with a mean age of 81 years (121 men and 255 women) consumed 300 mL/d of cranberry juice for 15 days (McMurdo *et al.*, 2005). The between-group difference in the number of occurrences of symptomatic UTIs was not significant. Moreover, the number of withdrawals was 115 (62/189 in the placebo group and 53/187 in the cranberry group), or 30% of the sample included in the study.

The authors of the meta-analysis concluded that cranberry had an effect, in particular when administered in the form of juice, on reducing the prevalence of UTIs in some population groups, mainly young women with recurrent UTIs. However, the authors drew no conclusions about the effect of consumption of cranberry on primary prevention and on the other population groups studied. Moreover, no effect was observed in patients with neurogenic bladder.

Among the four studies considered in this meta-analysis, two reported results suggesting an effect of consumption of cranberry (in the form of juice or extract) on the recurrence of UTIs in women with a history of UTIs (Kontiokari *et al.*, 2001; Stothers, 2002). The study by McMurdo *et al.* (2005) did not show an effect in the elderly and that of Waites *et al.* (2004) in subjects with neurogenic bladder. The open design of the study by Kontiokari *et al.* (2001) and its premature termination (6 months instead of one year due to the cranberry juice supplier ceasing production) limits the value of its results.
Finally, only the study by Stothers *et al.* (2002) showed a significantly lower UTI recurrence rate in the groups consuming 750 mL/day of cranberry juice or the same amount of juice in extract form for 1 year. However, these results have not been subsequently confirmed, as shown in the review of studies conducted after Jepson and Craig's meta-analysis (2007) presented below.

c) Review of studies published after the Cochrane Centre review

In the study by Bailey *et al.* (2007), 12 women aged from 25 to 70 years with a history of at least 6 UTIs in the previous year consumed 200 mg of cranberry extract twice daily as a dietary supplement for 3 months. No UTI occurred in any of the 12 subjects during the 3 months of treatment. A two-year follow-up showed no recurrence in eight of them. However, this study had significant methodological limitations including the absence of a placebo group and a limited population sample.

Wing *et al.* (2008) assessed in a randomised placebo-controlled trial the effect of daily consumption of 240 mL or 720 mL of cranberry juice on the prevention of asymptomatic bacteriuria in pregnant women. The authors observed fewer UTIs in the group consuming 720 mL of juice than in the groups consuming 240 mL or the placebo. The trial was however inconclusive due to its low statistical power and the low adherence to treatment, especially in the groups consuming cranberry.

A randomised double-blind placebo-controlled study evaluated the effect of cranberry extract (500 mg/d for 6 months) on recurrent UTIs in patients with neurogenic bladder (Hess *et al.*, 2008). No pH change in urine was observed in patients throughout the study. A significant decrease in the number of UTIs was observed during the period of cranberry consumption, with this decrease being greater in patients with normal renal function.

A randomised controlled trial versus *Lactobacillus* was performed in 84 girls aged from 3 to 14 years (Ferrara *et al.*, 2009). In the group that consumed 50 mL/d of cranberry juice 5 days a week for 6 months, the incidence of UTIs and the use of antibiotic treatment were significantly reduced compared to the group that consumed 100 mL/d of a drink containing *Lactobacillus* GG and the control group (no intervention). However, these results cannot be taken into account, considering the open nature of this study, the absence of a placebo control group and the short duration of follow-up (6 months) in view of the inclusion criteria (at least one UTI during the previous year)..

A randomised double-blind study compared the efficacy of 500 mg of cranberry extract to that of 100 mg of the antibiotic trimethoprim in preventing the recurrence of UTIs in 137 women aged over 45 years (mean age 63 years) (McMurdo *et al.*, 2009). Thirty nine subjects (28%) had a symptomatic UTI treated with antibiotics, 25 in the cranberry group and 14 in the trimethoprim group. This difference represented a non-significant relative risk of 1.6 (p=0.084). In addition, the between-group difference of median time to UTI recurrence (84.5 d in the cranberry group and 91 d in the trimethoprim group) was not significant. This study, designed to show that consumption of cranberry can have the same effects as an antibiotic treatment in preventing recurrent UTIs, had however several methodological shortcomings: clinical definition of recurrence of UTI without systematic microbiological confirmation and number of *E. coli* bacteriuria at baseline higher in the trimethoprim group compared to the cranberry group (6 against 2). This study cannot therefore be used to support the use of cranberry as a substitute for conventional antibiotic treatments in the prevention of recurrent UTIs.

A recent double-blind placebo-controlled study assessed the risk of UTIs recurring within 6 months in 319 women aged between 18 and 39 years with a UTI (bacteriuria ≥ 10^3 cfu/mL) at baseline (Barbosa-Cesnik *et al.*, 2011). Consumption of cranberry juice cocktail was 240 mL twice daily, providing 224 mg/d of PAC. Recurrent UTIs at 6 months were observed in 20% of women in the cranberry group against 14% of women in the placebo group. In the cranberry group, *E. coli* accounted for 28 of the 30 recurrences identified compared with 14/24 in the placebo group. This study therefore found no effect of cranberry consumption compared to a placebo in preventing a second UTI within 6 months in young women with UTI at baseline.

Overall, of the 16 studies reported in this opinion, 8 do not show any effect of consumption of cranberry on the recurrence of UTIs, or draw no conclusions due to lack of data. Furthermore, most of the results obtained on the effect of consumption of cranberry on the occurrence and prevention of UTIs cannot be taken into account: ANSES notes that the clinical trials evaluating the effect of consumption of cranberry often have methodological shortcomings, particularly limited sample sizes and/or absence of a placebo control group. Moreover, these studies use extremely variable amounts of cranberry juice, juice cocktail, or extracts, which are generally not standardised for their active ingredients. Finally, none of these studies indicate the total daily fluid intake of subjects, whose effect on the prevention of UTIs is well-known.

4.3. Safety of use of cranberry

In a study on the safety of consuming a dietary supplement containing 400 mg/d of cranberry juice extract for 8 weeks in 65 healthy young women (Valentova *et al.*, 2007), the biochemical and haematological parameters were unchanged. Hippuric acid, isomers of salicyluric acid and quercetin glucuronide were identified as the main metabolites. Similarly, regular intake of cranberry extract in 400 pregnant Norwegian women did not induce adverse effects during pregnancy and lactation (Dugoua *et al.*, 2008). No impact on the pharmacokinetics of cyclosporine, by interactions with cytochrome P450, were observed in humans (Grenier *et al.*, 2006). Several reviews and studies (Aston *et al.*, 2006; Pham & Pham, 2007; Zikria *et al.*, 2010) reported an absence of interaction of moderate cranberry consumption with anti-coagulants such as warfarin. The effect of very high juice consumption (more than 600 mL/d) was however not excluded.

In clinical trials, drop-out rates varied between 8% and 55%, and in general, adherence to the treatment was lower in the groups receiving cranberry in juice form than in tablet form, or in the placebo groups. In their meta-analysis, Jepson and Craig (Jepson & Craig, 2008) pointed out that side effects related to the consumption of cranberry juice or tablets (primarily gastrointestinal disorders) are common in all studies. For the authors, the high number of withdrawals indicates that consumption of cranberry juice is not well tolerated over long periods.
The most common adverse effects are symptoms of gastroesophageal reflux, nausea and digestive disorders, mostly related to excessive consumption of cranberry juice (Davies *et al.*, 2001); they are described in particular in children consuming more than 3 L/d (Dugoua *et al.*, 2008).

In situations of predisposition to kidney stones, some authors recommend caution because of the high oxalic acid content in cranberries and the potential risk of promoting oxalate lithiasis (Terris *et al.*, 2001). One study assessed the risk of urinary stones occurring after consuming cranberry juice

(Gettman *et al.*, 2005). In 12 healthy subjects and 12 subjects with oxalate stones, consumption of cranberry juice significantly increased excretion of urinary calcium (from 154 to 177 mg per day) and urinary oxalate (from 26.4 to 29.2 mg per day), thus increasing calcium oxalate saturation in urine by 18%. Urine pH decreased (from 5.97 to 5.67), and urinary ammonium, acidity and net acid excretion increased. Urinary uric acid decreased (from 544 to 442 mg per day) and the level of undissociated uric acid increased. The authors concluded that drinking cranberry juice increases the risk of oxalate and uric acid stone formation.

In the current state of knowledge, consumption of cranberry is n not of safety concern for the general population. Adverse effects are mainly digestive and usually occur after high consumption of cranberry over the long term, particularly as a beverage.
However, given the data showing increased urinary excretion of calcium oxalate, long-term consumption of cranberry in individuals prone to oxalate kidney stones is not recommended.

5. CONCLUSION

Concerning the data published *in vitro* and *ex vivo* data, ANSES considers that the activity of PACs contained in cranberry on *E. coli* adherence to urinary epithelial cells via P *fimbriae* has been demonstrated.
ANSES stresses however that the *ex vivo* studies were limited to assessing the anti-adherence activity of urine in subjects who consumed cranberry, and did not determine the concentration of cranberry PACs actually found in the tested urine. There is no evidence in the published studies conducted in humans that proves that the metabolites excreted in urine after consumption of cranberry are responsible for the inhibitory activity observed *ex vivo*.

Concerning the clinical studies conducted for therapeutic or prophylactic purposes, ANSES believes that the data available to date on cranberry consumption are insufficient to conclude that consumption of cranberry has a preventive effect on UTIs. This is in agreement with the findings of the AFSSAPS Working Group on "Anti-infectives".
No published study has demonstrated the efficacy of cranberry in the curative treatment of UTIs.
Moreover, of the studies conducted to date, most showed methodological bias. These studies did not specify the total daily amount of drinks ingested in the different groups studied and thus did not consider the possible preventive effect of a high fluid intake. Furthermore, the lack of standardisation of active ingredients in the products used greatly limits the value of the results. Finally, no clinical study has assessed in a single group of subjects the effect of consumption of cranberry on both the recurrence of UTIs and the adherence of bacteria *ex vivo*.

In addition, ANSES believes that in the current state of knowledge, there is no safety concern related to the consumption of cranberry by the general population.
Nevertheless, effects such as digestive disorders can be observed for high intakes and/or over long periods. Given the data indicating increased urinary excretion of calcium oxalate, the consumption of cranberry in individuals prone to oxalate kidney stones is not recommended.

The Director General

Marc MORTUREUX

KEY WORDS

CRANBERRY; *VACCINIUM MACROCARPON*; CLAIM; URINARY TRACT INFECTION; CYSTITIS; *ESCHERICHIA COLI*; PROANTHOCYANIDIN

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ANNEXES

Annex 1a: Main studies evaluating the activities of cranberry *in vitro*

Reference	Product tested	Cell model	Bacteria tested	Results
Sobota, 1984	cranberry juice cocktail (CJC) containing 33% cranberry juice (CJ)	Exfoliated epithelial cells collected in urine of women with no history of UTI and buccal cells	77 urine clinical isolates of *E. coli* (unspecified types of *fimbriae)*	75% inhibition in 60% of samples compared to control (solution of identical pH)
Schmidt & Sobota, 1988	CJC	Exfoliated epithelial cells collected in urine from healthy individuals with no history of UTI	Urine and non-urine clinical isolates of *E. coli, Proteus* and *Pseudomonas* (unspecified types of *fimbriae)*	After incubation of bacteria with the CJC, significant decrease in adherence compared to control (solution of same pH as the CJC) for all strains except *Proteus* After incubation of uroepithelial cells with the CJC, significant decrease in adherence of urine samples, no significant effect on non-urine samples
Zafriri *et al.*, 1989	CJC (25% CJ)	- yeast - animal tissue culture - human erythrocytes - mouse macrophages	Clinical isolates of 14 pathogenic strains of *E. coli* (7 uropathogenic strains and 7 strains from diarrhoea), including 5 P-fimbriated	Inhibitory effect on the adherence of P-fimbriated and type 1 *fimbriae* strains, no effect on strains isolated from diarrhoea expressing CFA/I adhesin
	CJ			Inhibitory effect on the adherence of P-fimbriated and type 1 *fimbriae* strains, no effect on strains isolated from diarrhoea expressing CFA/I adhesin
	pineapple juice			Inhibitory effect on the adherence of type 1 *fimbriae* strains, no effect on P-fimbriated strains or those isolated from diarrhoea expressing CFA/I adhesin
	orange juice			Inhibitory effect on the adherence of type 1 *fimbriae* strains, no effect on P-fimbriated strains or those isolated from diarrhoea expressing CFA/I adhesin
Foo *et al.*, 2000a	cranberry PAC	Surfaces with the same alpha-gal (1-4) beta-gal receptors as the urinary epithelium	Clinical isolates of uropathogenic P-fimbriated *E. coli*	Determination of the molecular structure of PACs with the inhibitory activity: epicatechins of DP 4 and 5 with at least one A-type bond
Foo *et al.*, 2000b	6 cranberry PACs	Surfaces with the same alpha-gal (1-4) beta-gal receptors as the urinary epithelium	Clinical isolates of uropathogenic P-fimbriated *E. coli*	3 A-type PAC trimers with inhibitory activity 1 A-type PAC trimer with weak inhibitory activity 1 monomer PAC and 1 B-type dimer were inactive
	PACs isolated from CJC, apple juice, grape juice, green tea and chocolate			Threshold of anti-adherence activity of 60 µg/mL PBS for the CJC, 1200 µg/mL for the grape juice PACs, no activity for the other PACs
Gupta *et al.*, 2007	cranberry powder (9 mg/g PAC)	vaginal cell cultures	Clinical isolates of uropathogenic P-fimbriated *E. coli*	Decreased cell adherence from 18.6 to 1.8 bacteria per cell for a powder concentration of 3 mg/mL
	cranberry PAC	bladder cell cultures		Dose-dependent decreased cell adherence between 5 and 75 µg/mL of PAC

Annex 1b: Main studies evaluating the activities of cranberry *ex vivo*

Reference	Product tested	n	Product consumed	Cell model	Bacteria tested	Results
Sobota, 1984	Mouse urine collected after consumption of CJC	30 (including 15 water controls)	CJC in place of water in the diet for 14 days	Exfoliated epithelial cells collected in urine of women with no history of UTI and buccal cells	77 urine samples of *E. coli* (unspecified types of *fimbriae)*	80% inhibition Significant difference compared to urine controls
	Human urine collected 1-3 h after consumption of CJC	22 (9 M and 13 W) aged 18-45 years	450 mL of CJC (1 dose)			Inhibition observed in contact with urine from 15/22 subjects
Schmidt & Sobota, 1988	Urine collected after consumption of CJC	unspecified	350 mL of CJC	Exfoliated epithelial cells collected in urine from healthy individuals with no history of UTI	Urine and non-urine clinical isolates of *E. coli, Proteus* and *Pseudomonas* (unspecified types of *fimbriae)*	Significant decrease in adherence compared to control (urine collected before consumption) for all strains
	Exfoliated epithelial cells in urine collected after consumption of CJC	unspecified	350 mL of CJC			Significant decrease in adherence compared to control (urine collected before consumption) for all strains except for 2 low-pathogen strains
Howell, 2002	Urine collected before and after consumption	healthy women (n unspecified)	240 mL of CJC	Isolated uroepithelial cells	39 clinical isolates of P-fimbriated *E. coli,* including 24 with antimicrobial resistance	In contact with urine after consumption of CJC, adherence of 80% (31/39) of isolates was inhibited. Effect was observed from 2 h after consumption and persisted for 10 h
Howell *et al.*, 2005	Urine collected before and after consumption every 2 hours up to 8 h after consumption	6 healthy subjects aged 25-45 years (4 W and 2 M)	Successive consumption in a single dose of 240 mL of CJC (83 mg of A-type PAC), apple juice (0.27 mg PAC), grape juice (39.1 mg PAC), green tea (4.4 mg PAC), 40 g of chocolate (106 mg PAC) with 3-day wash out	Mannose-resistant human red blood cell haemagglutination assay specific for P-fimbriated bacteria	Clinical isolates of uropathogenic P-fimbriated *E. coli*	After consumption of CJC: anti-adherence activity increased to a peak at 4-6 h, activity lasted at least 8 h after consumption No activity detected in urine after consuming the other products (apple juice, grape juice, green tea or chocolate)
Di Martino *et al.*, 2006	First urine on day after consumption	20 (10 M and 10 W) aged 21-25 years	Four successive regimes with 6 d wash-out periods, taken in a randomised order, double-blind: (1) 250 mL placebo + 500 mL water, (2) 750 mL placebo, (3) 250 mL CJ + 500 mL water, (4) 750 mL CJ	T24 epithelial cell lines	Urine clinical isolates of 6 *E. coli* strains, 3 P-fimbriated and 3 not expressing P *fimbriae*	No difference in urine pH For all strains: significant decrease in adherence after consumption of CJ (-62% with (4) compared to (1)), dose-dependent Effect also observed on each strain After consumption of placebo: improved adherence of P-fimbriated strains in contact with urine compared to non-P-fimbriated strains, difference not significant after consumption of CJ

Reference	Product tested	n	Product consumed	Cell model	Bacteria tested	Results
Lavigne *et al.*, 2008	First urine on day after consumption	8 healthy women aged 30-42 years	Three successive regimes with 6 d wash-out periods, taken in a randomised order, double-blind: (1) 3 cranberry dietary supplements (DSs) (108 mg PAC) (2) 3 placebo DSs (3) 1 cranberry DS (36 mg PAC) + 1 DS placebo	T24 epithelial cell lines	Samples of 4 uropathogenic *E. coli* strains, 2 P-fimbriated and 2 not expressing P *fimbriae*	Significant anti-adherence effect in urine after consumption of cranberry extract (CE) compared to the placebo, dose-dependent, irrespective of the strain
Jass & Reid, 2009	Urine collected 24 h and 1 week after consumption	12 healthy women aged 19-45 years, no history of UTI in the previous year	Control: 2 x 500 mL/d of water Regime 1: 2 x 500 mL/d CJ Regime 2: 500 mL CJ + 500 mL of water Regime 3: 1600 mg of CE + 500 mL of water twice a day Cross-over randomised study:1 w duration per regime with 1 week wash-out periods	T24 epithelial cell lines	Samples of 5 strains of *E. coli* and 1 strain of *E. faecalis* with type 1 and/or P *fimbriae*	Significant reduction in the adherence of uropathogenic P-fimbriated *E. coli* with regimes 1 and 3, no effect with regime 2
Howell *et al.*, 2010	First urine on day after and second day after consumption	32 healthy women aged over 18 years multicentric	CE standardised in PAC 16 subjects: 0, 36 or 72 mg/d PAC 16 subjects: 0, 18 or 36 mg/d PAC in cross-over with 6-day wash-out double blind randomised groups	T24 epithelial cell lines	Samples of *E. coli* expressing P *fimbriae*	Significant anti-adherence effect in contact with urine after consumption of CE compared to the placebo, dose-dependent In contact with urine collected 6 h after consumption significant difference between 18 mg and 36 or 72 mg. No difference between 36 and 72 mg In contact with urine collected 24 hours after consumption, significant difference between 72 mg and 36 or 18 mg

Annex 2: Clinical studies evaluating the effect of consumption of cranberry on urinary tract infections

Reference	Population group (at baseline)	Design	Intervention	Control	Duration	Withdrawals	Parameters measured	Results
Avorn *et al.*, 1994	153 women over 45 years (mean age 78.5 years), long-stay institutionalised in retirement homes	2 parallel arms double blind randomisation	300 mL/d of CJC (30% cranberry concentrate)	placebo: 300 mL/d of a juice of similar appearance and taste	6 months	12 CJ, 20 placebo	Bacteriuria (>10^5/mL)	Significant reduction in bacteriuria with pyuria (28% versus 22%)
Haverkorn *et al.*, 1994	38 subjects of mean age 81 years (9 M and 29 W)	cross-over randomisation	30 mL/d of CJ	30 mL/d of water	8 weeks (4 w CJ then 4 w water)	22	Bacteriuria (>10^5/mL)	Data analysed for 17 subjects 7 subjects had one or more UTI, significantly fewer UTIs with the CJ, total fluid intake higher during the cranberry period
Foda *et al.*, 1995	40 children aged from 1.4-18 years (mean 9 years) with neurogenic bladder	cross-over single blind	15 mL/kg/d of CJC (30% cranberry concentrate)	15 mL/kg/d of water	1 year (6 months CJC then 6 months water)	19 including 12 related to the cranberry	1. Number of months of positive cultures + 1 symptomatic UTI 2. Number of months of positive cultures + 1 asymptomatic UTI	No difference between the 2 periods
Walker *et al.*, 1997	19 women aged from 28-44 years (mean age 37 years) sexually active, having had recurrent UTIs (>4 in the previous year or at least 1 in the previous 3 months)	cross-over double blind	DS containing 400 mg of CE twice daily	DS placebo	6 months (3 m CE + 3 m placebo)	9 (unspecified causes)	number of symptomatic UTIs	Significant difference 21 UTIs in the 10 subjects who completed the study, 6 during the cranberry period, 15 during the control period
Schlager *et al.*, 1999	15 children with neurogenic bladder aged 2-18 years	cross-over double blind randomisation	300 mL/d of CJC (30% cranberry concentrate)	placebo: 300 mL/d of a juice of similar appearance and taste	6 months (3 m CJC + 3 m placebo)	0	1. Bacteriuria (>10^5/mL) 2. symptomatic UTI	No difference between the 2 periods
Kontiokari *et al.*, 2001	150 women (mean age 30 years) One previous case of *E. coli* UTI no antibiotic treatment	3 parallel arms open randomisation	group 1: 50 mL/d cranberry-lingonberry juice (7.5 g cranberry +1.7 g lingonberry) group 2: 100 mL *Lactobacillus* GG 5d/week	no intervention	6 months juice 12 months *Lactobacillus*	13	First recurrence of symptomatic UTI over 1 year	Significant difference: at 6 months 16% (6/50) of cranberry group, 39% (19/50) of *Lactobacillus* group and 36% (18/50) of control had at least one UTI Absolute risk reduction of 20% in the cranberry group compared to the control

Reference	Population group (at baseline)	Design	Intervention	Control	Duration	Withdrawals	Parameters measured	Results
Stothers 2002	150 healthy women, sexually active aged 21-72 years (mean age 42 years) at least 2 symptomatic UTIs in the previous year, negative bacteriuria	3 parallel arms double blind randomisation	group 1: 750 mL/d placebo juice + CE (1:30 juice concentrate) group 2: 750 mL/d CJ + DS placebo group 3: control	placebo: 750 mL/d placebo juice + DS placebo	1 year	6 (4 placebo, 2 CJ)	1. number of symptomatic UTIs/year 2. annual dose of antibiotics 3. benefit/cost of treatment	1. significant decreases in the number of subjects having at least one UTI in the year in groups 1 (18%) and 2 (20%) compared to control (32%) and in the average number of UTIs per group (0.72 control, 0.3 CJ, 0.39 CE) 2. durations of antibiotic treatments decreased in the 2 treatment groups versus the control 3. when comparing cost, CE is twice as effective as CJ
Lisenmeyer *et al.*, 2004	21 subjects with neurogenic bladder	crossover double blind	400 mg/d of CE	placebo	9 weeks (4 w per treatment +1 w wash-out)	16	Number of bacteria and white blood cells in urine	No significant difference between the 2 periods
McMurdo *et al.*, 2005	376 people aged over 60 years (mean age 81 years), hospitalised without antibiotic treatment, without symptomatic UTI, not regular consumers of CJ	2 parallel arms double blind randomisation	300 mL/d of CJ	placebo: 300 mL/d of a juice of similar appearance and taste	8 d of treatment 6 months of follow-up	115 (62 placebo, 53 CJ)	1. time of onset of first symptomatic UTI (bacteriuria $>10^4$ cfu/mL) 2. compliance, prescription of antibiotics, bacteria responsible for UTIs	Non-significant difference in the number of UTIs UTIs in 21/376 (5.6%): 14/189 in the control group, 7/187 in the cranberry group Significantly fewer *E. coli* UTIs in the cranberry group (4 against 13)
Waites *et al.*, 2004	74 individuals > 16 years with a neurogenic bladder, with negative bacteriuria	2 parallel arms double blind	2 g/d of CE in the form of a DS	DS placebo	6 months	26	Bacteriuria ($>10^5$/mL) every month, urine pH, symptomatic and asymptomatic UTIs	No difference between the 2 groups
Bailey *et al.*, 2007	12 women aged from 25 to 70 years, at least 6 UTIs in the previous year	1 arm open	DS containing 200 mg of CE twice daily	no control	3 months of treatment 2 years of follow-up	0	number of UTIs	No UTIs during treatment Absence of UTIs for 2 years in 8 subjects (who continued consuming DSs containing cranberry)

Reference	Population group (at baseline)	Design	Intervention	Control	Duration	Withdrawals	Parameters measured	Results
Wing *et al.*, 2008	188 women pregnant by less than 16 weeks	2 parallel arms randomisation double blind	group 1: 3 x 240 mL/d of CJC containing 27% of CJ group 2: 240 mL/d of CJC + 2 x 240 mL/d of placebo	placebo: 3 x 240 mL/d of a juice of similar appearance and taste	6 weeks	73 (39%) for gastrointestinal disorders	number of UTIs	27 UTIs in 18 subjects: 6 UTIs in 4/58 subjects from group 1, 10 UTIs in 7/67 subjects from group 2, 11 UTIs in 7/63 placebo subjects
Ferrara *et al.*, 2009	84 girls aged from 3 to 14 years (mean age 7.5 years), at least one *E. coli* UTI in the previous year Negative bacteriuria	3 parallel arms randomisation	group 1: 50 mL/d CJ (7.5 g of CJ concentrate) group 2: 100 mL/d L*actobacillus* 5 d/week	No intervention	6 months	4 (1 in group 1, 1 in group 2, 2 in control)	number of UTIs	34 UTIs: 5/27 (18.5%) in group 1, 11/26 (42.3%) in group 2, 18/27 (48.1%) in the controls Significant reduction in risk in the cranberry group compared to the other two groups 1 antibiotic treatment in the cranberry group, 5 in the *Lactobacillus* group and 7 in the control
Hess *et al.*, 2008	57 men aged 28-79 years (mean age 53 years) with neurogenic bladder	crossover randomisation double blind	500 mg of CE in the form of a DS twice daily	DS placebo	6 months CE, 6 months placebo	10	number of UTIs	Significant reduction in UTI episodes cranberry period: 7 UTIs in 6 subjects placebo period: 21 UTIs in 16 subjects Better results in patients with glomerular filtration rate > 75 mL min^{-1}
McMurdo *et al.*, 2009	137 women aged over 45 years, at least 2 UTIs treated with antibiotics in the previous year	2 parallel arms randomisation double blind	group 1: 500 mg of CE in the form of a DS once daily group 2: 1 tablet/d of 100 mg of trimethoprim	no control	6 months	17 (6 in group 1, 11 in group 2)	number of symptomatic UTIs	Non-significant difference UTIs in 25/69 cranberry subjects and in 14/68 trimethoprim subjects
Barbosa-Cesnik *et al.*, 2010	319 women aged 18-40 years with a UTI without antibiotic treatment	2 parallel arms randomisation double blind	250 mL/d of CJC containing 27% of CJ	placebo: 250 mL/d of a juice of similar appearance and taste	6 months	89 (equal number in the 2 groups)	first recurrence of a new UTI (> 1000 cfu/mL)	54 UTIs (31 in the cranberry group and 23 in the placebo group) Symptoms at 3 d, 1 w, 2 w and 1 month similar between the 2 groups No difference in risk of recurrence after adjustment for sexual activity and UTI history