

# Does Cranberry Juice Increase the Response to Warfarin?

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The product labeling of warfarin (Coumadin) lists a large number of drugs that can potentially interact with it and alter a patient's anticoagulant response. The label also includes listings of botanicals that may interact with warfarin. Some of these products are reported to contain coumarins (eg, celery, dandelion, licorice, and parsley) that may interact by enhancing the anticoagulant effect of warfarin. Others contain salicylates (eg, aloe, clove, ginger, and onion) that might inhibit platelets and increase the risk of bleeding. Recently, Bristol-Myers Squibb

other hypoprothrombinemic effects in these patients produced an elevated international normalized ratio (INR) and hemorrhage.

While cranberry juice contains salicylic acid, it is unlikely that the salicylic acid would affect the INR or even platelets.<sup>4</sup> Like many other natural products, cranberry juice contains compounds that could affect the metabolism of warfarin or clotting factors. No definitive studies have shown cranberry juice can inhibit any metabolic enzyme implicated in the metabolism of warfarin, however. In a study of the effects of cranberry juice on flurbiprofen (Ansaid) metabolism, a single, 240-mL dose of cranberry juice had no effect on flurbiprofen metabolism.<sup>5</sup> Flurbiprofen is metabolized by CYP2C9, the same enzyme that is primarily responsible for the metabolism of warfarin. Thus, this study indicates that a single dose of cranberry juice given to healthy persons does not appear to

other hand, the only prospective trial conducted to date failed to identify an effect of cranberry juice on CYP2C9 activity. The case reports are limited, as often happens, by the presence of other factors that may be responsible for changes in INR observed in the patients. The prospective study is limited by a design that may not reflect the typical consumption of cranberry juice by all patients. Additional studies are needed with the chronic administration of higher doses of cranberry juice to determine its potential to alter warfarin response. Insufficient data are available at this time to evaluate the potential mechanism of the interaction between cranberry juice and warfarin. While it is tempting to focus on the possible CYP2C9 inhibition of cranberry juice, perhaps other mechanisms are responsible for the effects that have been observed in some patients.

It has taken a number of years and many studies to define the interactive properties of grapefruit juice.<sup>6</sup> Currently, information on the interactive potential of cranberry juice is very limited. The labeling, as a precautionary approach, recommends avoiding cranberry juice or the consumption of cranberry products if taking warfarin. While this may appear to be a very conservative approach considering the available data and limited case reports, there is little potential harm in avoiding cranberry products if warfarin is being concurrently administered. **R**

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modified the warfarin label and patient medication guide to include a warning about an enhanced anticoagulant effect when patients consume cranberry juice or other products.

Several cases have been published that report enhanced warfarin effect in patients consuming cranberry juice.<sup>1,3</sup> In 2 of these cases,<sup>1,3</sup> the patients appeared to have infections and may not have been eating their normal diet; both of these events can increase the anticoagulant response to warfarin. It is possible that the cranberry juice added to the

affect warfarin metabolism. Patients taking cranberry juice for its antimicrobial or antioxidant effects will likely be consuming larger doses. Indeed, the case reports of enhanced warfarin effect have all noted chronic consumption of higher doses of cranberry juice. Further study is needed to determine what, if any, dose-dependent response is observed between cranberry juice and warfarin.

As with other purported warfarin interactions, several case reports suggest that cranberry juice may enhance the anticoagulant effect of warfarin. On the

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