

# The Evidence for the Safe Consumption of Cranberries with Warfarin Therapy

The health benefits of cranberries have been recognized for decades. For example, cranberries have been shown to help protect against urinary tract infections (UTIs) by preventing *E. coli* from adhering to the cells that line the urinary tract. This same effect may help prevent other types of infections involving host-tissue bacteria such as *H. pylori*, a major cause of gastric ulcers. In addition, the antioxidant properties of proanthocyanadins (PACs), a subclass of flavanoids, and other polyphenols - which are abundant in cranberries - may have a range of other health benefits including the support of cardiovascular health and reduction of the risk for some cancers. According to a recent USDA agricultural service report containing the results of the most comprehensive analysis on foods, cranberries scored among the highest of all commonly consumed fruits on the antioxidant scale.<sup>5,9</sup> Studies have concluded that these antioxidants may offer a natural defense on helping to lower LDL cholesterol, increasing HDL cholesterol, maintaining healthy blood pressure levels and protecting endothelial cells from oxidative and inflammatory injury.

Recent case reports primarily in the UK suggested that cranberries may interact with warfarin (Coumadin®). However, well-controlled clinical studies evaluating the pharmacokinetic and pharmacodynamic effects of cranberry consumption on warfarin have not confirmed a clinically significant interaction.<sup>4</sup> These Frequently Asked Questions (FAQs) were designed to help clarify this topic of ongoing research with the hopes of shedding some light on the safety of consuming cranberries while on warfarin treatment.

## **1. Why is there a concern about consuming cranberries and warfarin? Where did this issue originate?**

The issue originated from 12 anecdotal case reports to the UK Committee for Safety in Medicine (CSM) between 2003-2004, prompting the CSM to release warnings about warfarin and

cranberry consumption. Among these 12 case reports, eight people had an increase in INR (international normalization ratio) - a measure of blood clotting - three had an unstable INR and one had a decreased INR.<sup>4,6</sup> Since these were medically complicated cases, many other factors could have impacted INR besides cranberry juice.

In 2006, the United States FDA approved safety labeling revisions for warfarin, known commercially as Coumadin®, to warn about the risk of major or fatal bleeding with their use.<sup>10</sup> These revisions included a cranberry consumption warning which was included in packaging for warfarin.

The package insert for Coumadin, which is manufactured by Bristol-Myers Squibb states: "Avoid drinking cranberry juice or eating cranberry products." In addition, the Coumadin medication guide specifies certain botanicals - such as ginseng, garlic, Ginkgo biloba and cranberry - that have been associated most often with an increase in the effects of Coumadin.<sup>2</sup>

*The health benefits of cranberries have been recognized for decades.*

## **2. What studies have been conducted to address the concerns about this potential drug-food interaction?**

At present, three controlled, clinical pharmacokinetic, and pharmacodynamic studies have been published in scientific literature and did not show a clinically relevant interaction between cranberry juice and either warfarin metabolism or INR in subjects on warfarin.<sup>4,7</sup> One of these clinical trials, authored by Ansell et al, was the largest study to date assessing this potential interaction.<sup>4</sup> However, there was only one clinical trial, authored by Abdul et al, that showed a modest increase in INR in 12 healthy volunteers that were not already taking warfarin. In this study, a single large dose of warfarin (25 mg) and cranberry extract capsules, containing 3000 mg of cranberry juice concentrate, was used in a non-blinded, open labeled study.<sup>3</sup>



In 2006, *The Journal of the American Dietetic Association* (JADA) published an article titled "Cranberry Does Not Affect Prothrombin Time in Male Subjects on Warfarin" and found no significant interaction between the daily consumption of 250 mL of cranberry juice and warfarin.<sup>6</sup> In March 2007, Long Island University researchers reported in the *American Journal of Health Systems Pharmacy* that there did "not seem to be a clinically relevant interaction between cranberry juice and warfarin," but advised cautioning patients about a potential interaction. Most recently, in 2009, a randomized, double-blind trial by Ansell et al was published in the *Journal of Clinical Pharmacology*, which showed no clinically relevant interaction between cranberry juice and warfarin and suggested that "other factors were likely responsible for the findings in the anecdotal case reports."<sup>4</sup>

### **3. What was the design and results of the Ansell et al study?**

Thirty patients already on warfarin treatment and with stable INR levels participated in this study. Amongst the thirty patients, 14 were randomized to receive cranberry juice and 16 to receive the placebo. There was a 2-week lead in phase, 2-week intervention phase and 1-week follow-up phase (after exposure to cranberry or placebo). During the intervention phase, patients consumed one 8 oz. glass of cranberry juice or placebo at the same time each day with INR levels being measured at this time. Patients were also advised to maintain a consistent diet throughout the study.<sup>4</sup>

During the intervention phase, eight of the thirty patients developed a minimally elevated INR exceeding 3.3. In general, the therapeutic range for INR with patients on warfarin treatment is 2.0-3.0 and a stable INR range is defined as an INR between 1.7-3.3. Four of these patients were in the placebo group and four in the cranberry juice group and the reasoning for this elevation remained unclear, but is likely due at least in part to the well-known variability of warfarin activity. One of the patients in the cranberry juice group had an INR of 1.69. During the final day of the intervention phase, the mean INR was significantly higher in the cranberry juice group compared to the placebo group, but mean INR levels were about identical during the next measurement, which was 24-hours later (the first follow-up day).<sup>4</sup>

The measurement of plasma warfarin levels for the placebo and cranberry juice group were the same throughout. This suggests that cranberry juice does not affect warfarin

metabolism, which is consistent with the results of three other controlled, clinical, pharmacokinetic studies. *The Journal of Clinical Pharmacology* article finds that there is no clinically relevant pharmacodynamic or pharmacokinetic interaction between warfarin and cranberry juice.<sup>4</sup>

### **4. Are the amounts of cranberry juice and warfarin used in the clinical studies relevant to the average patient?**

The amount of cranberry juice selected for most of the clinical trials is 250 mL (about one 8 oz. cup). This is the amount that was initially shown to be effective in preventing UTIs. In addition, this amount also reflects a reasonable number of ounces of juice per day for the average patient.<sup>6,8</sup> Hospitals typically provide 4 oz. servings of juice.

Since warfarin dosage is highly individualized according to the patient's sensitivity to the drug as indicated by INR and prothrombin time, this is likely why some clinical studies did not indicate the exact amount of warfarin dosing. Instead one study, for example, stated that patients were consuming a stable dose of warfarin. In general, warfarin dosage usually starts at 2-5 mg/day and is maintained at 2-10 mg/day. Another study investigated the impact of consuming 600 mL of cranberry juice on patients consuming 10 mg warfarin.<sup>7</sup>

### **5. What were the design and results of the study evaluating the impact of 600 mL of cranberry juice on patients taking warfarin?**

In 2007, a study was published in the *Journal of Clinical Pharmacology and Therapeutics* that investigated the effects of 600 mL (about 2.5 cups) of cranberry juice on the primary enzymes involved in the metabolism of warfarin. This included CYP2C9, which is implicated as the enzyme that cranberry juice interferes with during warfarin metabolism. In this study, ten healthy volunteers were randomly provided with 600 mL of either cranberry juice or water daily for ten days. On day five, they were given 10 mg of warfarin with drug concentration and thromboplastin times being measured. This study showed that there was no impact on thromboplastin time and concluded that cranberry juice did not inhibit these enzymes. Based on these results, it was less likely to imply that there is a pharmacokinetic interaction between warfarin and cranberry.<sup>7</sup>



## **6. Have other forms of cranberry, such as dried fruit, powders, etc., been used to evaluate the potential interaction with warfarin? If so, what was the end result?**

The Abdul et al study (2008) used cranberry extract capsules at a dose of 3000 mg of cranberry extract daily. It is not clear what the equivalence is between cranberry extract capsules and cranberry juice. Abdul et al. was the only study that showed a potential interaction between cranberry juice and warfarin.<sup>3</sup>

## **7. Should patients be advised to completely avoid cranberry products while taking warfarin?**

Based on the current body of research, there is no evidence suggesting that normal daily consumption of cranberry products poses a clinically significant risk of interacting with warfarin.

Ultimately, it would be up to the discretion of the physician to decide on whether or not the patient should be advised to avoid or limit cranberry juice consumption while on warfarin treatment.

## **8. What is the current position of the Joint Commission on Hospital Accreditation regarding cranberries and warfarin?**

According to the 2009 hospital patient safety goals, the Joint Commission on Hospital Accreditation (JCAHO), has identified anticoagulant therapies as an area of focus under the goal to improve the safety of using medications.

The JCAHO has targeted improved compliance to precautions and guidelines for warfarin and other anticoagulant therapies. The JCAHO will not give hospitals specific information on what foods and beverages to avoid, but instead, will expect each hospital to have clear guidelines in place and to follow those guidelines. The individual hospitals will be making the decision on how they will handle cranberry products. As per the 2009 JCAHO patient safety guidelines, dietary services should be notified of all patients receiving warfarin and respond according to the hospital's established food/drug interaction program.<sup>1</sup>

## **10. What are the benefits of maintaining the availability of cranberry products in the hospital setting?**

According to an article published in the *Journal for Infection Control and Hospital Epidemiology* in 2008, hospital-acquired UTIs are the most common hospital acquired infections. In addition, UTIs are frequently encountered in nursing home facilities. Clinical evidence supports the claim that cranberry juice can help in the prevention of UTIs. Cranberries contain two compounds that inhibit certain harmful bacteria from adhering to the lining of the urinary tract, which is then flushed out of the body.

In more recent studies, compounds in cranberries have been shown to prevent the adhesion of certain bacteria in other areas of the body that can cause stomach ulcers and periodontal gum disease. Emerging research also suggests that the high level of flavonoids found in cranberries may support cardiovascular health and help to prevent conditions that can lead to atherosclerosis such as elevated LDL levels.<sup>9</sup>

## REFERENCES

1. (2008). National Patient Safety Goals. *The Joint Commission Accreditation Program: Hospital*. Retrieved (2009, September 18) from [http://www.jointcommission.org/NR/rdonlyres/31666E86-E7F4-423E-9BE8-F05BD1CB0AA8/0/HAP\\_NPSG.pdf](http://www.jointcommission.org/NR/rdonlyres/31666E86-E7F4-423E-9BE8-F05BD1CB0AA8/0/HAP_NPSG.pdf)
2. (2009). U.S. Food and Drug Administration. *Drug Details: Coumadin*. Retrieved (2009, September 18) from <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>
3. Abdul, MI, Jiang X, Williams KM, et al. Pharmacodynamic interaction of warfarin with cranberry but not with garlic in healthy subjects. *Br J Pharmacol*. 2008; 154: 1691-1700
4. Ansell, J., McDonough, M., Yanli, Z., Harmatz, J., & Greenblatt, D. (2009). The absence of an interaction between warfarin and cranberry juice: A randomized, double blind trial. *J Clin Pharmacol*, 49, 824-830.
5. Halvorsen, BL, Carlsen MH, Phillips KM, Bohn, SK, Holte K, Jacobs DR, and Blomhoff R. Content of redox-active compounds (ie antioxidants) in foods consumed in the United States. *Am J Clin Nutr* 2006; 84: 95-135. Full article available at <http://www.ajcn.org/cgi/reprint/84/1/95>
6. Li, Z., Seeram, N. P., Carpenter, C.L., & Thames, G. (2006). Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc.*, 106, 2057-2061.
7. Liliya JJ et al. Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam-probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther*. 2007 Mar 28; Epub ahead of print.
8. Lo, E et al (2008). Strategies to prevent catheter associated urinary tract infections in hospitals. *Infect Control Hosp Epidemiol*, 29, S41-S50.
9. Reed J. Cranberry flavanoids, atherosclerosis, and cardiovascular health. *Crit Rev Food Sci Nutr* 2002; 42 (Supp): 301-316
10. USDA, Nutrient Data Laboratory, Beltsville Nutrition Research Center, et al. (2007). Oxygen Radical Absorbance Capacity (ORAC) of Selected Foods-2007: <http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/ORAC/ORAC07.pdf>
11. Wakinine, Yael. (2007). FDA Safety Changes: Coumadin and Seroquel. *Medscape Medical News*. Retrieved (2009, October 13) from <http://cme.medscape.com/viewarticle/550891?rss>

