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Use of cranberry for prophylaxis of uncomplicated recurrent urinary tract infections

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ABSTRACT

Over the last few years, an increase in the use of cranberry (C) has been noted for the following two reasons: i) the high number of UTIs has lead to increased antibiotic use and thus increased antibiotic resistance; and ii) the main mechanisms of action in reducing UTIs have been identified. C inhibits the adherence of E.coli to uro-epithelial cells, the first and necessary step for UTI. This competitive inhibition is due to a non-dialyzable compound, a condensed tannin, the proanthocyanidin (PAC) type A. Among the three species of C vaccinium macrocarpon is only one to have PAC-A.

The first dosage used was 36 mg served as 300 ml of juice presentation (Avorn). In 2006, a double-blind randomised placebo-controlled cross-over trial comparing two dosages of C. juice presentation (250 and 750 ml) found a significant reduction of E. coli adherence ($p > 0,001$) dose dependent.

In 2008 a double-blind randomised placebo-controlled cross-over trial tested a commercially available capsule of vaccinium macrocarpon containing 36 mg of PAC. A statistically significant reduction of bacterial adherence of E. coli was found ($p < 0,001$), dose-dependent. For the first time this study established clearly thebio-activity of a C. capsule.

Two methods of PAC dosage are available: the reference DMAC and NP-HPLC with a conversion factor of one to two (36 mg PAC by DMAC = 72 mg PAC by NP-HPLC).

Quantification of bio-activity in urine: Given that 36 mg of PAC per day is necessary to obtain a preventive clinical effect on UTIs (Avorn Study); and given that we lack a method to evaluate active

metabolites in urine, surrogates are needed to quantify bio-activity in urine. There are two surrogates: i) the red blood cell hemagglutination test (Howell)and ii) the direct cellular adhesion test (Lavigne).

Jepson and Craig have recently reviewed the clinical studies for the Cochrane database. Juice presentation is too unwieldy to be recommended for long periods of time as a prophylactic treatment for recurrent UTI, thus the necessity to develop capsules/tablets. However, there is no standardisation for these; not in C species, in method of PAC measurement, nor in dosage of PAC per day. Apart from one capsule, there is no data about the bio-activity of the commercially available products, no dose-ranging and no direct correlation between in vitro and clinical effects.

SUMMERY OF RECOMMENDATIOS

1. Despite the lack of pharmacological data and the few, and weak clinical studies, there is evidence to consider C vaccinium macrocarpon to be useful in reducing the rate of lower urinary tract infections in women.
2. For everyday practice one could recommend (GoR C; LoE 2) the daily consumption of C products, giving a minimum of 36 mg of PAC (proanthocyanindin A, the active compound) per day, providing this amount is proven. The best approach would be to use those compounds that have demonstrated clear bio-activity in urine.

1. INTRODUCTION

The traditonal use of cranberry (C) to prevent UTIs has been found mainly in North America with limited spread to other countries, notably European Countries.

However, steadily over the last few years, increased C use outside North America has been noted. It can be seen that this is for the following reasons:

The high number of UTIs has lead to increased antibiotic use and thus increased antibiotic resistance. From the ARESC [1] study we have learned that only three of the antibiotic families are possible for empiric prescription. Thusit is mandatory to reduce antibiotic useand therefore to find some other products to replace antibiotics in certain circumstances, for example in prophylaxis.

The main mechanisms of action in reducing UTIs have been identified by Foo [2] and Howell [3]. In the past it was thought that C acted through acidification of urine like other fruits. In fact, the acidification linked to fructose contained in C (as well as in other fruits) only excretes low and transient acidifica-tion [4] and only inhibits pili type 1 [5]. The inhibition of pili type P is not concerned with fructose. Cranberry inhibits the adherence of E.coli to uro-epithelial cells, the first and necessary step for UTI. This competitive inhibition is due to a none-dialyzable compound; a condensed tannin, the proanthocyanidin (PAC) type A. Cranberry contains a high proportion of PAC A, unlike other fruit. Only the PAC-(A) is able to inhibit E. coli adhesion through inactivation of pili type P. The other PAC (B) found in most fruits does not have this capacity. There are three species of C: vaccinium macrocarpon is the only one to have PAC (A). The two others (vaccinium vitis idaea and oxycoccus) may contain some quantities of A-type PAC to inhibit E.coli adhesion but their efficacy has not been validated.

Despite the low number of clinical studies published, it is a trend to support the role of C products in preventing UTIs. But some limitations remain and have to be clarified.

The Cochrane Library [6] review published in 2008 is clear: "There is some evidence that cranberry juice may decrease

the number of symptomatic UTIs over a 12 month period, particulary for women with recurrent UTIs. Its effectiveness for other groups is less certain over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules)".

Taking into account all these data the French food and drug agency (AFSSA) delivered a clear allegation in 2004 [7]: "The daily consumption of cranberry vaccinium macrocarpon juice/powder containing 36 mg of proanthocyanidins/ day contributes to decrease the fixation of certain bacteria E. coli on the walls of the urinary tract". The 36 mg PAC were measured by DMAC method.

"It is the first-ever health claim for cranberries and it is believed to be the first time that any fruit anywhere has been permitted to make a specific health claim" [8]. Despite the traditional American use of juice presentation and the conclusions of the Cochrane review, more data are needed to confirm the role of C in the prevention of UTIs. Specifically, the pharmaco-kinetics and the correlations between the in vitro studies and clinical effects have to be developed.

2. METHODS

The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using ICUD standards (for details see Preface) [9–10].

3. PHARMACOKENETICS

We know that PAC is one of the active compounds of C but the other active compounds (metabolites) are not yet clearly identified. It is generally accepted that active dimers and trimers are absorbed in the gut. These small oligomers are unstable and they have a tendency to polymerize naturally under the influence of temperature and oxygen [11].

3.1 DOSAGE OF PAC

The first dosage used was 36 mg served as 300 ml of juice presentation [12]. In the vast majority of the other studies the amount of PAC was not clearly stated and only a certain amount of C was declared. In 2006 a double-blind randomised placebo-controlled cross-over trial in twenty healthy volunteers compared two dosages of C juice presentation: 750 and 250 ml using six E.coli strains and a direct anti-adhesion test [13]. There was a significant reduction of E. coli adherence ($p > 0{,}001$), dose dependent. Thus 300 ml of juice presentation may not be the right dosage per day. In this study it was also shown that the anti-adhesion effect was independent from antibiotic susceptibility and type P pili present.

Gupta [14] recently confirmed the dose dependent anti-adhesion effect of E.coli to uro-epithelial cells.

Table 1 Index of Adhesion of E. coli (IA) after 2 regimens of Urell® and placebo control.

Strains	Placebo	Urell Capsule 1	Urell Capsule 3	
FimH+ PapGII+	IA = 22,43 ±3,73	IA = 14,35 ±3,45	IA = 5,18 ±4,32	p. < 0,001
FimH- papGII-	IA = 4,80 ±0,70	IA = 3,37 ±0,97	IA = 1,74 ±0,75	p. < 0,001
FimH+ papGII-	IA = 7,50 ±1,60	IA = 4,73 ±0,87	IA = 2,78 ±1,12	p. < 0,001

One or three capsules of Urell® caused a highly significant reduction in bacterial adherence to T24 cells as compared with placebo (p< 0,001). The adherence index obtained with bacteria grown in urine samples collected after intake of three cranberry capsules was lower than that observed with one Cranberry capsule (p<0,001), even though a reduction in adherence was also noted with one Urell® capsule.

In 2008, a double-blind randomised placebo-controlled cross-over trial tested a commercially available capsule of vaccinium macrocarpon containing 36 mg of PAC (Urell®/Ellura) using T24 human epithelial cell line and three regimens intake in the morning : (placebo ; one capsule of Urell® = 36 mg of PAC ; 3 capsules = 108 mg of PAC) (13). A statistically significant reduction of bacterial adherence of E. coli was found (p< 0,001), dose-dependent and independent from antibiotic susceptibiliity and the type of P pili present.

For the first time this study established clearly the bio-activity of a C capsule.

In our last study, currently under revision, we correlated the bio-activity in urine after six and 24 hours with the same capsule of Urell® and using three regimens with intake in the morning : (half capsule = 18 mg PAC ; one capsule = 36 mg of PAC and two capsules = 72 mg of PAC). As shown in Table 2 anti-adhe- sion activity is significantly higher with 36 and 72 mg of PAC than with 18 at six hours. At 24 hours the anti-adhesion activity is significantly higher with 72 mg of PAC compared to 36 and there is no real activity with urine samples collected after intake of 18 mg of PAC.

3.2 METHODS OF PAC DAOSAGE

The DMAC/PAC003, a proprietary colorimetric method (4-diméthylaminocinnimaldéhyde), was the first described and is reliable with great precision (95 %) [15].

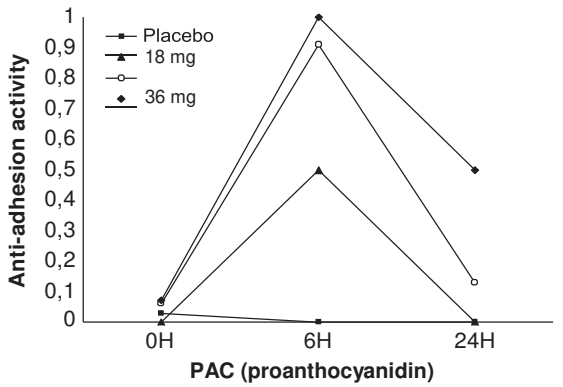
Meanwhile, the DMAC method has been simplified and shortened and is now validated by the USDA and four independent laboratories. The publication of the revised method yielding 36 mg for 300 g of Cranberry juice drink is currently under revision.

There are other methods but the results they produce are quite differentfrom the DMAC method :

DMAC	: 36 mg
NP-HPLC	: 72 mg (USA)
Pharmacopeia Europe	: 89 mg
Vannilin	: 174 mg
Bate Smith	: 187 mg

Therefore it is important to refer to the DMAC method which corresponds to the 36 mg PAC in 300 ml C juice drink.

Table 2 Anti-adhesion activity in urine measured by Lavigne Testwith three regimens of Urell® and placebo control.



4. QUANTIFICATION OFBIOACTIVITY IN URINE

Given that 36 mg of PAC per day is necessary to obtain a preventive clinical effect on UTIs (Avorn study [12]) and given that we lack a method to evaluate active metabolites in urine we therefore need surrogates to quantify bio-activity in urine. There are two surrogates:

The first is the red blood cell hemagglutination test, described by Howell [3]. Each E. coli strain is incubated for 20 minutes in the volunteer's urine at a concentration of 10^5 CFU/ml, to correspond to the bacterial concentration indicative of a clinical UTI. Hemagglutination is carried out on microplates (96 wells) in the presence of group A+ or O+ human red blood cells (HRBCs) newly drawn in citrated tubes. A 3% suspension of HRBCs is added to each well containing the bacteria/urine suspensions and the microplate agitated for 15 minutes. Each well is evaluated microscopically for the presence or absence of hemagglutination.

If the HRBCs in a well are not agglutinated, the urine in that particular well is considered to have C metabolites with antiadhesion activity. The results of this rapid and indirect test are given using 3 thresholds (0 ; 50% ; 100%). It is indeed a very good test for screening and to compare different available commercial products.

The second surrogate is a direct cellular adhesion test described by Lavigne [16], adapted from Di Martino [13]. This study consists of testing the capacity of the E. coli strains to adhere in vitro to urothelial T24 cell lines. Each strain is cultured in the volunteer's urine for 12 hours. These bacteria are then placed in contact with the urothelial cells for three hours. After fixing, the bacteria are stained with 20% Giemsa and examined under a microscope. An adherence index (AI) corresponding to the mean number of adherent bacteria per cell for 100 cells is then calculated. The morphologies of the different E. coli strains (morphology of rod, lengthening, thickening…) are evaluated using an electronic microscope after fixing the slides containing the bacteria in contact with the cells. Three independent experiments are carried out for each test. An anti-adhesion control test is carried out.

5. FORMULATION OF CRANBERRY

Besides the problem of measurement of bio-activity, there is another great concern about the chemical composition of commercialy available C products. Their composition is not standardized and thus bio-equivalence between all of them is not clear.

The first dosage proposed was 36 mg of PAC extracted from the Avorn study [12]. This 36 mg was given by 300 ml of juice presentation. But juice presentation is not convenient for long-duration leading to a withdrawal rate of up to 55% [17] . Thus capsules and tablets have been developed but there is no strict standarization for these products. Moreover their labels are very often unscientific, even dishonest, because there is little regulation (if any) in the field of food-supplements.

In addition a lot of capsules or tablets contain a mixture of C species: the validated form (vaccinium macrocarpon) and the non-validated forms (vaccinium vitis idaea (lingonberry) and vaccinium oxycoccus (European Cranberry)). Thus, it is impossible to compare by using the dosage of PAC written on the label. The only way to compare is by one or two of the surrogate bioactivity methods described, however if any surrogate is used for a precise product, it is still impossible to take into consideration the results present in the leaflet.

The final concern regarding the composition of capsules or tablets is their activity in connection with products other than PAC. Up to now, no compound of C other than PAC has been shown to be active in the prevention of UTIs.

6. CLINCAL STUDIES

The existing clinical studies have been recently reviewed by Jepson and Craig for the Cochrane database [6, 18]. For this reason we did not perform a systematic literature search, but used the results of the Cochrane database. Only ten stud-ies met their criteria and two were rap-idly excluded [17, 19] because they were published only in letter form and no additional data were available.

6.1 NEUROGENIC PATIENTS

For neurologic patients needing catheterisation (intermittent or indwelling) there was no statistical difference in the number of symptomatic UTIs between C (juice) and placebo [20–21]. Nevertheless in a recent study (randomised, double-blind, placebo-controlled with a cross-over design in a 12 month period) involving

47 patients with spinal cord injury, Hess [22] found a reduction of UTI to 0.3 per year during the C period. compared to 1.0 UTI per year while receiving pla- cebo. Interestingly he also reported that patients with a high glomerular filtration rate may receive the most benefit.

6.2 ELDERLY PATIENTS

In elderly patients three studies were available. The first one was conducted by Avorn [12] in asymptomatic bacteriuric patients. However, the group receiving placebo were significantly more bacte- riuric before their inclusion in the trial. Nevertheless, he concluded that the subjects receiving C juice were 58% less likely than the control group to have bac- teriuria. Here 300 ml of C juice was used containing 36 mg of PAC.

In the second study conducted by McMurdo [23] 376 hospitalised sympto- matic patients were recruited. There was no statistical difference between either group (C juice and placebo). Because the infection rate observed was lower than anticipated it made this study under- powered.

The final study was also conducted by McMurdo [24] in 137 women (mean age : 63 years) with two or more antibi- otic-treated UTI's in the previous twelve months. They were randomised to either receive 500 mg of C extract (the amount of PAC is not stated) or 100 mg of tri- methoprim for six months. The amount of UTIs treated by the G.P. were 36% in the C group versus 20% in the trimethoprim group, and the microbiologically con- firmed UTIs were respectively 16% and 12%. The authors concluded "trimetho- prim had a very limited advantage over C extract in the prevention of UTIs". In fact the actual infection rate with trimetho- prim was much higher than expected (1%) and this made the study inconclusive.

Furthermore UTIs often occur in clus- ters, with patients often being symptom free for several months. A preventive study in this field needs to be longer than six months.

6.3 SEXUALY ACTIVE WOMEN

In sexually active women with recur- rent cystitis there were only two studies. Kontiokari [25] and Stothers [26] each recruited 150 women for one year of treat- ment. In the Kontiokari study patients had one previous UTI, compred to two in the Stothers trial. The absolute risk reduction of UTI was respectively 20%and 14%. Nevertheless the Kontiokaristudy was stopped prematurely (at six months) because the C juice supplier stopped producing the juice.

6.4 SIDE-EFFECTS

Side effects were very uncommon, mainly related to juice presentation and limited to the gastro-intestinal area.

6.5 WITHDRAWLS

Withdrawals are common with juice pres- entation (up to 55%); the compliance is much better with capsule.

6.6 CONCLUSIONS AND RECOMENDATIONS

Juice presentation is too unwieldy to be recommended for a long period of time as a prophylactic treatment for recurrent UTI. Thus the necessity to develop cap- sules or tablets.

For these there is no standardization:

- In C species
- In method of PAC measurment
- In dosage of PAC per day
- Apart from one capsule, there is no data about the bio-activity of the commercially available products
- No dose-ranging
- No direct correlation between in- vitro and clinical effects.

At the least, as for active drugs, we need a minimum standardisation:

- the precise amont of PAC
- measured by DMAC method
- allowing clinical studies with stronger methodology

if we want to confirm the hopes regarding the efficacy of C in reducing UTIs.

Despite the lack of pharmacological data and the few and weak clinical studies, there is evidence to consider C vaccinium macrocarpon to be useful in reducing the rate of lower urinary tract infections in women.

Despite the GoR C (LoE 2) referring to the scientific data, it is logical in everyday practice to recommend the consumption of C products giving a minimum of 36 mg of PAC (vaccinium macrocarpon) per day providing this amount is proven.The best approach would be to use those compounds that have demonstrated their clear bio-activity in urine.

7. SUMMARY

Over the last few years, we have noted a spread of cranberry (C) use for the following two reasons: the high number of UTIs has lead to an increased use of antibiotics and thus increased antibiotic resistance; the main mechanisms of action in reducing UTIs have been indentified. C inhibits the adherence of E.coli to uro-epithelial cells, the first and necessary step for UTI. This competitive inhibition is due to a non-dialyzable compound; a condensed tannin, the proanthocyanidin (PAC) type A. Among the three species of C vaccinium macrocarpon is only one to have PAC-A.

The first dosage used was 36 mg served as 300 ml of juice presentation[12]. In 2006, a double-blind randomised placebo-controlled cross-over trial comparing two dosages of C juice presentation (250 and 750 ml) found a significant reduc- tion of E. coli adherence ($p > 0,001$) dose dependent.

In 2008 a double-blind randomised placebo-controlled cross-over trial tested a commercially available capsule of vaccinium macrocarpon containing 36 mg of PAC. A statistically significant reduction of bacterial adherence of E. coli was found ($p < 0,001$), dose-dependent. For the first time this study established clearly the bio-activity of a C capsule.

The method of measure of PAC is the DMAC method which yields a result of 36 mg PAC for 300 ml C juice drink.

7.1 QUANTIFICATION OF BIO-ACTIVITY IN URINE

Given that 36 mg of PAC per day is necessary to obtain a preventive clinical effect on UTIs (Avorn Study [12]) and given that we lack a method to evaluate active metabolites in urine we therefore need surrogates to quantify bio-activity in urine. There are two surrogates :

The first is the red blood cell hemagglutination test (Howell [3]) ; the second is the direct cellular adhesion test (Lavigne [16]).

7.2 CINICAL STUDIES

These have been recently reviewed by Jepson and Craig [6, 18] for the Cochrane database. Juice presentation is too unwieldy to be recommended for a long period of time as a prophylactic treatment for recurrent UTI. Thus the necessity to develop capsules or tablets. However, there is no standardisation for these: in C species, in method of PAC measurement, in dosage of PAC per day, apart from one capsule there is no data about the bio-activity of the commercially available products, no dose-ranging and no direct correlation between in-vitro and clinical effets.

8. CONCLUSION

Despite the lack of pharmacological data and the few and weak clinical studies there is evidence to consider C vaccinium

macrocarpon to be useful in reducing the rate of lower urinary tract infections in women (GoR C ; LoE 2).

Despite the GoR C (LoE 2) referring to the scientific data, it is logical in everyday practice to recommend the consumption of C products giving a minimum of 36 mg of PAC (vaccinium macrocarpon) per day providing this amount is proven.The best approach would be to use those compounds that have demonstrated their clear bio-activity in urine.

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