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Is Cranberryeffective in preventingrecurrent urinary tract infection in women

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Abstract:Urinary tract infection (UTI) is the most common infection in hospital settings. While antibiotics are quite effective at providing clinical cure for UTI, urogenital pathogen drug resistance is on the increase. In recent decades, cranberry has been shown to be solid means of alleviating and curing several illnesses that previously could only be treated with conventional drugs. The anti-adherence activity of cranberry products is the main mechanism involved in the preventive actions of UTIs, and it is a dose-dependent. For people with recurrent uncomplicated UTIs, routine utilization of cranberry products may offer an alternative methodology to antibiotic prophylaxis. The anti-adherence activity of cranberry and its PACs content is enough to produce their pharmacological activity, reduce the UTIs recurrences and improve patient's symptoms.

Key words:Cranberry, Recurrent Urinary Tract Infection, anti-adherence activity, A-type proanthocyanidins.

I. INTRODUCTION

I.I) Urinary tract infection

Urinary tract infections (UTIs) are infections that can happen anywhere along the urinary tract and defined as microbial colonization of the urine and infection of the structures of the urinary tract with or without infection of the adjacent structures[1-3]. UTI is one the most common infectious diseases of the community and of the hospital settings, resulting in high rates of morbidity and high economic costs associated with its treatment[3]. Uncomplicated UTI occurs in patients without any anatomic or functional abnormality in the urinary tract and may reach, on average, 6.1 days of symptoms, 2.4 days of restricted activity and 0.4 bed days[1]. Uncomplicated cystitis (infection of bladder) is the most common UTI and is responsible for 95% of all symptomatic urinary tract infection[2, 4, 5].

90% of UTIs occur in females, except during the neonatal period, in which they are predominant in males[6, 7]. UTIs account for more than 7 million visits to physicians per year (1.2% of all office visits by women)[2, 4]. The financial impact of UTIs, including recurrent and uncomplicated cases, is greater than 1 billion dollars in the United States alone[4, 5]. Over 80% of women who had previous UTIs have recurrent infections over the first 18 months ofobservation.Of these recurrent infections, three quarters are causedby reinfection with different organisms[1, 2, 5].Women with frequent reinfectionshave a rate of 0.13 to 0.22 UTIsper month (1.6 to 2.6 infections peryear)[4, 5]. For premenopausal, healthy,and active females, recurrent UTIs area major healthcare concern[1, 2].

The urinary tract has strong defenses against infection[1, 2, 8]. Urine is usually sterile and both ureters include a mechanism which prevents the urine from returning to the kidney [3, 5, 8]. The immune system of humans is in a constant battle against microorganisms and other damaging invaders[9-11]. Against all odds, urinary tract infectionis one of the most common and can arise at any time during an individual's life[9, 11-13]. Almost 95% of cases are caused by bacteria that normally multiply at the entrance to the urethra and reach the bladder (ascending route)[2, 3, 5, 9]. Less frequently, the bacteria propagate to the kidney via the bloodstream[9, 13].

The most common urinary tract infection (UTI) is cystitis; this infection appears in the lower urinary tract and affects the bladder and the urethra. However, it can also extend to the upper tract (ureters and kidneys) and is then known as pyelonephritis[1, 2, 8, 11, 12]. Sometimes asymptomatic bacteriuria may appear, that is, a patient's having bacteria in the urine without displaying any symptoms[9, 11, 13]. Analysing asymptomatic bacteriuria is not necessary in most medical check-ups, but it is important to do so in pregnant women and patients who have undergone urological surgery, as their conditions may cause significant infections[8, 9, 11-13].

Cystitis is characterised by burning sensation with urination and having to urinate frequently (or an urge to urinate) in the absence of a significant pain [1, 3]. These symptoms may vary from mild to severe with some pain above the pubic bone or in the lower back[9, 11]. People experiencing an upper urinary tract infection, or pyelonephritis, may experience flank pain, fever, or nausea and vomiting in addition to the classic

symptoms of a lower urinary tract infection. Rarely the urine may appear bloody or contain visible pyuria (pus in the urine) [1, 8, 9].

Women are more prone to UTIs than men because, in females, the urethra is much shorter and closer to the anus[9, 11, 14, 15]. As a woman's estrogen levels decrease with menopause, her risk of urinary tract infections increases due to the loss of protective vaginal flora[3, 5, 16].Frequent sexual activity increases the risk of urinary tract infection [1, 2, 17]. Women who are sexually active have a higher incidence of infection due to a number of different factors. Sexual behavior may influence the risk [1, 16, 17]. The onset or a sudden increase in sexual activities, use of the diaphragm, unlubricated condom and spermicides, may increase the risk of cystitis [3, 17].

Urinary catheterisation increases the risk for urinary tract infections. The risk of bacteriuria (bacteria in the urine) is between three to six percent per day and prophylactic antibiotics are not effective in decreasing symptomatic infections[1, 5, 16, 18].UTIs are frequent in children. Their prevalence in childhood varies from 2.1% to 8.7%[6, 7]. Approximately 8% of girls and 2% of boys will experience at least one UTI before reaching 7 years of age[1, 6]. In children UTIs are associated with vesicoureteral reflux (an abnormal movement of urine from the bladder into ureters or kidneys) and constipation[6, 7, 11].

The bacteria that cause urinary tract infections typically enter the bladder via the urethra. However, infection may also occur via the blood or lymph[7, 9, 12]. E. coli is the cause of 80–85% of UTI's, with Staphylococcus saprophyticus being the cause in 5–10% [9, 12]. Rarely they may be due to viral or fungal infections [9, 10]. Other bacterial causes include: Klebsiella, Proteus, Pseudomonas, and Enterobacter. These are uncommon and typically related to abnormalities of the urinary system or urinary catheterization[5, 7, 16, 19-21]. Urinary tract infections due to Staphylococcus aureus typically occur secondary to blood-borne infections [7, 9]. After gaining entry to the bladder, E. Coli are able to attach to the bladder wall and form a biofilm that resists the body's immune response [5, 9].

A number of measures have not been confirmed but seems to affect UTI frequency including: urinating immediately after intercourse, the type of underwear used, personal hygiene methods used after urinating or defecating, holding one's urine, tampon use, and douching[7, 9-11, 14].For those with recurrent infections, a prolonged course of daily antibiotics is effective[9, 11, 13, 21].Medications frequently used as a prophylaxes include nitrofurantoin and trimethoprim/sulfamethoxazole[9, 13].In cases where infections are related to intercourse, taking antibiotics afterwards may be useful[17]. In post-menopausal women, topical vaginal estrogen has been found to reduce recurrence[2, 17, 22].

While antibiotics are quite effective at providing clinical cure for UTI, urogenital pathogen drug resistance is on the increase [1, 5, 23-28]. On top of that, drugs have local side effects including disruption of the protective flora of the mouth, anal area, urethra and vagina, which create an increased risk of recurrent infections[23-28]. Also, antibiotics can cause general adverse effects including palpitations, flushes, nausea, vomiting, diarrhea, abdominal pain, rashes, headache and dizziness[25, 28]. The presence of a natural alternative that could prevent and treat UTI is preferableto any other treatment.

Naturally, the epithelial layer covering the entire urinary tract has intercellular junctions which are formed by glycoproteins [8, 29, 30]. These glycoproteins not only act as glue between cells but also, create a film across the entire epithelium which protects it from bacterial attacks [8, 29]. Glycoproteins naturally deteriorate due to micro-ischemic, immune system or chemical phenomena but, sometimes they deteriorate for unknown reasons [5, 8, 22].

Microorganisms produce different bioactive substances helping them to adhere to the urinary tract epithelial layer and then gain intracellular entrance, thus, causing inflammation and UTI [9-11, 28]. One of these bioactive substances is called adhesions, which is involved in bacterial adherence to the urinary tract epithelium and triggering the inflammatory response [8, 29, 30]. This process of bacterial adhesion to the epithelium allow them to remain at the urinary tract despite the drag effect of urinary flow[8, 29]. The main adherent structures of E. coli are fimbriae which are filamentous appendages on the surface of the bacteria and they are composed of filaments of protein with adhesions [5, 29, 30]. In turn, after E. coli adhesion, bacterial lipopolysaccharide act on receptor in the urinary tract epithelial cells to synthesis pro-inflammatory cytokines and the inflammatory process follow [23-25, 28].

I.II) Urinary tract infection prophylaxis

Different studies have raised serious doubts about the role of antibiotic prophylaxis of UTIs [31, 32]. Antibiotic treatment may cause bacterial resistance and may therefore be ineffective in preventing infection, and it has been associated with some secondary/adverse effects, particularly in the intestinal tract, suggesting that continuous antibiotic prophylaxis prolonged for months or even years, can be hazardous. The changing pattern of antimicrobial resistance to the causative microorganisms of UTIs is a mounting problem. There is growing concern regarding antimicrobial resistance worldwide, particularly of Escherichia coli [32, 33]. Initially, resistance was described to particular agents, such as ampicillin, trimethoprim, sulphur-based antimicrobials or

tetracyclines. More recently, the resistance has broadened to large families of agents, as the resistance to most ß-lactam antibiotics, aminoglycosides and fluoroquinolones [31, 33]. A strong evidence of an association at the individual patient level between the prescribing of antibiotics in primary care and antimicrobial resistance in bacteria in different sites, including the urinary tract, has been established. Effects were strongest in the month directly after prescription but were detectable for up to 12 months [34, 35]. A Cochrane review published in 2011 determines that long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and increases the risk of microbial resistance [31, 36]. Additionally, other Cochrane review, also published in 2011 concludes that there are insufficient data to recommend any specific antibiotic for treatment UTIs during pregnancy [1, 35].

The association between antibiotic use and breast cancer has been investigated in different studies. Although some studies showed no significant relationship [37], a recent meta-analysis corroborates this possible association[38]. Previously, elevated risk of breast cancer in women linked to the antibacterial treatment for urinary tract infection at premenopausal age. Nevertheless, their underlying nature cannot be defined at present [38]. At any case, this possibility is another factor to question the prophylactic use of antibiotics.

Acidification of urine has been used in traditional medicine for the prevention and treatment of urinary tract infections, although convincing findings for this concept from clinical trials are lacking. Probably other circumstances must occur simultaneously. Some authors speculate that ingestion of nitrate followed some hours later by acidification of urine could be prevent the bacterial conversion of nitrate to nitrite, that automatically convert to toxic nitrogen oxides, thereby leading to self-destruction, but in vivo and clinical studies should be performed. The question then remains if the amounts of nitrate-nitrite and ascorbic acid needed for bactericidal effects are physiologically achievable without troublesome side effects, and if urinary acidity can reach for a sufficient period of time. It is necessary take into account that infected urine often has a higher pH, and therefore, acidification is probably more difficult [39]. Indeed, the administration of one daily gram of ascorbic acid not produces a significant decrease in urine pH [40], and its use in urinary tract infections has not shown clinical benefit in certain studies [41].

In addition, other alternative strategies, including phytotherapeutic products, have gained interest such as the use of probiotics, vaccines, intravaginal estrogen therapy, bacterial immunostimulating fractions from Escherichia coli strains, inhibitors of bacterial adherence and colonization (cranberry and oligosaccharides) and antibacterial (bearberry leaf).

I.III) Cranberry

Cranberry is the fruit of Vaccinium Macrocarpon Aiton [8, 17, 42]. The name “cranberry” comes from the words “crane” and “berry”. The long white flower of the cranberry bush was thought to look like a crane. Both the bird and the plant were typical wild species in New England during its colonial period (17th century) [16, 42]. The plant produces small fruit with an intense red colour. These fruits were used by the Wampanoag people of Cape Cod and the Narragansett of what is now southern Massachusetts to "prevent kidney stones"1 and other urinary ailments [42]. In 1621, the red fruits were served by the Pilgrims with turkey or lobster, and are now a traditional part of the Thanksgiving meal. Sea-men brought the fruit back to Europe to be eaten during the voyage (they have a good, sweet flavor and are rich in vitamin C). When they reached the Old World, they were used in Scandinavia and Russia to produce wines and liquors. They were cultivated in the Netherlands most of all, and spread across northern Europe from there, no one can clearly ascertain when they began to be used to treat urinary tract infections. What is certain, however, is that it happened before the age of antibiotics [8, 29, 42, 43].

In recent decades, cranberry has been shown to be solid means of alleviating and curing several illnesses that previously could only be treated with conventional drugs[8, 16].For example, decreasing the risk factors of cardiovascular disease, prevent and treat dental caries and periodontal disease, reduction of the anti-inflammatory response with antimicrobial activity and the cytotoxic activity against cancer cells (specially against resistant ovarian cancer) [43-48].

Studies on the use of cranberries to fight urinary infections have been published since the 1950s [29, 42, 43]. Since then until now, three different mechanisms of action of cranberry have been postulated: urine acidification with increased hyppuric acid excretion, increase in urinary salicylates, and inhibition of the bacterial adherence to urinary tract epithelial cells [8, 29, 30, 42, 43, 45, 46]. Initially it was believed that its effect was due to its hyppuric acid increasing urine acidity. This led to the conclusion that hyppuric acid could be responsible for a bacteriostatic action and urine acidification [8, 29, 42, 46]. It was then shown that massive amounts of liquid (juice) would have to be used to lower urine pH [29, 42]. At a later date, it has been observed an increase in urine salicylates after consumption of cranberry. The impact of this effect is still unknown, although, it could be related to a local anti-inflammatory effect [8, 29, 30, 42, 43].

Cranberry ability to inhibit microbial adherence is due to the presence of polyphenolic tannins called A-type proanthocyanidins (PACs) [8, 16, 29, 30, 42, 43, 45, 46]. It is well known that each 100 grams of

cranberry contains 65-75 mg of PACs [42-46]. The activity of PACs is the most relevant and well-documented mechanism of cranberry, and these compounds are identified as the main responsible for the inhibition of bacterial adherence [8, 29, 30, 42, 45]. These compounds inhibit the adhesion of bacterial fimbriae, thus, preventing bacteriuria from turning into a urinary tract infection [29, 30, 42]. This action could be related to the ability of PACs to bind to proteins, such as the adhesions present on these fimbriae [8, 29, 30, 42]. It produces a length reduction, causing a decrease of adhesion forces between the bacteria and the urinary tract epithelial cells [29, 42]. Moreover, PACs of cranberry could also bind irreversibly to small molecules on the surface of bacterial cells such as lipopolysaccharides affecting its ability to trigger cytokines production and inflammatory process [29, 42, 46].

It was thought that the only limitation for the use of cranberry juice and extracts is its interaction with warfarin causing increased bleeding time in patient using warfarin [29, 30, 49]. Clinical trials confirmed that cranberry does not affect bleeding time or the degradation (metabolism) of warfarin and, so, cranberry juice and extracts are safe to be used by patients who are on warfarin [49-52].

I.IV) What is PACs and how important it is?

A-type proanthocyanidins are identified as the main responsible for the anti-adherence activity of American cranberry. This action could be related to the ability of PACs to bind to proteins, such as the adhesions present on these E. coli fimbriae [53, 54]. A-type PACs from American cranberry differs from B-type PACs found in most berry fruits, and are considered the main active ingredient for inhibiting P-fimbriated E-coli adherence to uroepithelial cells. The main difference is anti-adhesion effect of these A-type PACs against Escherichia coli, whereas B-type PACs from other berries were devoid of anti-adherence properties [55]. The A-type PACs produces a change of the conformation of the P fimbriae, with a length reduction, causing a decrease of adhesion forces between the bacteria and the uroepithelial cells [56]. Also, the PACs of cranberry bind irreversibly to small molecules on the surface of E. coli such as lipopolysaccharides [57].

Moreover, the inhibition of adherence activity of the PACs from cranberry has been observed not only to E. coli and antibiotics sensitive bacteria but also multi-drug resistant bacteria and to asymptomatic bacteriuria [53, 54, 57].

I.V) Cranberry anti-adherent activity

It has been shown that the anti-adherence activity of cranberry is the main mechanism involved in the preventive actions of UTIs, and it is a dose-dependent in humans. Moreover, A-type proanthocyanidins are the main responsible for the anti-adherence activity, preventing the adhesion of P-fimbriated E. coli to uroepithelial cells and thus the main compounds responsible for the beneficial effect on UTI prevention[53, 54, 58].

The bacterial adhesion is a critical first step prior to invasion, thus it is a key event to test the pharmacological activity of a cranberry product in the bacterial pathogenesis. Anti-adhesion is the functional concept for prevention of pathogens. Robust in vitro and ex vivo assays for bacterial adhesion on host cells have long been used for the screening of potential therapeutic agents for the ability to minimize pathogen colonization of human tissues. In fact, if bacteria cannot attach to the inner urinary wall it cannot colonize and grow[54, 58].

Although some laboratories have previously proposed dose of 36 mg/day of PACs, it is interesting to see how subsequent studies have shown that higher doses of PACs provide greater activity. Recently, a multicentre, randomized, placebo-controlled and double-blind study confirm the anti-adherence activity ex-vivo and shown the reduction of virulence against E. coli[59]. Samples from volunteers that consumed cranberry product (capsules of cranberry powder) significantly produce dose-dependent anti-adhesion activity of E. coli. The effect is particularly important at dose of 72 mg of PACs (DMACA method) and the effect is prolonged until 24 h (T24 cell line and HRBC assays). In urine samples collected at 24 h, there was a significant difference between the anti-adherence activity of urines belonging to patients who had consumed American cranberry dosages containing 72 mg of PACs and the anti-adherence activity of urines belonging to patients who had consumed 18 or 36 mg of PACs [59]. This is another example of the dose-dependent activity of PACs. However, as already discussed and demonstrated, higher doses produce a greater benefit and it can be established the dose of 118 mg as adequate daily amount of PACs.

Additionally, studies to address molecular level adhesion have been performed. It is likely that cranberry can act on both biospecific and non-biospecific ways to induce changes in either bacteria or the adhering substrate. Several possible mechanisms to explain the interactions between cranberry and the surfaces of bacteria were suggested. It is also possible that more than one mechanism act simultaneously [56, 60-62]. Some of these mechanisms include, Alteration of the conformation of the P-fimbriae, binding adhesions in the P-fimbriae, decrease in the adhesion forces of the fimbriae between the cell surface and the bacteria, loss of the P-fimbriae from E. coli surface, changes at genetic level in bacteria with P-fimbriae, causing non-expression of the fimbriae and disruption of the bacterial ligand and uroepithelial cell receptor binding[60, 62].

Alterations to the growth rate of bacteria were implicated in contributing to the overall antimicrobial activity, in addition to the anti-adherence action [63]. The antimicrobial mechanisms of cranberry are not as well studied or clearly defined as the anti-adherence properties. PACs were the major contributing factor to the impact of cranberry juice on reduction of the growth rate of bacteria [63]. The inclusion of PACS from cranberry juice in bacterial growth media was found to significantly impact the duplication time of E. coli. The gene expression results revealed altered expression of genes associated with iron transport (dmsA, dmsB, ydhV, ydhX, ydhY and tdcG) causing iron depletion and, to a lesser degree, to direct disruption of metabolic enzymes, as well as with ATP synthesis (fumB, atpD) and fumarate hydratase in these cultures [63]. These results are consistent with the strong iron chelating capability, dose-dependent, of PACs [63]. The impact of iron depletion on the growth of bacteria is well documented [64, 65]. It is known that under aerobic conditions, microbes need iron for a variety of functions including reduction of the ribonucleotide precursor of DNA and formation of heme [63]. Furthermore, against bacteria, sugars and organic acids from cranberry caused visible osmotic stress, while phenolics and anthocyanins caused disintegration of the outer membrane [66].

I.VI) Clinical trials and medical literature data

Clinical evidence supports that the consumption of cranberry products prevents the recurrent UTIs [67-70]. This effect has mainly been studied in women, but has also shown a significant reduction in the frequency of these infections in men and in children.

All clinical trials studied the effect of cranberry in preventing urinary tract symptoms. In some of them, the primary parameter tested was UTI, and in other studies, bacteriuria was the primary endpoint. Added to that, cranberry treatment is a safe, well-tolerated and does not have significant drug interactions[71].

A Cochran review concluded that there was preliminary evidence supporting the efficacy of cranberry for the prevention and treatment of UTI[68]. The findings highlighted that cranberries are effective for the prevention of recurrent UTI, especially in young sexually active women. Meta-analysis was performed using the data from four randomized controlled trials [72-75], where women, subjects with spinal cord injury or the elderly people were involved, the results show that cranberry significantly reduced the incidence of symptomatic UTIs in 12 months compared with placebo or control, particularly in women with recurrent UTIs [68].

Other reviewers also demonstrated the effectiveness of cranberry juice in women with recurrent UTIs [67, 69]. Although, some limitations such as the lack of uniformity with regard to the intervention, (type of cranberry, concentration or content, dosage and duration of the intervention) they all concluded that the number and severity of infections could be reduced in patients with frequent recurrent UTI using cranberries [69].

Medical literature data about the use and safety of cranberry during pregnancy and lactation supports the use of cranberry for UTIs during pregnancy [76, 77]. The study surveyed 400 women using cranberry fruit juices as the most commonly used herbal therapy during pregnancy, and did not uncover any adverse events with regular consumption[77]. The effect of regular intake of cranberry on bacteriuria and pyuria in elderly has also been studied and the reduction of UTIs was observed [78, 79].

Compared to antibiotics, trimethoprim (100 mg/day) has only a very limited advantage over cranberry extract (500 mg/day) in the prevention of recurrent UTIs in older women and has more adverse effects. The median time to recurrence of UTI was 84.5 days for the American cranberry groups and 91 days for the trimethoprim [80]. Moreover, it has been shown that cranberry does not alter the pharmacokinetics of oral antibiotics [81]. Although these studies did not include a control group, their results are equivalent or similar to those reported for other cranberries[82].

II. DISCUSSION

Cranberries are foods that areeffective in UTIs prophylaxis as demonstrated clinically and exhibited potent inhibition on bacterial adherence, witha good tolerability, treatment compliance and efficacy to prevent recurrent urinary tract infection.

Urinary tract infections (UTIs) are among the most common types of bacterial infection in outpatient medicine. After respiratory tract infections, they are the most common reason why antibiotics are prescribed. Rising rates of antibiotic resistance and a better understanding of the adverse effects or collateral damage of antibiotics warrant a re-evaluation of the treatment recommendations for uncomplicated UTI. Antibiotic prophylaxis of UTI may cause bacterial resistance and may therefore be ineffective in preventing infection, and it has been associated with some negative effects. Different studies have raised serious doubts about the role of this treatment and recommended alternative strategies, including cranberry extracts.

The inhibitory effect on adherence of E. coli to urothelium is highly desirable in children because UTI is particularly common and recurrence worsening with vesicoureteral reflux. In those cases, continuous antibiotic prophylaxis, prolonged for months or even years, causes undesirable effects, particularly in the intestinal tract, and increases bacterial resistance. Therefore, the availability of an effective cranberry extract to replace antibiotic prophylaxis is a great advance.

Cranberry products significantly reduce the incidence of symptomatic UTIs, particularly in women with recurrence. Their main mechanism of action is the inhibition of the bacterial adherence to uroepithelial cells and PACs are identified as the main responsible for this activity. PACs produces a change of the conformation of the P fimbriae, with a length reduction, causing a decrease of adhesion forces between the bacteria and the uroepithelial cells. Moreover, the inhibition of adherence activity of the PACs from cranberry has been observed not only to sensitive but also multi-drug resistant bacteria and to asymptomatic bacteriuria.

Since the level of the PACs determines the effectiveness of a cranberry product, it is very important to know the PACs content of these extracts. Colorimetric methods, mainly vanillin and DMACA, are the most commonly used in quantifying PACs, but there is no official established method. The different analytical methods do not allow correct comparison between different products and pharmacological assays on the adherence of bacteria could be a good alternative to compare different cranberry products. Due to lack of a standard accepted analytical method to measured PAC concentration and PAC composition, cranberry extract anti-adhesion activity should be the best way to guarantee the preventive effect of cranberry extracts.

Clinical evidence supports that the consumption of the cranberry products prevents the recurrent UTIs and their use is safe and well-tolerated, without significant drug interactions. The use of cranberry treatment is supported by European Scientific Cooperative on Phytotherapy(ESCOP) monograph, meta-analysis and different published reviews.

Clinical data have shown the high efficacy and good tolerance of cranberry in children and women with frequent urinary tract infections. Also, the use of cranberrycould reduce the antibiotic use, the recurrence of postcoital urinary tract infections and the quality of life of those patients.

III. CONCLUSIONS

There is strong in vitro, ex vivo and clinical evidence confirming the hypothesis that UTIs can be prevented by decreasing bacterial adherence to uroepithelial cells, which is the main mechanism of cranberry extracts. A-type PACs is the main compound responsible for the anti-adherence activity and thus may be the compound responsible for the beneficial effect on UTI prevention and it is dose-dependent. For people with recurrent uncomplicated UTIs, routine utilization of cranberry products may offer an alternative methodology to antibiotic prophylaxis.

IV. CONFLICT OF INTEREST

None known.

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