

Chapter

Cranberry Effects in Urinary Tract Infections

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Abstract

Cranberry is scientifically known as *Vaccinium macrocarpon*, belongs to the family of Ericaceae, and grows in humid environments, such as forests and swamps in North American countries. It is widely used by Native American peoples and by Europeans as a food and also in traditional medicine for health benefits such as cardioprotective and anticarcinogenic properties and prevention of stomach ulcers. Some studies have demonstrated the potential against bacteria that reach the urinary tract and cause infections. According to the research by Salo, the fruit is composed of 88% water, acid organic, fruits, vitamin C, flavonoids, catechins, and anthocyanidins. It can be found in the form of dried fruits, extracts, and juices, which usually contain only 10 to 25% cranberry concentrate. In addition, it was revealed that anthocyanidins and the proanthocyanidins present in cranberry are tannins with a natural defense function against microorganisms, such as those responsible for urinary tract infections (UTI). This berry has a potential curative and preventive effect for various diseases, especially urinary tract infection. Therefore, it becomes relevant to clarify the effect of this natural product on urinary tract infections.

Keywords: natural product, treatment, infections, cranberry, urinary tract infections

1. Introduction

The American cranberry is one of the main native fruit cultures from North America. The so-called marvelous fruit, which belongs to the *Ericaceae* family and the species *Vaccinium macrocarpon*, has recently become the center of attention due to its significant therapeutic potential [1] and being a unique source that is rich in various bioactive classes, including flavonoids, anthocyanins, type A proanthocyanidins, polyphenols, carotenoids, and vitamins C and E [2].

This plant's extract has been cultivated mainly for use in the industry as a meat preservative. In the medical industry, its main use is for wound healing, as well as to treat dental cavities and stomach ulcers, to prevent bacterial infections of the urinary tract caused by *E. coli*, and is likely to have anticancer properties. Several varieties of fungal pathogens are also susceptible to cultivated cranberry [3].

The daily consumption of a variety of fruit is recommended to keep healthy nutrition standards, to meet a suitable intake of micronutrients, and to promote the intake

of a diversity of phytochemicals. Wild berries, including cranberries, represent a rich source of phenolic bio-actives that can contribute to human health [2].

Although they are not usually eaten raw, cranberries are available in a wide range of choices including juice and sauce, as well as dried fruit in cereal bars, cheese, chocolate, and other confectionary. All these choices of product are beneficial to health in a similar way and are easy to include in daily meals. Moreover, cranberry powder and extracts are now used in food and dietary supplements [2].

2. Effects of cranberry

Cranberry products have been used for centuries in popular medicine for the urinary tract health, and their antioxidant and antibacterial properties have been long reported [4, 5]. Cranberry's biological activities are attributed to a diversified phytochemical profile with flavonoids such as flavonols, anthocyanins, and proanthocyanidins and catechins, phenolic acids, and triterpenoids [6].

The cranberry fruit has a vast class of phenolic compounds, responsible for its antioxidant activities. Chlorogenic acid and quercetin found in cranberry fruit are associated with a reduction in blood pressure, obesity, dyslipidaemia, and the effects of vasodilation improvement dependent on the endothelium [7–9].

Triterpenoids found in the wax of the cranberry fruit peel are associated with anti-inflammatory, anti-tumor, and anticancer activities [10, 11]. Previous studies have reported the efficacy of cranberry extracts to inhibit the growth and induction of apoptosis against different lineages of cancer cells, such as lung, ovarian, breast, prostate, and cervical cancer [4, 12, 13]. These antitumorigenic properties can be related with its antioxidant activity, which attenuates oxidative stress through the modulation of endogen enzymes and the reduction of oxidative markers [3, 14].

The polyphenols, anthocyanins, and proanthocyanidins found in cranberries act in the cell signaling pathways responsible for inflammation [4, 15]. The anti-inflammatory activity of cranberry products has been shown in the modulation of inflammatory markers of different inflammatory diseases such as colitis [16], hepatic inflammation [15], inflammatory intestinal disease [17], and pancreatic inflammation [14]. The administration of cranberry capsules standardized with proanthocyanidins has shown effect on the occurrence and severity of cystitis by radiation in prostate cancer patients [4].

Cranberries have been associated with the urinary tract health. Previous studies suggest that cranberry reduces urinary tract infections through negative regulation and interference on multiple virulence factors, which are associated with stress tolerance and microorganism survival in the urinary tract [18]. Cranberry products showed action against motility of the pathogens *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus mirabilis*. Furthermore, a modulation of *quorum sensing* has been shown, which is a signaling pathway that influences several other bacterial virulence factors [19–21].

Bioactive compounds with selective antiviral activity in pathogenic bacteria can be extremely useful in the fight against bacterial infections caused by pathogens resistant to broad-spectrum antibiotics [20]. It has been shown that cranberries and propolis act to protect against adherence, motility, biofilm, and bacterial multiplication in the urinary tract when used as an alternative in the treatment for urinary tract infections by *E. coli* [22].

A number of studies have shown the potential of this species for pharmacological application directed to oral health. In this context, cranberry hydroalcoholic extracts inhibited the growth of six oral pathogenic microorganisms on the cariogenic, periodontal, endodontic, and candida order, namely, *Streptococcus mutans*, *Lactobacillus acidophilus*, *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*, *E. faecalis*, and *C. albicans* [23, 24].

Cranberry products are associated with benefits to digestive health. They contain fibers and polyphenols related to the beneficial modulation in the gut microbiota, promoting the development of beneficial microorganisms, decreasing the occurrence of pathogenic microorganisms, and modulating the production of microbial metabolic products that help digestive health, such as short-chain fatty acids (SCFA) [16, 25, 26].

Proanthocyanidins are associated to the benefits against *Helicobacter pylori* infections, and the daily intake of cranberries is indicated for at least eight weeks [27].

Clinical studies with humans using cranberry products have focused mainly on the health of the urinary and cardiovascular tracts, oral health, and gastrointestinal epithelium [14] and have shown the high biotechnological potential of this species; however, it is still underestimated regarding other biological activities and therapeutic and pharmacological applications.

3. Cranberry effects on the treatment of urinary tract infections

Urinary tract infections (UTIs) are the most disseminated bacterial infections, and they represent a heavy economic and medical burden worldwide [28]. UTI is a pathology that predominates in all populations, even though women are the most affected. Approximately 50 to 70% of women have at least one episode of UTI during their lives, and 20 to 30% have recurring episodes [29].

In the majority of the infections of cystitis, 85%, the main etiological agent is *E. coli* (UPEC), but other microorganisms cause infections; Gram-negative bacteria *Klebsiella pneumoniae* and gram-positive coccus such as staphylococcus and enterococcus seem to be implicated in these infections [30, 31].

In Latin America, high percentages of *E. coli* strains were found to be resistant to fluoroquinolones (17.5–18.9%), ampicillin (61.4%), amoxicillin, clavulanic acid (18.6%), ceftriaxone (20.5%), gentamycin (25.0%), and trimethoprim/sulfamethoxazole (45%) [32].

It is important to point out that uropathogens can form biofilm to more easily adhere and increase their resistance. This affects the remaining microorganisms, causing higher adherence and multiplication, which may result in thick biofilms that significantly reduce the efficacy of antimicrobial treatments. When biofilm resources are limited, mature bacteria detach and can colonize a new surface to repeat the cycle [33].

Conventionally, the use of antibiotics to treat this pathology has been effective but may lead to resistance among uropathogens and other adverse side effects such as damage to gut microbiota. For these reasons, there is increasing interest in the search for natural therapies to prevent and treat UTIs to fight against the increase of bacterial resistance to antibiotics and the high recurrence rates [31, 34].

In these circumstances, one of the most studied alternative therapies against UTIs is the treatment with *V. macrocarpon* [32]. Salo et al. [35] have brought to light that anthocyanidins and proanthocyanidins found in cranberries are tannins with

a natural defense function against microbial cells, and are a source of high-quality antioxidants.

Several clinical studies suggest that the intake of cranberry juice or cranberry supplements can reduce the occurrence of UTIs in healthy women [36, 37]. These observations were supported by the results of *in vitro* research, which show that compounds derived from cranberry (polyphenols and type A proanthocyanidins, for example) can interfere with bacterial adherence to epithelial cells of the urinary tract, attenuate the uropathogenic reservoir in the gastrointestinal tract, and suppress the inflammatory cascade [38, 39].

Among other possible mechanisms behind the protective effects of cranberries against UTIs is the ability of cranberry polyphenols to act as antiadhesive agents to prevent/inhibit the adherence of pathogens to uroepithelial cell receptors, which seems to be an important step in the pathogenesis of these infections [40].

As an alternative for the treatment of UTIs caused by *E. coli*, Ranfaig et al. [22] presented a study that assessed the levels of genome expression of this bacteria and measured them in the presence of cranberry and propolis products separately, and later compared with the non-treated isolate. They observed that cranberry along with propolis acted favoring protection against adherence, motility, biofilm, bacterial multiplication, and virulence of the urinary tract. Furthermore, the authors affirmed that the administration of both compounds was able to make the propolis intensify the action of cranberry, thus reaching the desired therapeutic effect.

Samarasinghe et al. [41] performed a study with an isolate of *E. coli* CTXM-15, chosen due to its fast dissemination and resistance to some groups of antibiotics. It was submitted for analysis by qRT-PCR (quantitative reverse transcription-polymerase chain reaction) of the behavior of virulence factors after treatment with Cysticlean®, a cranberry product containing around 240 mg of proanthocyanidins.

The ten selected genes performed significant roles in normal cell functions such as iron absorption, toxin production, and stress survival in *E. coli* resistant to third-generation cephalosporin, and its relative genic expression was determined after exposure to Cysticlean® using qRT-PCR. Results showed that Cysticlean® significantly reduces the expression of a large variety of genes responsible for aptitude and virulence [41].

Two complementary mechanisms were suggested to explain the ability of American cranberry to reduce urinary tract infections. The first mechanism was credited to its biocide activity, which is made possible by the production of various elements that can damage the uropathogenic bacteria. Other mechanism to its antiviral activity through the negative regulation and interference with others virulence factors associated to stress tolerance and survival in the urinary tract [18].

Ventura [32] has shown the report of a patient who has suffered from recurring urinary infections for 20 years and made use of oral Ciprofloxacin for three days, later finding out they had *E. coli* following urine culture and resistance to the antibiotic they were using. Therefore, it was suggested to the patient to have treatment with cranberry extract.

The treatment described by Ventura [32] consisted of the intake of 5 g of the fruit, the equivalent amount to 18 mg of proanthocyanidins, dissolved in 250 mL of water, twice a day for 20 days, with follow-up attention. Six days after the end of treatment, the patient was asymptomatic, urine culture was normal, and antibiogram was negative. Thirteen weeks later, the patient was still asymptomatic, and urine cultures remained negative regarding bacterial growth.

4. Conclusion

The information obtained through the studied papers allows to conclude that the use of *V. macrocarpon* is an effective therapy in cases of urinary tract infections and has prophylactic action in cases of recurrent infections due to proanthocyanidins and anthocyanidins, which impair bacterial adherence to the urinary tract wall, and antiviral action that causes bacterial weakening and inactivation.

Finally, this natural product is promising for the treatment of urinary infections caused by gram-negative and -positive bacteria.

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