

Garlic and Warfarin-Is there a risk with concurrent use?

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In our internet information age, it can be easy to be overwhelmed by the mixed messages about herb-drug safety. A quick google search yields multiple and contradictory perspectives on any given plant, and it may be challenging to elicit an unbiased perspective from our other health care providers. This paper explores the relationship between a commonly prescribed anticoagulant medication, warfarin, and a well-known anti-coagulant herb, garlic.

Garlic (*Allium sativum*) is a member of the onion genus. Relatives of garlic include onions, scallions, leeks, and chives. Garlic and other onion-family plants are widely used in culinary traditions across the globe, and it is perhaps one of our oldest plant allies in herbal medicine. When we eat garlic, we are ingesting the dried bulb, and much of the garlic we consume in the United States is grown in Gilroy, California. There are also many other commercial herbal products now available--capsules, standardized extracts, fermented capsules, oils --ranging widely in their efficacy and availability. An herbalist might suggest garlic for a variety of conditions; garlic is commonly used for respiratory infections, to lower cholesterol and blood pressure, and to reduce the risk of cardiovascular disease and cancer.

Like its cousins, much of garlic's pharmacological power is thought to be due to its high sulfur content. Raw garlic is rich in sulfur compounds alliin, allicin, and thiosulfinate that are released by crushing and chopping (Henningsen, K., 2017). The amount of sulfur available in garlic products varies widely depending on how it is processed. Garlic powder and garlic essential oil do not contain allicin or ajoene, and the efficacy of many commercial capsules is debatable. Scientific research suggests that sulfur compounds and their breakdown products kill bacteria directly, reduce the number of platelets in the blood and slow clotting, and reduce the level of lipids in the blood. Compounds called ajoenes may also play a role in garlic's ability to prevent blood clots. Garlic may also reduce blood pressure through its action as a blood thinner. How garlic protects against cancer is still unknown, though research suggests these same compounds may decrease tumor cell growth or stimulate the immune system (Memorial Sloan Kettering Cancer Center, 2018). Garlic is also rich in many minerals including zinc, calcium, iron, magnesium, potassium, phosphorus, and selenium, and undoubtedly these play some role in its function as a medicinal herb (Henningsen, K., 2017). Garlic is often recommended as a culinary herb for overall well-being. For medicinal use, an herbalist might recommend 1 clove daily as a tonic, and up to 3 for acute respiratory infections. A tincture of fresh garlic may be recommended; common dosing is 3-5 mls up to four times daily. Standardized allicin extract capsules are usually dosed around 3-5 mg per day.

Warfarin (Coumadin, Jantoven) is a prescription blood-thinner commonly used in the treatment of cardiovascular treatments including deep vein thrombosis, stroke, post-myocardial infarction, and other cardiovascular conditions. It is orally prescribed in

doses ranging from 1 to 10 mg. Warfarin works as an anticoagulant because it prevents clotting. It does this by depleting the body's vitamin K reserves which in turn reduces the body's ability to synthesize active clotting factors by competing with enzymes needed for their metabolism. Because of its impact on vitamin K, a prescribing doctor may caution that sudden increases or decreases in foods rich in vitamin K (broccoli, cauliflower, cabbage, brussels sprouts, kale, spinach, and others) may affect drug metabolism. Warfarin also interferes with the liver's ability to synthesize proteins needed for blood clotting (Medscape, 2017). Warfarin requires accurate dosing to work properly, and it is important that providers be sensitive to warfarin's therapeutic window.

The liver metabolizes much of what we ingest. However, not everything that passes through the liver interacts with each other. The liver has various processing mechanisms, and each is given a different "code name" (e.g. liver pathway CYP3A4). Warfarin is metabolized in the liver by mechanism named CYP2C9 and exerts its anticoagulant effect by inhibiting the protein VKORC1 (Medscape, 2017). Garlic is metabolized by the liver as well, and some animal studies suggest that it can potentially inhibit substrates of CYP2C9, CYP19, and CYP3A4 (Busti, et al., 2015). For this reason, there is some caution around its coadministration with anticoagulant drugs. However, much of this caution depends on the dose of both warfarin and garlic as well as a person's clotting abilities--which can and should be regularly tested using an INR test.

The American Herbal Products Association (AHPA) Safety Handbook cites a 2006 study in which patients taking up to 15 ml of a garlic extract showed no clinically significant hematological factors, including INR, platelet count, and incidents of

hemorrhage. APHA also cites two reported cases of suspected herb-drug interaction in which there was both increased INR and clotting time. Dose was on the higher end for both patients (600 mg and 2 fresh cloves, respectively), and both patients were in their 80s and were taking other medications. The American Herbal Products Association Safety Handbook further elaborates on the interaction potential between warfarin and garlic. The handbook notes that the concerns around interactions are only in higher therapeutic doses (above 2 grams of fresh clove daily), and not in garlic's use as a culinary herb (American Herbal Products Association, 2013).

The scientific conclusions on the risk between warfarin and garlic are mixed, in part because studies vary widely in their duration and various forms and doses of garlic are used. For example, a 2006 study monitored 50 patients over 12 weeks and concluded that an aged garlic extract posed no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy. Furthermore, the study agreed with many herbalists in suggesting that garlic might be beneficial to people with a high risk for a cardiac event or who are taking cardiovascular medications (Macan, et al, 2006).

A 2014 comprehensive review looked at warfarin's potential to interact with 38 herbs, including garlic. While the researchers noted the importance of staying within warfarin's therapeutic window, they concluded that the case reports and clinical evidence for garlic-warfarin interaction were inconsistent with each other. Though there are some case reports in which garlic influenced INR when ingested concomitantly with warfarin. Garlic may decrease platelet aggregation, which could increase the risk of bleeding, but this would not increase INR on its own, and the mechanism for the increased INR effect in

reported cases is still unknown. Though an interaction between the herb and drug is hypothetically possible, it is unlikely that serious interactions would occur (Ge, et al. 2014).

Warfarin's efficacy is usually tested using an INR (international normalized ratio) test that measures the blood's ability to clot. In people who do not have associated risk factors, an INR level of 1.1 or below is considered normal. 5.0 is considered high-risk for clot, and most people taking warfarin are between 2.0-4.0 (Mayo Clinic, 2018). Because of the potential for interaction between garlic and warfarin, it is important to regularly test INR levels. This can be done in a clinic or using a home test. A prescribing provider can adjust warfarin's dose accordingly.

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