

Cranberry Juice is Safe to Consume with Warfarin!

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There is no creditable scientific evidence to link an interaction between the moderate consumption of cranberry juice and warfarin.

In September 2003, the UK Committee on Safety of Medicines (CSM) issued a warning of a possible interaction between warfarin and cranberry juice. This warning was based on five spontaneous brief case descriptions (nothing more than a few sentences) suggesting such an interaction, leading to changes in INR values. The Committee indicated that the interaction is biologically plausible since cranberry juice contains various antioxidants, including flavonoids, which are known to inhibit specific cytochrome P450 enzymes. They acknowledged that further investigation was needed and recommended that until this matter was concluded, it would be prudent for patients taking warfarin to be advised to limit or avoid drinking cranberry juice. Similar warnings appeared on the labels for the FDA-approved products Coumadin® (warfarin, Bristol-Myers Squibb) and several generic warfarin products.

A review of all 16 suspected reports from the UK reported to the Medicines and Healthcare products Regulatory Agency (MHRA) via spontaneous reporting schemes found that the cases were poorly documented.¹ There are several other factors that could have been responsible for the changes in INR observed in these patients, including multiple co-morbidities, nutritional impairment, use of a number of other drugs, and exorbitant amounts of cranberry juice consumed. In one case, the INR actually decreased, the opposite of what is attributed to the interaction. The number of reports is also remarkably small considering the extensive use of warfarin and cranberry juice, often concurrently, by the elderly.

Against this anecdotal and poorly documented evidence from spontaneous reports is the overwhelming and ever-accumulating evidence from well-designed specific drug interaction studies. Recent publications have concluded that there is no interaction between cranberry juice and warfarin. There are seven separate interaction studies assessing valid and accepted pharmacodynamic (PD) and/

or pharmacokinetic (PK) endpoints, examining a total exposure of 75 patients and healthy volunteers, of which six concluded that a cranberry juice-warfarin interaction is unlikely. The studies are summarized in Table 1.

Summary of Results

The data show that, in both healthy subjects and patients, there is no evidence of a PK or PD interaction between cranberry juice and warfarin – with the exception of the Abdul study. Abdul and colleagues² claimed a potential PD interaction on the basis of assessment of an inappropriate and unconventional AUC-based PD parameter and the use of a single, very high dose (25 mg) of warfarin in healthy volunteers. An integrated assessment of the seven formal drug interactions studies, investigating an interaction between cranberry juice and warfarin in vitro and in vivo leads to the following conclusions:

- Using flurbiprofen or diclofenac as the probe substrates, studies indicate that, overall, there is no consistent in vitro evidence of a significant inhibition of CYP2C9 by normal quantities of cranberry juice (i.e., two 250 ml glasses of CJ/day or less). The evidence for in vitro inhibition of CYP2C9 by cranberry juice is conflicting at best. In any case, in vitro performance of cranberry juice is not predictive of its in vivo performance.
- Li et al³ showed that cranberry juice does not inhibit the in vivo activities of CYP1A2 or CYP3A4.
- Evidence consistently shows that cranberry juice does not affect the PK of either warfarin or other probe substrates of CYP2C9.
- Evidence consistently shows that cranberry juice does not affect warfarin-induced changes in INR or vitamin K-dependent clotting factors unless the data analysis employs PD AUC, whose clinical relevance is uncertain.
- Consumption of cranberry juice at a daily volume of 250 ml (used in most studies) or even as high as 200 ml t.i.d for 10 days, as used by Lilja et al⁴, or 250 ml of pure cranberry juice twice daily, as used by Mellen et al⁵, is without effect on the in vivo pharmacological properties of warfarin. At present, no conclusions can be drawn on the effect of larger volumes.



Conclusions

In conclusion, there is no evidence of risk of a clinically relevant interaction between warfarin and cranberry products from peer-reviewed interaction studies when cranberry juice is consumed in moderation. One cannot exclude the possibility of an interaction with the consumption of excessive quantities of cranberry products. Thus, it does not appear necessary to avoid normal levels of usage of cranberry products (two 8 oz glasses/day).

Table 1. Summary of studies examining a potential cranberry juice-warfarin interaction from the literature

Study	Participant numbers	Study design	Treatment groups	Duration of cranberry juice exposure	PK result*	PD result*
Li et al (2006) ³	7 patients (warfarin for AF)*	Crossover	Warfarin + cranberry juice/placebo	Extended	Not determined	No effect (INR)
Greenblatt et al (2006) ⁵	14 healthy volunteers	Crossover	Flurbiprofen (single dose) (preceded by cranberry juice, placebo, grape juice, tea or fluconazole)	Short-term	No effect	N/A
Lilja et al (2007) ⁴	10 healthy volunteers	Parallel	R-S warfarin, tizanidine, midazolam (5 days) + cranberry	Extended	No effect	No effect (thromboplastin time)
Abdul et al (2008) ²	12 healthy male volunteers	Open label, randomized crossover	Single dose 25 mg warfarin, alone or after 2 weeks of cranberry juice concentrate capsules or garlic tablets	Extended	No effect	INR AUC increased by 28% (max 8% difference at any individual time point) in warfarin/cranberry juice group
Ansell et al (2009) ⁷	30 patients (16 placebo; 14 cranberry juice) AF (9), DVT (9), PE (4), VHD (3), CVD (4), CHF (1)*	Parallel	Cranberry juice vs. placebo	Extended	No effect	No significant effect on INR
Ushijima et al (2009) ⁸	6 male, 2 female healthy volunteers, mean age 30.5 (range 23–44 years)	Open-label, two-period, crossover design with a wash-out period of >2 weeks	Cranberry juice vs. water with or without diclofenac (a medication metabolized by CYP2C9)	Medium duration (5 days), dosing of cranberry juice 180 ml, twice a day	No effect in healthy volunteers	No interaction with diclofenac in vivo, although inhibition of CYP2C9 in microsomal preparation in vitro
Mellen, et al (2010) ⁵	10 patients, ages 62–86, on warfarin for AF (3), PE (5), DVT-stroke or DVT and AF (1 each)*	Open-label, prospective	On stable warfarin dose, INR 2-3.	Cranberry juice (100%), 240 ml, twice/day x 7 days	N/A	No significant difference found in the mean PT at baseline vs. anytime during the study*

*AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism; VHD = valvular heart disease; CVD = cerebrovascular disease; CHF = congestive heart failure; AUC = area under the curve; PT = prothrombin time.

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Disclosure

Dr. Ansell has been asked by the Cranberry Institute to clarify the relationship between cranberry juice consumption and warfarin effect based on sound clinical science. As such, he is paid a small honorarium for his efforts. The Cranberry Institute is a not-for-profit organization to support cranberry growers through agricultural and environmental research, promotion and education.

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