

Interaction Between *Lycium barbarum* (Goji) and Warfarin: A Case Report

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Abstract

A markedly elevated INR time was observed in a 71 year-old Ecuadorean-American woman hospitalized following the consumption of Himalayan Goji Juice. The woman was managed with warfarin following knee surgery three months prior. She reported no changes in dietary habits and lifestyle other than drinking goji juice four days prior to hospitalization. On presentation, she described symptoms of epistaxis, bruising, and rectal bleeding. Following discontinuation of the goji juice, warfarin, and the administration of phytonadione, her INR decreased from a markedly elevated, indeterminate level (prothrombin time greater than 120 seconds) to 2.6 over two days.

Lycium barbarum is a Chinese herb that has been used as an herbal supplement for health benefits. Traditionally, Chinese ethnic communities have used the herb in the form of tea. This report highlights the consumption of *L. barbarum* through goji juice, a widely available beverage in the United States. This case report adds further evidence to two other reports with similar interactions described after ingestion of a tea beverage containing the herb. In the current case report, the INR time was markedly elevated accompanied by signs and symptoms of bleeding. The application of the Naranjo adverse drug reaction probability scale yielded a probable relationship between *L. barbarum* and warfarin (score of 6). A chart review and thorough patient interview did not yield any other potential contributing factors to this elevation of INR and associated bleeding events.

The consumption of goji juice while on warfarin may have resulted in significant bruising, bleeding, and an elevated INR. Popular drinks such as goji juice containing *L. barbarum* should be avoided while taking warfarin. Before prescribing medications such

as warfarin, medical providers should probe patients about their use of various forms of herbal alternatives. Finally, documenting the use of alternative therapies in the medical chart while a patient is receiving warfarin would be of benefit to providers if an elevated INR level is observed during treatment.

Introduction

The use of complementary and alternative medicine (CAM), including dietary supplements, vitamins, minerals, amino acids and herbs has risen dramatically in the United States in the last decade.¹ The CDC recently reported that 38.3% of adults in the United States use complementary or alternative medicine.² Though some alternative therapies have been studied, few practitioners are aware of the possible dangers associated with available herbal supplements and are unable to provide adequate recommendations to patients regarding their use. Of great importance is the potential harm from interactions between herbal medicines and drugs, particularly since herbal products are infrequently labeled with possible herb-drug interactions,³ and herbals are also frequently used as food additives without individual labeling.

Warfarin, one of the most frequently prescribed drugs in the United States and the most commonly prescribed anticoagulant, has been known to interact with a number of herbal, supplement, and food products. For instance, herbs that may potentiate the anticoagulant effect of warfarin include Danshen, devil's claw, garlic, Ginkgo biloba, Dong quai, Fenugreek, Vitamin E, White willow, Feverfew, Chuan xiong, Tao ren, Hong hua, and Shui zhi, among others.⁴ Adverse reactions between warfarin and herbal

supplements have become an increasing concern for providers as the use of anticoagulants and herbal remedies continues to grow more commonplace.

One particular herbal product, goji (*L. barbarum*), has been markedly growing in use due to intensive marketing.⁵ To date, there have been two case reports of an interaction between *L. barbarum* and warfarin.^{6,7} In these two cases, *L. barbarum* was ingested through traditional Chinese herbal tea. In both cases, there was evidence of INR elevation following stabilized INR levels (2-3). This third case report provides additional evidence for the interaction between warfarin and *L. barbarum* through a juice product commonly sold in the United States.

Case Report

A 71 year-old Ecuadorean-American female with a history of hypertension, diabetes, asthma, and arthritis was admitted to our hospital with ecchymosis, epistaxis, and one episode of hematochezia. Upon admission, the patient was found to have an elevated INR of indeterminate level (prothrombin time greater than 120 seconds). The patient was taking warfarin daily for venous thromboembolism prophylaxis following complete left knee arthroplasty. Her other medications included the following: alprazolam 0.5 mg daily (as needed for anxiety), diphenhydramine 50 mg daily (as needed for insomnia), ezetimibe 10mg daily, lisinopril 20 mg daily, famotidine 20 mg twice daily, and meclizine 12.5 mg twice daily. The patient did not report smoking or drinking alcohol, nor did she endorse any changes in dietary habits or lifestyle. Through additional history, it was determined that she had not used any antibiotics, vitamins, or additional over-the-counter therapies in the previous month.

The patient stated that she had been taking warfarin since she underwent a left total knee arthroplasty, three months prior to hospitalization for her elevated INR. At that time, she was started on warfarin following knee surgery. After surgery, she received in-patient rehabilitation for 15 days. During this time, she took 1.5 mg of warfarin daily and her INR measurements ranged from 1.7 to 2.4. On the day prior to discharge, her INR measured 1.9. On discharge, she was prescribed 3 mg of warfarin daily and was scheduled to follow up with her community physician for INR monitoring. However, the patient never returned to her community physician. Instead, she reported that she continued to take 3 mg of warfarin daily for six weeks. Unfortunately, no INR levels were available for review during this time. Subsequently, four days prior to hospitalization, the patient reported drinking 30 mL of *Himalayan Goji Juice* in the morning and evening. In total, she drank 60 mL of juice for four days prior to presentation, which is equivalent to two servings daily, according to product labeling.⁸

The proprietary Himalayan Goji Juice is reconstituted from the *L. barbarum* fruit. She had purchased the juice from her hairstylist in an attempt to “cleanse her body.” Her symptoms of epistaxis, bruising, and rectal bleeding began on the fourth day after she began drinking the juice. Prior to drinking the juice, she did not report any similar symptoms such as bruising or bleeding. Upon admission, her INR level was indeterminate (prothrombin time greater than 120 seconds). This value was repeated with a second laboratory test and confirmed. The value exceeded the limit for calculating INR based on the vendor’s recommendations. The patient immediately discontinued drinking the Himalayan Goji Juice and warfarin was withheld, as an interaction between warfarin and *L. barbarum* from the juice was suspected. Application

of the Naranjo adverse drug reaction probability scale yielded a probable relationship between warfarin and the *L. barbarum* (score of 6).

Initially, the warfarin was withheld, and the patient received 5 mg of phytonadione for management of her supratherapeutic INR. On the second day of hospitalization, the INR declined to 7.5, and the patient received a 10 mg dose of phytonadione. On the third day, the INR declined to 2.6, and the patient received a final 10 mg dose of phytonadione. Clinically, no further bleeding was observed, and she was discharged after three days without further complication.

Discussion

L. barbarum is a Chinese shrub with red berries, and has been utilized as an herbal supplement for over two thousand years.^{4,9} Its antioxidant activity in combination with other physicochemical properties have been purported to have many potential health benefits. Among these, *L. barbarum* has been promoted to improve eyesight, kidney and liver function, weakness, and blood sugar control, among other uses.¹⁰ In addition, no side effects of *L. barbarum* have been documented in placebo-controlled clinical trials.¹¹

Among the greatest safety concerns is the potential for interaction with concomitantly prescribed medications. The Natural Medicine Database (2011) warns that warfarin dose adjustments may be necessary when using *L. barbarum*, as it may potentiate the anticoagulant effect of warfarin and increase the risk of bleeding.¹² Goji is metabolized by Cytochrome (CYP) P450 enzymes, the main metabolizing enzymes for hepatically metabolized drugs. Goji is known to significantly inhibit CYP-1A2 and -3A4

activity in hepatic cells *in vitro*, suggesting direct effects on the P450 protein.¹³ Goji has also been known to inhibit CYP P450 2C9, the primary metabolizing enzyme of warfarin.⁶ Other substances that are known to inhibit this enzyme are those that have been cited as very likely to increase INR and bleeding risk from warfarin. Examples of other 2C9 inhibitors include sulfamethoxazole/trimethoprim and fluconazole.¹⁴

This case report describes an important suspected drug-herb interaction resulting in a markedly prolonged prothrombin time accompanied by clinically significant bruising and bleeding. This interaction builds upon evidence from two other case reports describing similar scenarios.^{6,7} In these two cases, patients with stable INR trends (range 2-3) experienced elevations of their INR following ingestion of *L. barbarum*. In contrast to the previously reported cases that describe this interaction, the Latino patient in this case was using a widely available juice drink rather than a Chinese herbal tea. In addition, we were unable to determine if the patient had stable INR levels prior to the ingestion of goji juice, which would have provided further supportive evidence of the suspected interaction. Still, this case uniquely highlights potential interactions between prescription medications and the widely growing trend of ‘nutraceutical’ products, and foods and beverages infused with herbal substances. A review of the ingredients of goji juice the patient was consuming revealed no additional potentially active ingredients other than the *L. barbarum*.⁸

Many racial and ethnic groups have a rich history of traditional, folk, or complementary alternative medicine. Although the use of *L. barbarum* has not been specifically studied, it has been shown that certain ethnic groups may demonstrate greater use of particular alternative medications. For instance, Asian-Americans are

more likely to use green tea, soy, and dong quai, while African-Americans are more likely to use garlic extract and American-Indians frequently use ginseng for presumed medicinal purposes.¹⁵ For comparison, Latinos have long partnered with *curanderos*, *espiritulistas*, and herbalists for guidance in maintaining health. Despite these differences, alternative therapies such as *L. barbarum* appear to cross ethnic groups with product availability. Additional factors may further affect the propensity to use alternative medications. For example, in the United States, higher education is associated with greater overall CAM use, while less English proficiency is associated with greater ethnic-specific CAM use, especially among Latinos.¹⁵ In addition, less acculturation contributes to the pursuit of alternative therapies.¹⁶

The importance of identification of CAM use by practitioners cannot be overstated in light of the possible interaction with pharmaceutical drugs. It is imperative that providers speak with patients treated with warfarin about alternative therapies in addition to traditionally prescribed medications. Providers should be aware of widely available alternative therapies and their use in the community. *L. barbarum* product labeling with a warning regarding concurrent warfarin use may also help mitigate further interactions. Further investigation is also needed to better understand the pharmacokinetic mechanism by which *L. barbarum* inhibits the metabolism of warfarin.

References

1. Kessler RC, Davis RB, Foster DF, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. *Ann Intern Med* 2001;135:262-8.
2. Barnes PM, Bloom B, Nahin R. Complementary and alternative medicine use among adults and children: United States, 2007. *CDC National Health Statistics Report* 2008;12.
3. Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: a literature review. *Drugs* 2005;65:1239-82.
4. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health Syst Pharm* 2000;57:1221-7.
5. Potterat O. Goji (*Lycium barbarum* and *L. chinense*): Phytochemistry, pharmacology and safety in the perspective of traditional uses and recent popularity. *Planta Medica* 2010;76:7-19.
6. Lam AY, Elmer GW, Mohutsky MA, Chang J. Herb/Drug Interaction? *California Journal of Oriental Medicine (CJOM)*. 2002;13:10.
7. Leung H, Hung A, Hui AC, Chan TY. Warfarin overdose due to the possible effects of *Lycium barbarum* L. *Food Chem Toxicol* 2008;46:1860-2.
8. FreeLife International. 2011. Available from <http://corporate.freelife.com/international/usa/index.cfm/home>. Accessed September 20, 2011.

9. Burke DS, Smidt CR, Vuong LT. *Momordica cochinchinensis*, *Rosa roxburghii*, Wolfberry, and Sea Buckthorn: highly nutritional fruits supported by tradition and science. *Current Topics in Nutraceutical Research* 2005;3:259-266.
10. Liu Z, ed. *Essentials of Chinese Medicine*. New York: Springer, 2009.
11. Amagase H, Farnsworth NR. A review of botanical characteristics, phytochemistry, clinical relevance in efficacy and safety of *Lycium barbarum* fruit (goji). *Food Research International*, 2011;44:1702-17.
12. Natural Medicines Comprehensive Database. *Lycium*. Available from <http://naturaldatabase.therapeuticresearch.com>. Accessed September 20, 2011.
13. Eck PO, Shah PA, Nerurkar PV. Modulation of cytochrome P450 1A2 and 3A4 by *Morinda citrifolia* (noni), *Euterpe oleracea* (acai), *Lycium barbarum* (goji) and *Garcinia mangostana* (mangosteen). *FASEB J* 2009;23:688.6.
14. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. *Br J Clin Pharmacol* 1998; 45:525–38.
15. Hsiao AF, Wong MD, Goldstein MS, et al. Variation in Complementary and Alternative Medicine (CAM) Use Across Racial/Ethnic Groups and the Development of Ethnic-Specific Measures of CAM Use. *J Altern Complement Med* 2006;12:281-90.
16. Chao MT, Wade C, Kronenberg F, Kalmuss D, Cushman LF. Women's reasons for complementary and alternative medicine use: racial/ethnic differences. *J Altern Complement Med* 2006;12:719-20.