Cranberry (Vaccinium macrocarpon) and urinary tract infections: study and review of the literature

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Summary

Today many studies focus on the cranberry *(Vaccinium macrocarpon)* because of its beneficial effect observed in the present prevention of urinary tract infections. Among the components of cranberries *(V. macrocarpon)* are proanthocyanidins (PAC) that are the origin of the anti-adhesion activity of *strains* of Escherichia *coli* uropathogenic on urothelial cells. These work by inhibiting CAP the synthesis of P-fimbriae and distorting the cell bodies of the bacteria. The interest of the cranberry *(V. acrocarpon)* lies mainly by its activity on all *E. coli* strains that are sensitive or resistant. This article aims to present the latest advances in Knowledge of anti-biofilm effect of cranberry *(V. macrocarpon)*.

Abstract

Cranberries *(Vaccinium macrocarpon)* Long-have-been the focus of interest for their beneficial effects in preventing urinary tract infections. Among cranberry compounds, a group of proanthocyanidins (PACs) with A deviation linkages were isolated that exhibit anti-bacterial adhesion activity against uropathogenic *Escherichia coli* Strains. These PAC inhibit P-fimbriae synthesis and induce a bacterial deformation. This activity was demonstrated on both antibiotic susceptible and resistant bacteria. This review focused on the last discoveries in the knowledge of cranberry effects.

Keywords: Anti-adhesion; Cranberry; *Escherichia coli; Vaccinium macrocarpon;* Bacterial virulence

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1. Vaccinium macrocarpon (Cranberry) is a small rounded dark red fruit, fodder firm and crisp with a fruity flavor and slightly acid astringent due to a high content of tannins (polyphenols). Larger than its cousin the cranberry, it measures 1 to 2 cm diameter. Only the American cranberry or cranberry was studied for its biological properties can be used in clinical practice (urology). It is native to America North and belongs to the *Ericaceae* family. Today it is industrially grown in cranberry bogs, land fitted which, like the rice fields may be flooded for culture and especially for the harvest, which takes place by flotation berries. The cranberry *(V. macrocarpon)* contains approximately 80% water and 10% carbohydrates [1] . Other components are identified antioxidants such as flavonoids of, anthocyanins (natural pigments giving color cranberry), catechins, as well as triterpenoid, of organic acids (citric acid, malic acid, quinic acid, benzoic benzoic, glucuronic ...) and a low ascorbic acid levels [1]. From cranberry *(V. macrocarpon),* were produced beverages (juice), dietary supplements, sauces, concentrates include dry powders in the form of capsules.

In fact, for many, many years, the cranberry *(V. macrocarpon)* is known for its preventive properties urinary tract infections. It is only recently that research was conducted on the mode of action and effects of this bay. This review aims to describe the current data on cranberry *(V. macrocarpon)* including in vitro results obtained from commercial capsules.

2. Effect of anti-adhesion of cranberry (V. macrocarpon)

The adhesion of bacteria is the first uroepithelial step in the pathogenesis of urinary tract infections followed by bacterial growth and colonization of the urinary tract [2]. The adhesion will allow especially *Escherichia coli* to go up through the urethra into the bladder avoiding their elimination by the urinary flow. To enable this adherence, the bacteria have extensions called fimbriae or adhesions. Proteinaceous these adhesins are specific, binding the corresponding hydrocarbon receptors on the surface of uroepithelial cells [3] . *In* E. *coli,* two types of fimbriae are essentially identified; morphologically identical, they adhere to different receptors: type 1 pili that have the receptor D-mannose; virtually all strains *of* E. *coli (uropathogenic* or not) can express these pili that are said "Mannose-sensitive"; P-fimbriae that bind to polysaccharide receptors (a-Gal (1-4) β-Gal) and are responsible for cystitis and / or pyelonephritis; these strains are called "mannose-resistant" [4]. Other fimbriae (including Sfa, F1C, F17, Afa, Dr, F1845) are present in less than 20% of the strains *E. coli* uropathogens. In 1984 Sobota was the first to suggest that the benefits provided by the cranberry juice consumption *(V. macrocarpon)* could be due to its ability to inhibit bacterial adhesion [5] . Sobota demonstrated that cocktails containing cranberry juice *(V. macrocarpon)* significantly reduce the adhesion of *E. coli* isolated in patients who have had a urinary tract infection (over 75% reduction). This effect was noticeable one to three hours after absorption of 450 ml of cranberry juice [6]. Since then, other studies have confirmed the effectiveness of the cranberry *(V. macrocarpon)* in preventing urinary infections related to its anti-adhesion properties. The connection between the ends of the fimbriae and the surfaces of uroepithelial cell occurs as an associations specific ligand-receptors [7] favored by hydrophobic interactions [8]. The long assumed mechanism action of cranberry *(V. macrocarpon)* was the effect of the acidity of the fruit creating a bacteriostatic effect in the urine. Subsequently, it was discovered that the action of

the cranberry compounds would act as an analogue to the receptor, competitively preventing the adhesion *of* E. *coli* cells of the uroepithelium. More recently, the mechanisms accurate action of cranberry *(V. macrocarpon)* have been discovered. They are:
● Inhibition of the synthesis to a complete disappearance of P-fimbriae adhesins resulting from prolonged exposure;
● Deformation or elongation of the cell body of the bacteria [9.10] . These changes make *E. coli* unable to adhere to the bladder wall;
● A change in properties at the surface of bacteria causing a shift in the distribution of ζ potential (potential existing power across the interface of all solids and liquid) in a positive direction [11].

It was in 1989 that Zafriri et al. [12] identified two components contained in the cranberry *(V. macrocarpon)* which inhibit adhesins *of* E. *coli.*

● Oligomers of proanthocyanidins with a significant proportion Type A is called CAP
● Fructose.

Even if all fruit juices contain fructose, only the cranberry juice *(V. macrocarpon)* contain CAP these are the proanthocyanidins that demonstrate a strong inhibitory activity against mannose resistant adhesions produced by *E.* uropathogenic *E. coli,* but also a anti-adhesion activity against moderate strains of *E. coli* faecal [13-15].

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Meanwhile, studies have shown that fructose inhibits the adhesion of type 1 pili (mannoses sensitive) by a saturation effect of the binding sites of bacteria, but this effect has been demonstrated in vitro only [12,16]. To date no studies have shown that a diet with fructose administered orally inhibits bacterial adhesion. The fructose, as all sugar is normally metabolized before reaching the urine; so it cannot end up in urine except in people with diabetes: it explains why sugar has never shown any biological effect in prevention of urinary tract infections in vivo. Furthermore, P-fimbriae are not inhibited by fructose. As these are mainly adhesins that are involved in urinary tract infections, the second component (PAC) seemed therefore play a key role in reventing infections.

PACs are components produced by plants response to environmental stress and during bacterial infections [17,18] . The stringency of the CAP protects young fruit from animals or insects [19] . One of the characteristics CAMP c is their ability to bind to proteins[20]. This feature explains that bind to CAP adhesins, preventing bacteria to bind to the urinary walls. Mass spectrometry analysis demonstrated that anti-adhesive biological activity of CAP was due to the fraction of oligomeric epicatechin having a unique A type double bond [15]. The most recent studies have shown that the effect of anti-

adhesion of cranberry *(V. macrocarpon)* is valid in all strains of *E. coli* that are sensitive or resistant to antibiotics [21] . It is especially for this that the use of inhibitors of adhesion as the cranberry is interesting. The administration of cranberry *(V. macrocarpon)* could potentially reduce the use antibiotics in the prevention of urinary infection recurrences promoting the proper use of these antibiotics. Classical, the effect of anti-adhesion begins two hours after cranberry juice ingestion *(V. macrocarpon)* and persists over ten hours after absorption [22] . A study on urine obtained from healthy patients who drank juice Cranberry *(V. macrocarpon)* has demonstrated that *E. coli* cultures placed in the urine had no adhesion activity in vitro model of urothelial cells [23] .

3. Clinical Studies

The first clinical study evaluating the effects of cranberry *(V. macrocarpon)* was published in 1966 by Papas et al. [24] . It was conducted in patients with bacteriuria showed, for the first time, a beneficial effect in these patients. Since then, nearly twenty clinical trials have been performed to evaluate the different products containing cranberries *(V. macrocarpon)*. These trials have focused on the preventive effect of urinary infections with studies in different populations: women in genital activity, elderly, children (including those with malformations) and people with repeated urinary tract infections [24-33] . Most studies have confirmed the beneficial effects of cranberry *(V. macrocarpon)* on infection prevention urinary tract infections regardless of the age of the patients with the exception of children for whom no significant benefit of cranberry *(V. macrocarpon),* on the prevention of asymptomatic bacteriuria and urinary infections, has been demonstrated [28,31] . Furthermore, an epidemiological study evaluating the relationship between sexual debut of young women and the first episode of UTI showed that regular intake of cranberry juice *(V. macrocarpon)* was associated with a decreased risk of urinary tract infections these young women [34] suggesting that cranberry was not only beneficial in preventing recurrence infections, but also to avoid the inaugural episodes. Since these studies, interest for the cranberry *(V. macrocarpon)* seems more and more obvious, and more authors propose the use of the cranberry in the prevention UTI [1.34 to 38] . Currently, the oral form (juice) was best studied, and a daily dose of 240- 300 ml is recommended for avoiding the infection recurrence in more than half the cases [32] . Other forms have also demonstrated beneficial effects (capsules, dried fruits or sauces) [39-42] . However, subsequent studies needed to define the dose and efficacy of these products. In the Cochrane database, using cranberry *(V. macrocarpon)* in preventing urinary infections seems to be an essential therapeutic "weapon", helping the clinician to manage patients with urinary tract infections repetition. The issue of the use of cranberry *(V. macrocarpon)* in the treatment of urinary tract infections remains unresolved; no studies have been conducted to date. The only published data are few side effects induced cranberry *(V. macrocarpon)*. Laxative effects light, depending on the amount of cranberry ingested were described [1,43,44]. Terris et al. exposed the formation of calasses after absorption of high doses of cranberry for a long time due to the increased excretion of oxalate and slight acidification of the urine [45] . Current issues are therefore know the effectiveness marketed and the value of these products produced in treating urinary tract infections in addition to antibiotic.

4. In vitro study of the action of proanthocyanidins

To evaluate the effectiveness of CAP contained in a commercial preparation, we conducted a double-blind, randomized, cross comparing administration study of Urell ® (capsule containing a total polyphenol extract of *V.* powder *macrocarpon,* dosed at 36 mg PAC measured [DMAC method validated according to] and fructose-free) versus placebo in eight volunteers. In addition to food normalization, each volunteer received three capsules (caps.) containing either 3 caps. of placebo or 3 caps. of Urell® Or 1 caps. of Urell ® and 2 caps. of placebo. Each volunteer performed the three regimes randomized with 6 days between schemes. After taking capsules, the previous evening, morning urine were collected. Four strains *E. coli (2 FimH papGII + + + MIF papGII* 1 - 1 and *MIF - PAP GII* -) isolated from patients with urinary tract infection, have were cultured in different urine of volunteers and tested for their ability to adhere in vitro lines urothelial T24. For this, we determined an index adherence (IA) represents the average number of bacteria adherent per cell for 100 cells. Four independent experiments were performed for each test. This study observed a significant decrease of bacterial adhesion dependent absorbed dose of Urell®.

In vitro, for *MIF papG* + + strains, in the presence 3 caps of Urell®.
The AI was 5.61 ± 2.90; in the presence of placebo, the AI was 22.30 ± 2.47 in the presence of a capsule of Urell®.
The AI was 14.40 ± 2.54 *(p <0.001)* for the strain *MIF - papG* - in the presence of a capsule of Urell®.
The AI was 1.70 ± 0.46; in the presence of placebo, the AI was 4.84 ± 0.26 in the presence of a capsule of Urell®.
The AI was 3.42 ± 0.49 *(P* <0.001). Finally, the strain *MIF papG* + -, in the presence of a capsule of Urell®.
The AI was 2.84 ± 0.77; in the presence of placebo, the AI was 7.37 ± 0.77 in the presence of a capsule of Urell®.
The AI was 4.61 ± 0.48 *(p* <0.001).

For the first time, we demonstrated the effect in vitro capsules of cranberry *(V. macrocarpon)* sold in pharmacy on an *E. coli* panel. Interestingly, this effect anti-adhesion was not reduced to a particular group of *E. coli* strains. The cranberry *(V. macrocarpon)* inhibited adhesion strains regardless adhesion capacities of these bacteria (presence of P-fimbriae and / or type pili 1), and regardless of resistance (sensitive or resistant strains aunts to particular antibiotics secreting β-lactamases Extended Spectrum [CTX-M *(MIF* strain - *papG* -) and TEM (often che *MIF papG* + -)]). Moreover, the calculation of the AI in placebo patients who had confirmed that P fimbriae were indeed the main adhesins involved during urinary infection as they contribute to over 85% of full membership of the infection group, because the net adhesion of type 1 pili was 2.5 (AI *(MIF papG* + -) - AI *(MIF - papG* -), 7.3 to 4.8) while for the strains having two adhesins this Membership was 17.5 (AI *(MIF papG* + +) - AI *(MIF - papG* -), 22.3 to 4.8). This confirms that the action CAP on P-fimbriae is essential for anti-adhesion effect, in particular compared to the fructose content in some preparations. In addition, strains devoid of the two main adhesins adhere to uroepithelium via accessories adhesin synthesis or action is also inhibited in part by the CAP contained in urine of patients consuming cranberry capsules *(V. macrocarpon)*. These results suggest that during the growth of *E. coli in* urine with volunteers consumed cranberry *(V.*

*macrocarpon)(*Urell®), the bacterial adhesion is much lower due to inhibition different adhesins, especially P-fimbriae. This study confirms that food supplements such Urell®, can be an alternative in the prevention of urinary infections and that this effect is dose-dependent.

5. Conclusion

Currently, the critical rise of multidrug resistance bacterial, in particular in strains *of* uropathogenic E. *coli* [46] , incents us to find new therapeutic strategies. The cranberry *(V. macrocarpon),* small red berry of American origin and its essential component, the CAP have demonstrated in vitro and in vivo real benefits on prevention urinary tract infections. It appears as an alternative to antibiotics to reduce their use in urinary tract infections.

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