

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Dietary Supplements and Oral Anticoagulants

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**H&O** Why is there a need to investigate the risks of drug interactions between dietary supplements and anticoagulants?

**AW** First, it is important to note that there is a wide variety of dietary supplements, including megavitamins and nonvitamin/nonmineral natural products, available in the United States for patients to purchase without prescriptions. There are many reasons why people are interested in these products: some may think they can treat and manage disease states on their own without turning to a physician for prescription medication; cost could be an issue; some may insist on more “natural” approaches to health and health maintenance. This is a 2–3 billion dollar industry in the United States today, and numerous kinds of products are available and heavily used.

At issue is the fact that there is very little regulation of these kinds of products. The 1994 Dietary Health and Education Act put legislation into place to protect consumer access to these nondrug products. This act requires that manufacturers of dietary supplements need to include a statement on their product label that says that the product has not been evaluated by the US Food and Drug Administration (FDA) and is not intended to cure or prevent disease. But safety and efficacy assurances are not required for marketing, and the Good Manufacturing Practices (GMPs) that apply to prescription drug products are not required. GMPs for prescription drugs

assure standardization of the contents (ie, by validating that the content and the description on the label are the same) and prevent drug product adulteration (ie, by prohibiting unlisted ingredients and contaminants); dietary supplements do not have to confirm to these GMPs. This means that what people are swallowing, applying, or inserting, may, firstly, not be what it says on the label, and secondly, may include many other ingredients that are not described in the labeling.

The third issue is that there is little to no information about how dietary supplements interact with other drugs, such as antithrombotic agents. In the United States, the primary oral anticoagulant is warfarin; warfarin is more susceptible to drug interactions than any other marketed agent and requires ongoing monitoring and dosage adjustment to maintain its safety and effectiveness. There is much information on how prescription drugs interfere with warfarin, so adjustments in that context are possible. However, there is very little information on how dietary supplements interact with warfarin. It is possible that they can alter the effectiveness, and more importantly, the safety of oral anticoagulation.

**H&O** Is there an entity that can regulate or investigate these risks?

**AW** The United States Pharmacopeia (USP) has a Dietary Supplement Verification Program. It is a voluntary testing and auditing program that helps dietary supplement manufacturers ensure the production of their products for consumers. Products go through comprehensive laboratory testing, manufacturing and quality control document review, on-site manufacturing facility audit, and random off-the-shelf testing for compliance with USP standards. Products that have adhered to this testing get a *USP Verified* mark to use on labels, packaging, and promotional materials. The mark indicates the confirmation of integrity (ie, the ingredients stated on the label are the ingredients that are involved), purity (ie, the content does not contain harmful levels of contaminants), dissolution (ie, it will be properly absorbed and released in the body), and quality assurance (ie, it has been manufactured according to safe and sanitary manufacturing standards). There

are some manufacturers that voluntarily participate in the USP Dietary Supplement Verification Program, but certainly not all.

**H&O** What type of evidence do we have so far that suggests a drug-drug interaction between dietary supplements and warfarin?

**AW** Unfortunately, the bulk of the evidence available comes from anecdotal or case reports, which is thought to be the least reliable and confirmatory type of report in the hierarchy of evidence. There are values to case reports—they help generate hypotheses, and they can be used as demonstrations of potential problems. However, case reports are not a valid way to confirm drug interaction causality, variability, consistency, or any other parameter. In fact, anecdotal reports are likely to describe exceptional or dramatic response. Cranberry is a good example: a number of years ago, several case reports described patients who were exposed to very high quantities of either cranberry supplements or cranberry juice and had drastic elevations in their international normalized ratio (INR)—a blood test that is used to measure the effectiveness of warfarin. In some of those case reports, patients had severe bleeding complications. Therefore, the suggestion was that cranberry was very dangerous when taken with warfarin and can increase the risk of bleeding. Subsequent clinical trials have not found that to be true. When investigated in a more controlled way, it was determined that there is no interaction between cranberry supplementation and warfarin. Additionally, a careful look at those original case reports showed that patients had other factors that could have driven the elevation in INR and bleeding. For example, in 1 case, a male patient had a very poor appetite and ate almost nothing, which was far more crucial than just the presence of cranberry juice. Dietary vitamin K intake influences the production of clotting factors and therefore the response to warfarin, and a significant reduction in vitamin K intake can escalate the response to warfarin.

In the same way, however, there could be many potential interactions between warfarin and available natural products that we know nothing about; this could be very harmful in terms of increasing the risk of bleeding or even increasing the risk of thrombotic complications in patients who are exposed to antithrombotic agents. Without evidence to support what is happening or what to do when those products are combined with anticoagulant therapy, it may be quite dangerous for patients to use them.

**H&O** Are there any other types of dietary supplements that have been suggested, by case reports, to have drug interactions?

**AW** Some interactions can influence the response to warfarin in a manner that increases or decreases the INR. In theory, adverse events from those interactions may be prevented by timely adjustment of warfarin doses to maintain the INR within the therapeutic range. More concerning, however, are interactions that can increase the risk of bleeding or thrombosis without influencing the INR. Use of ginkgo and ginger supplements has been reported to increase the risk of intracranial hemorrhage. This danger occurs not only in patients who are on anticoagulants but also in people who are not. It indicates that the underlining antiplatelet activity of some of these products can be very dangerous.

For clinicians, the most important lesson is to recognize the very high rate of use of natural products and the underreporting of natural product use by patients to their providers (ie, many patients are not likely to reveal that they take any herbal or natural products). Clinicians who manage patients taking anticoagulation medication need to develop the kind of clinician-patient relationships that will encourage patients to be forthcoming about exactly what they ingest on a day-to-day basis. This will enable the clinician to discourage the use of natural products in general and to increase the frequency of monitoring or increase the patient's vigilance for adverse effects when these kinds of dietary supplements are taken.

**H&O** What kind of regulation system do you think is necessary to educate and build awareness of the potential risk of this drug interaction?

**AW** First of all, I think that the USP Dietary Supplement Verification Program needs to be mandatory rather than voluntary. Because of their inherent dangers with warfarin and other prescription drugs as well, dietary supplements need to be regulated on a federal level to ensure potency, integrity, dissolvability, etc. I do not know that we will ever see such a regulatory system, but ideally, all natural products available without a prescription would be controlled in a manner that assures their safety. At this time, I do not think that there is sufficient information available for the general public to understand the potential risks of dietary supplements, particularly with respect to drug interactions. Most people tend to think that “natural” means safe, which clearly is not the case.