

# Therapeutic effect of cranberry active components on E.coli urinary tract adhesions: A review

## Abstract

Cranberry (*Vaccinium* spp.) has been used by North American Indians to treat many medicinal properties. It is also recommended for the treatment of urinary tract infection (UTI) which is caused by adhesion of bacteria called *Escherichia coli*. We conducted this meta-analysis to assess the effect of cranberry in preventing the adhesion of *E. coli* in the urinary tract. Cranberry appears to work by inhibiting the adhesion of type 1 and P-fimbriated *Escherichia coli* to the uroepithelium, thus hinder the colonization and upcoming infections. Adhesion is prevented by 2 ingredients of cranberries: laevulose that prevents binding of type 1 fimbriae and pro-anthocyanidins, which prevents p- fimbriae binding. The anti-adherent effect began in 2 hours and remains for up to 10 hours after consumption. These results suggest that cranberry can be an effective in preventing and treating urinary tract infections; however, larger high-quality studies are needed to confirm these findings.

**Keywords:** Urinary Tract Infection; Cranberry; Anti-adherence; Prevention; *Escherichia coli*.

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Shahnai Basharat,<sup>1</sup> Ayesha Khalid,<sup>2</sup> Aiman Sohail,<sup>2</sup> Khadija Abdul Wahab,<sup>2</sup> Muhammad Ali,<sup>3</sup> Areesha Omer,<sup>2</sup> Aleena Qureshi,<sup>2</sup> Raida Nadeem,<sup>2</sup> Huma Sajjad,<sup>2</sup> Sanabil Anmol<sup>4</sup>

<sup>1</sup>Associate Professor, PhD Human Nutrition and dietetics, University of Lahore, Pakistan

<sup>2</sup>Doctor of Diet & Nutrition sciences, University of Lahore, Pakistan

<sup>3</sup>Research Assistant, Newfoundland University, Canada

<sup>4</sup>Dietitian/Nutritionist, PAF Hospital, Islamabad

**Correspondence:** Sanabil Anmol, Dietitian/Nutritionist, PAF Hospital, Islamabad, Tel +923018119228, Email sanabilanmol97@gmail.com

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## Introduction

A Urinary tract infection (UTI) is an infection in any part of urinary system including kidneys, ureters, bladder and urethra.<sup>1</sup> UTIs are almost 50 times more common in grown-up females than males because women have shorter urethras that permit bacteria easily to climb the bladder. The risk factors that put the women to repeated UTIs are antibiotic resistance, menopause, sexual intercourse, bacterial attack and the use of birth control pills.<sup>2</sup> Urinary tract infections are caused by a number of microbes but mainly by enterococcus faecalis, escherichia, proteus mirabilis, klebsiella pneumoniae, and staphylococcus saprophyticus.<sup>3</sup>

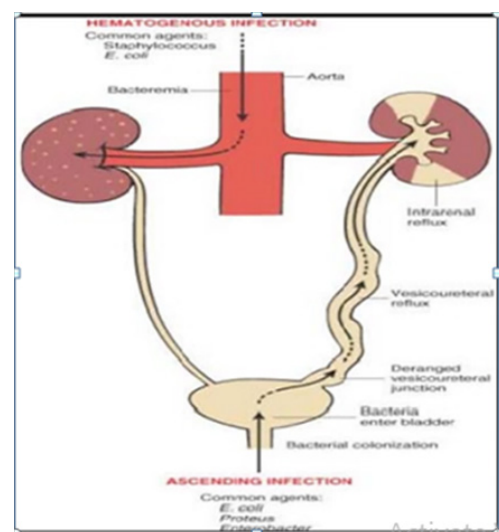
The initial phase in an infection is the colonization of the peri-urethral tissues, followed by the entrance of bacteria through the urethra. The next phase is the attachment of bacteria to the urethra and walls of bladder and started to grow.<sup>4</sup> The people at more risk are infants, pregnant women, the old people, patients with catheters, diabetic patients, patients with multiple sclerosis or acquired HIV and patients with any complicated urologic diseases.<sup>5</sup> About 1 in 3 women have affected 1 time by UTI by 24 years and needs antibiotic treatment. But the more use of antibiotic can cause antibiotic resistance.<sup>6</sup> Therefore, non-antibiotic methods are gaining much interest to prevent UTI especially for mild cases.<sup>7</sup> Almost 50% of all females encounter UTI one time in their lifetime.<sup>8</sup>

## Cranberry

The scientific name for Cranberry plant is *Vaccinium macrocarpon*. Local Americans were the first one who utilize cranberries for the treatment. Cranberries are used for a number of complaints like fever, blood disorders, liver problems, and stomach diseases.<sup>9</sup>

Cranberry or cranberry juice help to reduce the symptoms of UTI by reducing the inflammation as a natural defense against bacterial attack.<sup>10</sup> Cranberry juice enriched with Omega-3 helps in reduction of Total cholesterol and LDL cholesterol.<sup>11</sup> And also improve the plasma lipid profile & insulin resistance.<sup>12</sup> Polyphenols present in Cranberry have effective role as anti-inflammatory, anti-allergic, antifungal,

antiviral, and antihypertensive properties, and minimize the chances of metabolic diseases.<sup>13</sup>



## Composition

Cranberries contain water more than 80% and almost 10% carbohydrates. The other components of cranberry are flavonoids, catechins, anthocyanins, polyphenols, triterpenoids, organic acids, and a little amount of Vitamin C.<sup>14</sup> The organic acids present are malic, citric and quinic acids, with very little quantity of benzoic acid and glucuronic acids.<sup>15</sup> The other compounds like anthocyanidins and pro-anthocyanidins (PAC) are only found in vaccinium berries and these give natural protection against microorganisms. The cranberries are consumed like fresh berries, whole berries, juices (usually 10-25% pure juice), powdered form and capsules.<sup>16</sup>

## Health Benefits related to UTI

There are two compounds that are responsible to block attachment of *E. coli* in UTI patients. First is fructose, which restrains mannose-

sensitive fimbrial adhesions; the second is a high atomic weight compound that restrains the mannose-resistant adhesions of uropathogenic *E. coli*. Almost all fruit juices contain first compound i.e., fructose, but only Vaccinium berries juices (i.e., cranberries and blueberries) contain this extraordinary second compound, later named as “pro-anthocyanidin.” Interestingly, pro-anthocyanidin is strongly effective against mannose-resistant adhesins that is produced by *E. coli* present in Urine samples but show very light effect against *E. coli* present in fecal samples.<sup>17</sup> Proanthocyanins in cranberry have important role in reduction of bacterial adhesion, urine PH and chances of UTI.<sup>18</sup>

Cranberry is a natural alternative used to prevent the severity & occurrence of UTI and decreases the adherence of pathogen to urinary tract.<sup>19</sup> Regular consumption of cranberry juice was also effective in patients with UTI caused by antibiotic-resistant.<sup>20</sup> The metabolites of microbial extract in cranberry polyphenols have effective role in preventing the adherence of bacterial pathogen to urinary tract epithelium, colonization of bacteria and occurrence of urinary tract infection.<sup>21</sup> The anti-adhesive property of cranberries probably helps to prevent UTI in 2 ways: first, it directly prevents *E. coli* from adhering to uroepithelial cells; and second, it chooses less invasive bacterial strains in the stool. The anti-adherent effect began in 2 hours and remains for up to 10 hours after consuming.<sup>22</sup> Cranberry polyphenol (flavonoids & phenolic acid) and gut bacteria have a “2-way interaction” against UTI. Gut microbiome is associated with metabolism of cranberry polyphenol, and cranberry polyphenols are involved in prevention of uro-pathogens colonization in intestine.<sup>23</sup>

## Review of literature

### Routes of Infection

**Ascending Route:** Uro-pathogen enters the urinary tract by urethra into the bladder which is called the ascending route.<sup>23</sup>

**Hematogenous Route:** Staphylococcus aureus bacteremia or candida fungaemia arise in immune-suppressed patients and sometimes, the renal parenchyma can be ruptured.<sup>24</sup>

**Lymphatic Route:** With the help of lymphatics, bacteria penetrate in the urinary tract with adjoining organ.<sup>25</sup> The clinical situations related with the lymphatic route are retroperitoneal abscesses and chronic bowel infections.<sup>26</sup>

### Occurrence of urinary tract infection

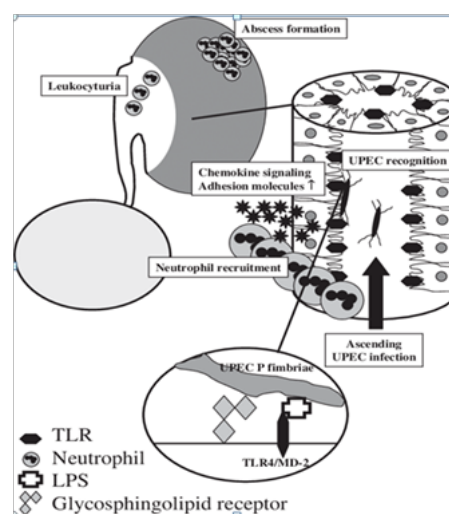
As a result of relationship between uro-pathogen and host, UTIs occur. Their pathophysiology requires a multiple step process.<sup>27</sup> Initially, the uro-pathogen binds to the epithelial surface. Then it subsequently colonizes and spreads across the mucosa which causes the tissue to be damaged. After the early colonization period, the pathogens can then enter into the urinary bladder which results in symptomatic or asymptomatic bacteriuria.<sup>28</sup>

Polynephritis and renal dysfunction can contribute to further progression of this process. The unique virulence factors living on the membrane of uropathogen are responsible for bacteria resisting the host defense mechanism.<sup>29</sup> Recently, bacterial adhesins and their linked epithelial binding sites have been recognized.<sup>30</sup>

### Mechanism

Cranberry includes citric acid, malic acid and quinic acid with small amount of benzoic acid, ascorbic acid and glucuronic acids

those shows antibacterial properties and acidify the urine by excreting large amount of hippuric acid.<sup>31</sup> Uropathogenic *E. coli* attaches to uro-epithelia in the lower UT and towards renal tubular epithelial cells in the kidney by the connection through P-fimbriae and other aspects.<sup>32</sup> Crossconnection of toll-like receptor 4 with glycol-sphingolipid receptors decrease the lack of cluster-of-differentiation 14 in these epithelia. Ligation of the lipopolysaccharide's receptor complex creates local countenance of chemokine ligand 2/Interleukin 8. The adjacent endothelial cells of peritubular capillaries get activated and up regulated. Local neutrophil conscription, renal abscess formation and leukocyturia are followed with linkage molecules and chemokines.<sup>33</sup> The pro-anthocyanidins has an active down regulation action on the aptness, virulence and resistance of antibiotic in the extended spectrum beta-lactamase (ESBL) producing the strain of *E. coli* CTX-M 15.<sup>34</sup> Cranberry powder is a powerful agent which enables the growth and replication of bacteria.<sup>35</sup> The rest gets flushed as the waste from the body.<sup>36</sup>

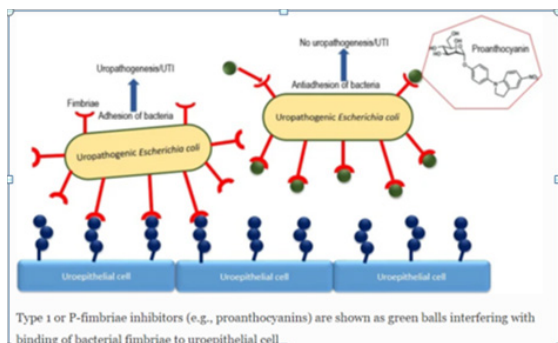


A significant element of *Escherichia coli* is resistance to host cell. The adhesin proteins are known as pilus and fimbriae.<sup>37</sup> Attachment of bacteria is achieved by lectins attachment discovered by target cells of these pilus of carbs of host cell. Pilus are tiny strands which allow to bind bacteria to cells; sometimes some protein is mannose-resistant or mannose-sensitive. Bacterial binding to urothelium is enabled by the mannose-sensitive pili, termed type 1 pili; the pilus are hindered due to fructose.<sup>38</sup> The present theory is that cranberries function mainly by prohibiting the urothelium from adhering to type 1 pili and Pap strains. Bacteria can't affect the surface of mucosa without attachment.<sup>39</sup>

In micro-organism study binding are affected by 2 ingredients of cranberries: laevulose, that prevents binding of type 1 fimbriae and proanthocyanidins, which prevents p-filli binding. A receptor ligand attachment is supported by hydrophobic nature, that occurs as attachment of a protein's bacterial fimbriae edges to uro epithelium layer. One underlying strategy is that the cranberry metabolites such as propionic acid, hippuric acid and catechol-O-sulphate that profitably suppresses the adhesion that function like binding site analogues via connecting the fimbriae edges to target tissues.<sup>40</sup>

Another In Vitro study of cranberry action decrease of p-filli function in *Escherichia coli* by altering surface compounds composition. It has been shown that *Vaccinium subg. Oxycoccus* (cranberries) reduces the infectivity strains of *Escherichia coli*. More study shows that extract of cranberries has many different effects on p-filli. In present research

PH neutralised juice of cranberries induced structural changes in p-filli and *Escherichia coli* by decreasing volume and size. In spite of suggested data, cranberries have active moieties. The route from digestion to urinary system is not clearly mentioned. Few authors think that in vivo, Proanthocyanins wasn't activate as they have large particles that cause difficulty in GIT absorption.<sup>41</sup>



In human colorectal adenocarcinoma cell, the structure of proanthocyanins is porous as they might get whole absorbed. Some studies evaluate human excretion of proanthocyanin. In urinary tract and large bowel there are other chances that proanthocyanins may be active, some strains bind and *E. coli* separates. By that means, giving them non sticking agents before they introduce in urinary tract. They stop the growth of bacteria in large bowel.<sup>42</sup> After consuming twelve hundred milli grams of dry juice of cranberry, there were decreased level of anthocyanin and pro anthocyanin in urine output. As experimenting in the studies, it was concluded that only 0.078 of five percent of human anthocyanin were excreted out after consuming the juice of cranberry.<sup>43</sup> After three to six hours of juice intake, high concentration of anthocyanins was observed and in first twelve hours the urine output was completed.<sup>44</sup> Many investigations mentioned *E. coli* and its strains, but in in vitro study shows hindrance of attaching with gram negative proteobacteria, *pseudomonas aeruginosa*, *enterococcus*, *staphylococcus*, *salmonella* and *klebsiella*.<sup>45</sup>

In spite of all available data, it is not proved that the process of absorption, metabolism and excretion of juice of cranberries in urine output is not effective from protecting any bacterial growth.

## Evidenced based effect of cranberry on UTI

### Original Research

In 2016, 185 women with recent history of UTI came across and were provided with low calorie cranberry (240 ml) for the time period of 6 months. After 6 months, it was observed that the women reported the culture-confirmed UTI ( $\geq 105$  CFU/mL) as a sub-analysis.<sup>46</sup> After that in 2015, 89 women with recent history of UTI came across and were provided with Cranberry fruit powder capsule (500 mg) for the time period of 6 months. After 6 months, it was observed that after 4 trials of the consumption of this powder confirmed bacteria in urine. But the gateway was different from  $\geq 103$  (31) to  $\geq 105$  CFU/mL.<sup>47</sup> Then in 2013, 107 women with already resolved UTI came across and were provided with Vacciniumsubg. Oxycoccus juice (125ml/d) for the time period of 6 months. After 6 months, it was observed that results were not shown until the antibiotics were administered after UTI diagnosis.<sup>48</sup> Then in 2012, 25 women with recurrent UTI came across and were provided with Vaccinium-macrocarpon, Vaccinium oxycoccus, Vaccinium-microcarpum, and Vaccinium for the time period of 6 months. After 6 months, it was observed that components of Vacciniumsubg. Oxycoccus has beneficial protective results for Urinary tract infection.<sup>49</sup> In 2014, it was seen that 25 young and

middle age women came across and were provided with Vaccinium-macrocarpon for the time period of 6 months. After 6 months, it was observed that preventive role of Vacciniumsubg. Oxycoccus for young and middle age women are more powerful than other groups.<sup>50</sup>

In 2013, 25 women with urinary tract infection came across and were provided with Vaccinium-macrocarpon for the time period of 6 months. After 6 months, it was observed that Vacciniumsubg. Oxycoccus juices or beverage mainly prevent UTI, but researches are less.<sup>51</sup> In 2014, it was seen that 25 females with recurrent UTI came across and were provided with Vacciniumsubg. Oxycoccus capsules on daily basis for the time period of 6 months. After 6 months, it was observed that Antibiotic has strong effect than cranberry for UTI but Vacciniumsubg. Oxycoccus lowers UTI with less cost.<sup>52</sup> In 2013, it was observed that 25 adults with UTI were under consideration and were given Cranberry liquid / juice for almost 6 months of time. After that time period, the results were such as cranberry juices & pills lower the risk for UTI than placebo.<sup>53,54</sup>

## Conclusion

It is concluded that the juice of cranberries treats the urinary tract infection equated to placebo. It is affected for temporary diminishing the occurrence of the urinary tract infections. The cranberry juice has a plausibility factor which contemporaneous inhibits the P-fimbriated *Escherichia coli* strains adhesion. Knowingly different pharmacological drugs like antibiotics have side effects so nutritional sources are better cure of such averting infections.

## Conflicts of interests

There is no specific conflict of interests.

## Acknowledgments

There are no specific acknowledgments.

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