

# *In vitro* Evidence of Dose-dependent Decrease of Uropathogenic *E. coli* after Consuming Commercial Cranberry Capsules in Type 2 Diabetic Premenopausal Adult Women: A Literature Review

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## ABSTRACT

Urinary tract infections (UTIs) arise due to the invasion of pathogenic microorganisms in the urinary tract, resulting in inflammatory reactions in the epithelial linings of the urinary tract. The presence of pathogenic bacteria colonization more than 100,000 microbes of the same strain per milliliter of the urine in two consecutive urine samples is said to be a positive specimen for infection.

An electronic search was conducted by using the PubMed database of the library of Unitech Institute of Technology with key research terms "cranberry," "urinary tract infections," and "type 2 diabetes." These specifications resulted in a number of research studies and review articles, but for this literature review, only random controlled trials, comparative studies, pilot studies, and controlled clinical trials were considered. A total of twelve studies were selected for this review, out of which nine were randomized controlled clinical trials, two were co-relational or observational studies, and one was pilot study. The search was not limited to studies on women; rather, an extensive search was carried out in other subpopulations like children, older age-group people, pregnant women, males, and healthy females that were carried out and published between 2008 and 2014. The random controlled trials in the present review provide level 2 evidence, observational studies provide level 4 evidence, and pilot studies provide level 6 evidence. These levels of evidences are mentioned according to the guidelines provided by Polit and Beck.

**Keywords:** Cranberry, Premenopausal, Type 2 diabetes, Urinary tract infection.

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## BACKGROUND

The positive specimen for infection resulting in inflammatory responses in the urinary tract are common and frequent in people suffering from type 2 diabetes besides other infections according to several studies.<sup>1-5</sup> Various contributing factors that predispose a type 2 diabetic patient to UTI include impairment in the immune system, insufficient metabolic control of diabetes<sup>6-9</sup>, and incomplete emptying of the bladder because of diabetic neuropathy.<sup>6,10</sup> The classification of UTI can be broadly stated according to the site of infection.<sup>11</sup>

Blood infection in type 2 diabetes can range from asymptomatic bacteriuria to lower urinary tract infection in the form of cystitis, pyelonephritis, etc. Even more serious complications like renal sepsis or necrosis are also observed more frequently in type 2 diabetes compared to other subpopulations.<sup>12,13</sup> Patients with type 2 diabetes are prone to develop resistant pathogenesis, specially  $\beta$ -lactamase-positive enterobacteria, carbapenem-resistant enterobacteria, etc. The high risk of UTI in type 2 diabetes along with the high rates of antibiotic prescribing further increases the risk of development of resistant strains of urinary pathogens.

## DIAGNOSIS AND TREATMENT

UTIs can be classified according to the mode or route of infection. It can be catheter acquired or community acquired. The other predisposing risk factors contributing to these infections include pregnancy, diabetes mellitus, type 2 diabetes (suppressing the immune system), and hormonal changes during menopause,

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urinary tract abnormalities like enlarged prostate, kidney stones and other factors like use of birth control agents, anatomical characteristics in women like short urethra. Statistical figures are suggested by Schappert and Burt.<sup>14</sup> One million of the visits in the emergency department, ten thousand of the admission in the hospital, and seven million visits in the clinics are because of community-acquired urinary tract infections.

The UTI prevalence rates in females are also found to be 50 times more than males.<sup>15</sup> It is suggested that asymptomatic bacteriuria is more common in women because of anatomical characteristics like small size of the urethra and its proximity to the perianal area where there is an abundance of enteric bacteria.<sup>16</sup> Furthermore, pregnancy also increases susceptibility for these infections, especially in the 6th and 24th week of gestation<sup>17</sup> often progressing to complications

like pyelonephritis leading to outcomes like premature deliveries or low birth weight babies.<sup>18</sup>

According to the Ministry of Health, New Zealand, diabetes is the fastest growing health concern, and together with cardiovascular diseases, it is the main factor contributing to more death every year. The data generated by the Ministry of Health estimate that over 24,000 people in New Zealand are diagnosed with type 2 diabetes and approximately 100,000 people are unaware of this underlining health problem from which they are affected. It is found to be more frequently present in Maori and Pacific Islander populations, where the data show 11.6% cases in Pacific Islander, 12.4% cases in South Asian ethnic groups, and 7.8% in Maori people. The obesity-related type 2 diabetic population is growing every year; it is evident by the data, which suggest an estimate of 42% of adult Maori and 63.7% of Pacific Islanders is categorized as obese. The complications related to diabetes like urine infections, neuropathy, and skin infections are one of the leading causes of rise in not only the morbidity and mortality but also pose a burden on the Nation's economy.

An observational study in patients with type 2 diabetes in the UK found UTI incident rates higher in diabetic patients than in other general populations.<sup>19</sup> An estimate ranging from 8 to 27% of a symptomatic bacteriuria is reported in type 2 diabetes by many other studies.<sup>6,8,20</sup> Diabetes is among one of the risk factors for urinary tract infections, others being catheterization, urinary retention intercourse, etc. Many potential mechanisms that are distinct in type 2 diabetes responsible for the increased risk of UTI as suggested by some of the studies include increased level of renal parenchymal glucose, presence of favorable medium for the growth, and multiplication of pathogenic strains.<sup>21,22</sup> Diabetic women were found to be 6 to 15 times more hospitalized than non-diabetic women according to a Canadian study. In addition to this, according to Freeman et al.<sup>23</sup> and Williamson et al.,<sup>24</sup> for the high endemicity of extended-spectrum  $\beta$ -lactamase enterobacteriaceae (ESBL-E) found in New Zealand in community-onset urinary infections, the treatment is posing a great therapeutic challenge. This fact is also confirmed by the data generated by the laboratory, New Zealand in 2005, which described an expenditure of \$12.5 million for performing urine cultures in the hospitals.

The standard treatment for UTI is the antimicrobial therapy, which includes medicines like amoxicillin, quinolones, and trimethoprim. These empirical medications are not only expensive but also often accompanied by unnecessary side effects. This widespread antibiotic prescribing has raised the concerns globally regarding the development of antibiotic-resistant strains of uropathogens, especially *Escherichia coli*. Thus, this fact notifies us to consider some non-antibiotic or alternative method to treat or prevent urinary infections.

### Treatment with Vaccinum Macrocarpon

Cranberry and various products derived from it have been used as a complementary and alternative therapy in the prevention and treatment of UTI over the decades. There are many suggested theories explained for its action. In 1920, acidification of the urine after its consumption is considered as its mode of action, whereas Liu et al.<sup>25</sup> described two of its constituents, i.e., fructose and an unknown polymeric compound with their antibacterial antiadherence activity as a possible way of action. Despite the limited and varied knowledge of the science behind the cranberries action in urine infections, it continues to be famously used in the prophylaxis of these infections.

According to the Cochrane meta-analysis, it was stated that there are evidences of prevention of recurrent UTI in women after cranberry consumption, but it did not mention its effectiveness in other subpopulations.<sup>15</sup> This shows that though the cranberry prophylaxis is a popular practice in the management of urine infections, the clinical significance in urine infections, especially in a population of type 2 diabetes remain inconclusive. Keeping this in mind, the aim of this review is to examine the literatures and studies since 2008 in order to identify the usefulness of cranberry and its products in the prophylaxis of urine infections, particularly in women population affected with type 2 diabetes. This literature will also try to determine the gaps in other research studies conducted using cranberry products. Jepson and Craig<sup>15</sup> conducted a meta-analysis in which an effort was made to systematically combine the results from various studies. It was concluded from this meta-analysis that more large, randomized, double-blind placebo-controlled studies are required in order to identify the mode of action of cranberry product. It also identified the need for finding the optimum dose and mode of its administration for achieving its maximum protective effect. Moreover, previous studies have also shown high dropout rates where cranberry is used as an intervention. All these facts together call for additional evidence-based studies, which can address these gaps.

It is essential to produce evidence-based knowledge to healthcare practitioners like general practitioners, nurses, and pharmacists, who play an integral role in educating and encouraging the valid use of cranberry products in the prophylaxis of urinary tract infections to the patients. Thus, combining the patient's cultural knowledge together with the recent research in clinical practice should be used as a guiding tool in all educational efforts surrounding the use of cranberry or cranberry-based products in the management of UTI.

### SYNOPSIS OF THE EVIDENCES

Twelve studies that utilized cranberry juice and capsules in various doses for treatment or prevention of UTIs were reviewed, and mixed results were found. The levels of evidences in the selected studies are mentioned according to the guideline provided by Polit and Beck.<sup>3</sup> Six studies that utilized cranberry capsules as the intervention: One was an observational study, the other was a pilot study, and the rest four were randomized clinical trials (RCTs). The other six studies that were reviewed used cranberry juice as the intervention and were also randomized control studies. The comparisons in all these studies were made against placebo. The results of these studies indicated positive outcomes (decrease in the urine infection) in trials conducted by McMurdo et al.,<sup>26</sup> while results from Lee et al.<sup>27</sup> showed no differences in the infection rates. The study of cranberry intervention in older age-group<sup>28</sup> found the consumption of cranberry useful and effective, especially in those who are at high risk of UTI, whereas Sathosi et al.<sup>29</sup> did not find any difference in the elderly women population. Studies conducted among children<sup>30,31</sup> and the result findings with cranberry juice intervention were found to be contraindicatory. The former study showed a positive influence of the intervention in UTIs, whereas the latter showed no significant difference in the first UTI recurrence in children. The intervention of cranberry juice in pregnant women showed positive results in the prevention of UTIs.<sup>32</sup> The randomized double-blind study<sup>33</sup> with the intervention of dry form of cranberry in women population also suggested a significant effect of cranberry in those

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**Table 1:**

Author	Evidence type	Sample	Method	Result	Comment
Sathosi et al. <sup>29</sup>	Double-blind placebo-controlled trial (RCT)	n = 150 (age = 20–79 years), with acute cystitis with past history of multiple relapses	Cranberry juice (UR65), 40 mg of PAC/125 mL vs placebo (dose = 1 mL once daily for 24 weeks)	No significant difference in the relapse rate of UTI between these two groups	Limited number of participants analyzed in the final stages Sample size for young women was small Duration of study in elderly women was only one month Primary outcome was to determine the frequency and not the prevention Positive outcome in the old age-group
Howell et al. <sup>33</sup>	RCT	32 females (age > 18)	Cranberry powder (18–36 mg of PAC/day/placebo)	Significant dose-dependent antiadhesion activity was observed in the cranberry group	Good study that revealed a dose-/time-dependent effect More such studies are needed to correlate such activities in the clinical UTIs
Monique et al. <sup>28</sup>	RCT	LTCF residence (women), n = 928 (total), n = 516 (high UTI risk group) n = 100 (placebo group), and n = 412 (low UTI risk group, median age 84)	Cranberry capsules 500 mg PAC/placebo/twice daily for 12 months	In high UTI risk group, the incidence of clinically defined UTI was found to be lower with the intervention group than with the placebo group (n = 100), whereas in n = 412 (low UTI risk group), no differences were observed	High adherence rate found only in the fifth month so the results cannot be generalized Good evidence as far as tolerability is concerned as very negligible side effects were observed No treatment effect in high UTI risk group in spite of big sample size Optimum dose of cranberry is not clear as the recommended dose of 3 capsules (36 mg PAC), the daily use of 18 mg seemed insufficient Lacks generalizability to older people living at home
Ferrara et al. <sup>30</sup>	RCT	84 female children with recurrent UTIs, n = 28 (intervention group), n = 27 (lactobacillus group), n = 29 (control group)	50 mL juice daily/100 mL of lactobacillus GG probiotic/control (5 days/month for 6 months)	Reduced reoccurrence of UTI compared to the placebo group and lactobacillus group	Underpowered study
Philippe et al. <sup>36</sup>	RCT	171 adults	Cranberry extract (36 mg pack/day twice daily for one year). Placebo	No difference in time to first symptomatic UTI across one year	Underpowered study due to high withdrawal rates owing to poor compliance No evidence of standardization of the cranberry; comparing it with similar studies is difficult

Contd...



Contd...	Evidence type	Sample	Method	Result	Comment
Burleigh et al. <sup>34</sup>	Observational studies	n = 20 women with recurrent UTI	One serving dry cranberry (42 g daily for 2 weeks)	Significant reduction in first UTI reoccurrence in the intervention group	Small sample size Comparison of the cranberry group with the control group from the previous study
Lee et al. <sup>27</sup>	Pilot study	n = 20 patients without urine infection	Examination of urine sample prior and post-ingestion of 900 mg cranberry/control sample for antimicrobial activities at 2/4/6 hrs	No evidence of antimicrobial activity for <i>E. coli</i>	No evidence of exact mechanism for antimicrobial activity after intervention No evidence of relationship between the dose and action Antimicrobial activity using different forms and doses still need to be explored
McMurdo et al. <sup>26</sup>	RCT	n = 376 (old patients), age 60 years (both sexes), without recurrent UTI	150 mL of cranberry juice vs placebo twice daily	Significantly fewer infections in the cranberry group	Underpowered study (infection rate observed was lower than anticipated) Study showed acceptability in older people Large trials are required to establish the effect of intervention in the prevention of UTI in elderly patient
Salo et al. <sup>29</sup>	RCT	n = 263 children, age 1–16 years with UTI	5 mL/kg–300 mL/day cranberry/placebo twice daily doses for 6 months	No statistically significant difference in the first UTI reoccurrence, though the recurrence number significantly reduced	Compliance in the cranberry group was poor High number of dropouts This study detracts from the preventive efficacy of cranberry juice and its usefulness in clinical practice Samples were collected at the start and end of the trial only
Wing et al. <sup>32</sup>	RCT	N = 188 (total), n = 58 (group 1), n = 67 (group 2), n = 63 (group 3) pregnant subjects < 16 weeks with asymptomatic bacteriuria	240 mL cranberry juice/, Placebo. Group 1 = cranberry thrice, group 2 = cranberry once, placebo 2 times, group 3 = placebo thrice	57 and 40% reduction in the frequency of asymptomatic bacteriuria in group 1 and group 2, respectively	Low compliance, tolerability leading to 30% of the dropouts Poor tolerance led to dose modification More large clinical trials are needed
Lavigne et al. <sup>37</sup>	RCT	n = 8 healthy females, age 30–40 years	Administration of three capsules of cranberry (108 mg) vs three capsules of placebo vs one capsule of cranberry (36 mg) and two capsules of placebo	The first urine after 12 hr of consumption was collected for the <i>in vitro</i> study of the bacterial addition activity. Significant reduction in the bacterial adherence was found with 108 and 36 mg of cranberry as compared to placebo	Lack of quantification of PAC Lack of standardization Immunity changes are not explained An interesting approach but requires more analytical depth

suffering from recurrent UTI, whereas on the contrary, similar population studies in women<sup>34</sup> did not find any statistical benefit of cranberry in the prevention of UTI. A similar study in women,<sup>35</sup> but in a different pathology, cervical cancer, found an effect with using cranberry juice as an intervention. The randomized placebo-controlled trial by Phillips et al.<sup>36</sup> failed to identify the influence of cranberry extract on adults suffering from multiple sclerosis when comparing it to placebo. Only few *in vitro* studies have been observed in the cranberry interventional studies. One of the special types of *in vitro* studies by Howell et al.<sup>33</sup> and by Lavigne et al.<sup>37</sup> suggested antibacterial antiadhesion activities of cranberry as the potential reason for its use in UTI. One such study clinically proved the bacterial antiadherence properties of cranberry using two different types of doses, whereas another pilot study using similar mechanism showed divergent facts where antimicrobial activities after cranberry consumption were noted only against *Klebsiella pneumoniae* and not against *E. coli*.<sup>37</sup> According to Howell et al.,<sup>33</sup> a lower dose of 18 mg was found to be ineffective, whereas a higher dose of 72 mg was found to be more efficient producing 100% antiadhesion activity. But, this study was conducted on healthy volunteers with no signs and symptoms of urinary infections. The present recommended dose of cranberry, i.e., 500 mg with 36 mg PAC in UTI, is highly arguable as far as PAC concentration and its action on the uropathogens are concerned as evident by the results from these different reviewed studies. The following table displays the information:

## SUMMARY

On reviewing various abovementioned studies, the clear consensus of cranberry and its products for the prevention of UTIs cannot be validated; although majority of the trials (9/12) showed its positive effect, the overall action is still not clear. This might be due to a number of limitations found in these trials like small sample size, high withdrawal rate, short treatment period, insufficient result outcomes to claim generalizability, use of control groups from other previous studies, inclusion of both sexes, lack of standardization of cranberry products making it difficult to determine the optimal therapeutic dose, no clarity on the mode of administration, and improper blinding reporting of the adversarial effects on insensitive groups.

There is no evidence-based study found in determining the efficacy of cranberry products and urine infections in women affected with type 2 diabetes. The evidences regarding the potential effectiveness of cranberry products in UTI prophylaxis or treatment in women population are also found to be arguable. Even the *in vitro* studies are found to be also limited. Thus, in order to make clinical decisions, more dose-dependent evidence-based large-scale trials are needed. There is much-needed requirement of conducting a trial, which not only suggests a potential mechanism of the action of its constituents like proanthocyanidins but also gives an idea of its concentration to be effectively used, especially in these groups of infections.

## INFERENCES FOR PRACTICE

While discussing the management options with females who are prediagnosed or unknowingly suffer from urinary infections as a complication of type 2 diabetes, healthcare providers can recommend cranberry or its products as an alternative or a complimentary prophylactic product, supporting this recommendation with the evidences, which provides a positive result and no other serious

adversarial outcomes. However, the treatment should not be replaced with antibiotics until an effective dose, type, and mode of administration are clearly confirmed by further trials; therefore, till that time, it is imperative to consider the patients' personal beliefs and preferences for the treatment so that the best healthcare benefit can be provided in the interest of the sufferers.

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