



The Effectiveness of Cranberry in Pregnancy: An Analysis

Anu Chopra¹ and Shiwani Singh^{2*}

¹Department of Immunochemistry Laboratory, National Institute of Immunology, New Delhi, India.

²Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India.

(Corresponding author: Shiwani Singh*)

(Received 25 June 2022; Accepted 27 August 2022)

(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: Cranberry products such as juice and extract are the most advised herbal medicine to prevent recurrent urinary tract infections (UTIs). It is believed that the active ingredient in cranberry prevents adherence of pathogens to the epithelial cells in the urogenital tract, thereby preventing infection. The incidence of UTIs is reported to be significantly higher in pregnant females. Owing to increasing antibiotic resistance and their side effects in pregnancy, it is of importance to identify and study the safety and efficacy of cranberry as herbal medicine for prevention or treatment of UTIs.

This review evaluates the studies and clinical trials available till date and identifies that high doses of cranberry are safe in pregnancy and may be effective in preventing UTIs. The major challenge faced by the trials is low compliance rate of the participants owing to the unpalatable taste of cranberry extract. A formulation with high levels of cranberry active ingredient and acceptable taste or better mode of administration would be an effective solution to improve compliance for future studies.

Key words: Cranberry, pregnancy, urinary tract infection, UTI, proanthocyanidin.

Use of cranberry in UTI

Cranberries (*Vaccinium macrocarpon*) have been classified as super-food owing to their high nutritive value and antioxidants. Various studies have highlighted their potential in managing systolic blood pressure, reducing Basal Metabolic index (BMI), improving levels of high density lipoprotein (HDL) [1]. A recent study has also shown regulation of blood sugar, down-regulation of inflammatory biomarkers and improvement in HDL levels in obese population upon consumption of single dose of low calorie cranberry beverage [2]. But the most important and well known use of cranberry lies in its prevention and treatment of urinary tract infections (UTIs) in both males and females [3,4]. Due to numerous adverse effects and development of resistance against antibiotics, identification of an effective alternative medication for treatment of UTI has always been an interesting area of research. Moreover, the choice of antibiotics is further limited in pregnancy owing to their teratogenic potential, it is of benefit to research for alternate measures to treat UTIs in females especially during pregnancy.

A number of studies have been conducted to understand the efficacy and mechanism of action of Cranberry as a treatment of UTI. Though not completely elucidated, it is believed that cranberry exerts a dose-dependent inhibition of the adherence of pathogens to the uroepithelial cells. This activity has been well demonstrated *in vitro*: cranberry juice is reported to inhibit adherence by at least 75% in over 60% of 77 clinical isolates of *Escherichia coli* [5]. This has also

now been proven *ex vivo* from the urine of individuals consuming cranberry juice or its extract [6].

Uropathogens such as *Escherichia coli* (*E. coli*) have hairlike fimbriae protruding from their surface. These fimbriae produce two types of adhesins - mannose sensitive and mannose resistant which help them to attach to the uroepithelial cell receptors and cause infection [7]. Cranberries have been found to contain fructose and proanthocyanidin which have a potent anti-adherent activity against *E. coli* [9]. Fructose has been found to inhibit mannose-sensitive fimbrial adhesins while proanthocyanidin exerts a strong inhibitory activity against mannose resistant adhesions [9, 10]. Further, a mild antimicrobial activity against stool *E. coli* probably helps select less adherent bacterial strains in stool thereby preventing UTI.

A number of randomised controlled trials and intent to treat trials have been conducted over the years to check for the efficacy of cranberry- juice and powdered or capsule form to prevent recurrence of UTI in susceptible population. A systematic review and meta-analysis based on 7 RCTs published in 2017 comprising of 1498 healthy women at the risk of UTI suggested that cranberry reduced the risk of UTI by 26% [11].

UTI and pregnancy. Increased incidence of urinary tract infections is a frequent problem associated with pregnancy. Its estimated incidence is approximately 20% in all pregnant women. Hormonal changes and compression of the ureters by the gravid uterus resulting in urinary stasis are the main reasons leading to the increased frequency of infections. *Escherichia coli* is the major pathogen responsible for UTI in both pregnant and non-pregnant women. UTI in pregnant

females could also lead to complications like pre term birth, low fetal birth weight, fetal intrauterine growth retardation (IUGR), pre eclampsia, and post-partum endocarditis [12, 13].

Cranberry for UTI in pregnancy. Since cranberry has studies demonstrating its safety and its effectiveness in preventing UTIs it is logical to study its utility in pregnant females as they are more prone to UTIs.

Safety profile of cranberry in pregnant females. The Norwegian Mother and Child Cohort Study (MoBa) and the records from the Medical Birth Registry of Norway (MBRN) were used to conduct a study to figure out the safety and efficacy of cranberry juice in pregnant women. This study analysed data from 68,522 women out of which 919 (1.3%) women had used cranberry while pregnant. The analysis of data showed that cranberry is completely safe in pregnancy and its consumption is not associated with any increased risk of congenital malformations, stillbirth/neonatal death, preterm delivery, low birth weight, small for gestational age, low Apgar score and neonatal infections. This was the first study to investigate the risk of any malformations owing to cranberry ingestion in pregnancy [14].

Another multinational cross section study conducted on 9483 women in 18 countries in five regions over the world was undertaken to evaluate the use of herbal medication in pregnancy. As per definition, cranberry was evaluated as a “safe to use” during pregnancy. The definition of a safe drug for the study was according to The Australian text book “The Essential Guide to Herbal Safety”, The European Medicines Agency and North America (Herbal Medicines in Pregnancy & Lactation), Botanical Safety Handbook, Botanical Medicine for Women’s Health, and Natural Medicines database [15].

Another systematic study analysed the literature for evidence on the use, safety and pharmacology of cranberry [16]. A survey conducted on 400 pregnant females identified that no adverse effects were observed in mother or fetus because of consumption of cranberry during pregnancy. The safety or harm of cranberry in lactation is unknown. The study concludes that cranberry can be valuable in pregnant females to prevent/treat UTIs due to its safety profile.

A systematic review published in 2018 also concluded that though some studies point towards the beneficial effects of cranberry but the effectiveness of study has been limited by sample size and increased withdrawal rates of the test subjects. The study highlights that because of its safety profile, pregnant females may consume cranberry juice to prevent UTIs as a part of self-care routine [17].

Effectiveness of Cranberry in pregnant females. A randomised, controlled pilot study was published by Wing *et al.* [18] to study the effects of drinking cranberry juice in pregnancy. 188 pregnant females at less than 16 weeks of gestation were enrolled in the study and were randomly assigned to ingest 240ml bottle of either cranberry juice or placebo, at each meal (three-times daily) until delivery. The juice contained mean proanthocyanidin concentration of 106 mg per

bottle. The outcome was measured as the number of cases of bacteriuria – symptomatic or asymptomatic, acute cystitis or acute pyelonephritis.

It was observed that multiple daily dosing of cranberry juice resulted in 57% reduction in frequency of asymptomatic bacteriuria (ASB) and 41% reductions in the frequency and all UTIs in pregnant women. The study suggested a protective effect of cranberry ingestion against ASB and symptomatic UTIs in pregnancy. Though many females withdrew during the study due to gastrointestinal upset, it provided early evidence of any beneficial effect of cranberry juice.

Another randomised controlled trial conducted on 760 pregnant females compared the effects of ingestion of 250ml cranberry juice four times daily to equal amounts of water [19]. Even with a high withdrawal rate owing to gastrointestinal disturbance, a significant 70% reduction in incidence of UTI in pregnant females post cranberry juice consumption was observed as compared to water (32%). The study reported a protective effect of cranberry juice against UTI [19].

In order to overcome the limitation of unpalatable taste, another pilot study was conducted wherein instead of juice, cranberry capsules were used to ensure compliance in pregnant females [20]. The participants were instructed to ingest two cranberry or placebo capsules twice daily with meal. Each set of cranberry capsules was biochemically equivalent to one 250-mL dose of cranberry juice cocktail. 49 pregnant females were evaluated for compliance and tolerability of the drug as a primary outcome. The study though could not identify any significant benefit of cranberry in ASB prevention in pregnancy but highlighted on the increased compliance and tolerability as compared to juice formulation [20]. It offered an alternative approach for ingestion of cranberry other than juice formulation to overcome the obstacle of compliance and tolerability.

A preliminary study reported lowered levels of IL-6 in the urine of pregnant women taking multiple daily dosage of cranberry juice [21]. IL-6 is a pro inflammatory cytokine with increased levels reported in the urine of females suffering from UTI [22, 23]. Though the beneficial effect of this research needs to be further studied because of a smaller sample size, it may point towards the effectiveness of cranberry juice.

CONCLUSION

Cranberry juice is one of the most commonly used alternative measure to prevent or treat UTIs in females. A number of studies have reported its consumption to be completely safe during pregnancy with no adverse effects either in mother or fetus. Further, there are pilot studies which shown that cranberry may prove to be effective in preventing UTI in pregnancy. The effectiveness though proved by some studies has been questioned by the Cochrane review which reported a non-significant decrease in symptomatic UTIs over a period of 6-12 months [24]. However, recent studies have highlighted that a high dose of cranberry active ingredient is essential to have a statistically significant reduction in cases of bacteriuria [6]. It is believed that

many clinical trials considered for the Cochrane review may be under dosed. If future clinical trials are conducted with appropriate dosage, better clarity could be obtained to identify the effectiveness of cranberry in prevention of UTIs in pregnancy.

Compliance and tolerability are the major obstacles as the above mentioned trials reported a high withdrawal rate mostly due to gastrointestinal disturbances which can limit its use on grounds of acceptability to women.

FUTURE SCOPE

A limitation of cranberry juice seen in current studies was the high volume of juice that needed to be ingested [18, 19]. An alternative formulation such as tablet or powder which may contain the high (required) amount of the active ingredient without inducing any distaste can help in improving compliance and tolerability. Therefore, a high dose cranberry product which is palatable is essential to achieve the beneficial result of reduction in UTIs. This would greatly improve the sample size in a study and provide a better evidence on the effectiveness of cranberry in UTIs.

REFERENCES

[1]. Pourmasoumi, M., Hadi, A., Najafgholizadeh, A., Joukar, F., and Mansour-Ghanaei, F. (2020). The Effects of Cranberry on Cardiovascular Metabolic Risk Factors: A Systematic Review and Meta-Analysis. *Clinical nutrition (Edinburgh, Scotland)*, 39: 774–788.

[2]. Chew, B., Mathison, B., Kimble, L., McKay, D., Kaspar, K., Khoo, C., Chen, C. Y. O., and Blumberg, J. (2019). Chronic Consumption of a Low Calorie, High Polyphenol Cranberry Beverage Attenuates Inflammation and Improves Glucoregulation and HDL Cholesterol in Healthy Overweight Humans: A Randomized Controlled Trial. *European Journal of Nutrition*, 58: 1223–1235.

[3]. Eichhorst, A. M., Janke, J. K., and Mullen, T. M. (1997). The Therapeutic Value of Cranberries in Treating and Preventing Urinary Tract Infections. *Online Journal of Knowledge Synthesis for Nursing*, 4: 2.

[4]. Avorn, J., Monane, M., Gurwitz, J. H., Glynn, R. J., Chodnovskiy, I., and Lipsitz, L. A. (1994). Reduction of Bacteriuria and Pyuria after Ingestion of Cranberry Juice. *Journal of the American Medical Association*, 271: 751–754.

[5]. Sobota, A. E. (1984). Inhibition of Bacterial Adherence by Cranberry Juice: Potential Use for the Treatment of Urinary Tract Infections. *Journal of Urology*, 131: 1013–1016.

[6]. Davidson, E., Zimmermann, B. F., Jungfer, E., and Chrubasik-Hausmann, S. (2014). Prevention of Urinary Tract Infections with Vaccinium Products. *Phytotherapy Research PTR*, 28: 465–470.

[7]. Beachey, E. H. (1980). *Bacterial Adherence*; Chapman and Hall: London; New York.

[8]. Zafriri, D., Ofek, I., Adar, R., Pocino, M., and Sharon, N. (1989). Inhibitory Activity of Cranberry Juice on Adherence of Type 1 and Type P Fimbriated Escherichia Coli to Eucaryotic Cells. *Antimicrobial Agents and Chemotherapy*, 33: 92–98.

[9]. Ofek, I., Goldhar, J., and Sharon, N. (1996). Anti-Escherichia Coli Adhesin Activity of Cranberry and Blueberry Juices. *Advances in Experimental Medicine and Biology*, 408: 179–183.

[10]. Howell, A. B. (2007). Bioactive Compounds in Cranberries and Their Role in Prevention of Urinary Tract Infections. *Molecular Nutrition & Food Research*, 51: 732–737.

[11]. Fu, Z., Liska, D., Talan, D., and Chung, M. (2017). Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. *The Journal of Nutrition*, 147: 2282–2288.

[12]. Christensen, B. (2000). Which Antibiotics Are Appropriate for Treating Bacteriuria in Pregnancy? *The Journal of Antimicrobial Chemotherapy*, 46, Suppl A: 29–34.

[13]. Habak, P. J., and Griggs, J. (2022). Urinary Tract Infection In Pregnancy. In *StatPearls*; StatPearls Publishing: Treasure Island (FL).

[14]. Heitmann, K., Nordeng, H., and Holst, L. (2013). Pregnancy Outcome after Use of Cranberry in Pregnancy--the Norwegian Mother and Child Cohort Study. *BMC Complementary and Alternative Medicine*, 13: 345.

[15]. Kennedy, D. A., Lupattelli, A., Koren, G., and Nordeng, H. (2016). Safety Classification of Herbal Medicines Used in Pregnancy in a Multinational Study. *BMC Complementary and Alternative Medicine*, 16: 102.

[16]. Dugoua, J. J., Seely, D., Perri, D., Mills, E., and Koren, G. (2008). Safety and Efficacy of Cranberry (Vaccinium Macrocarpon) during Pregnancy and Lactation. *Canadian journal of clinical pharmacology*, 15: e80-86.

[17]. Ghouri, F., Hollywood, A., and Ryan, K. (2018). A Systematic Review of Non-Antibiotic Measures for the Prevention of Urinary Tract Infections in Pregnancy. *BMC Pregnancy Childbirth*, 18: 99.

[18]. Wing, D. A., Rumney, P. J., Preslicka, C. W., and Chung, J. (2008). H. Daily Cranberry Juice for the Prevention of Asymptomatic Bacteriuria in Pregnancy: A Randomized, Controlled Pilot Study. *Journal of Urology*, 180: 1367–1372.

[19]. F. Essadi, M. O., and Elmehashi (2010). POSTER SESSION 1 Thursday, 27 May 2010 11.30 a.m–03.00 p.m.

[20]. Wing, D. A., Rumney, P. J., Hindra, S., Guzman, L., Le, J., and Nageotte, M. (2015). Pilot Study to Evaluate Compliance and Tolerability of Cranberry Capsules in Pregnancy for the Prevention of Asymptomatic Bacteriuria. *Journal of alternative and complementary medicine*, 21: 700–706.

[21]. Wing, D. A., Rumney, P. J., Leu, S. Y., and Zaldivar, F. (2010). Comparison of Urinary Cytokines after Ingestion of Cranberry Juice Cocktail in Pregnant Subjects: A Pilot Study. *American Journal of Perinatology*, 27: 137–142.

[22]. Benson, M., Jodal, U., Agace, W., Hellström, M., Mårild, S., Rosberg, S., Sjöström, M., Wettergren, B., Jönsson, S., and Svanborg, C. (1996). Interleukin (IL)-6 and IL-8 in Children with Febrile Urinary Tract

Infection and Asymptomatic Bacteriuria. *Journal of Infectious Diseases*, 174: 1080–1084.

[23]. Benson, M., Jodal, U., Andreasson, A., Karlsson, A., Rydberg, J., and Svanborg, C. (1994). Interleukin 6 Response to Urinary Tract Infection in Childhood. *Pediatric Infectious Disease Journal*, 13: 612–616.

[24]. Jepson, R. G., Williams, G., and Craig, J. C. (2012). Cranberries for Preventing Urinary Tract Infections. *Cochrane Database of Systematic Reviews*, 10: CD001321.