5-2010

Significant Interactions with the Most Commonly Used Herbal and Nonherbal Supplements Impact Warfarin Safety and Efficacy

Brittany Jean Sagers
Utah State University

SIGNIFICANT INTERACTIONS WITH THE MOST COMMONLY USED HERBAL AND NONHERBAL SUPPLEMENTS IMPACT WARFARIN SAFETY AND EFFICACY

by

Brittany Jean Sagers

**Thesis submitted in partial fulfillment
of the requirements for the degree**

of

DEPARTMENTAL HONORS

in

**Dietetics
in the Department of Nutrition, Dietetics and Food Sciences**

Approved:

Thesis/Project Advisor Megan Bunch, RD, MS	**Departmental Honors Advisor** Megan Bunch, RD, MS

Director of Honors Program
Dr. Christie Fox

**UTAH STATE UNIVERSITY
Logan, UT**

Spring 2010

Table of Contents

Abstract

Background:
Nearly 20% of adult Americans used herbal therapies in 2007, but greater than two-thirds failed to report such use to their medical provider. Significant patient harm may occur when herbal supplements are taken in conjunction with warfarin; however, patients and medical providers may not be aware of these interactions and this may place patients at risk for life-threatening bleeds or thrombotic complications.

Methods:
The authors determined the top 25 herbal and 25 nonherbal supplements used by Americans using sales data from 2008, and each product was reviewed for its potential to interact with warfarin. Electronic searches were conducted using the Natural Medicines Comprehensive Database, AltMedDex (Micromedex) and Natural Standards databases. Search terms included common herbal names, warfarin, and anticoagulants. Databases were reviewed for herb-drug interactions with warfarin. Supplements with a purported *theoretical* interaction only were excluded from the analysis.

Results:
Of the most commonly used herbal and nonherbal supplements used, more than half demonstrate a clinically significant drug interaction with warfarin therapy. Specifically, 8 of 13 were found to potentiate a bleeding risk, and 5 of 13 were found to decrease the effectiveness of warfarin. Documented bleeding events have been linked to the use of some of these products (e.g. cranberry, garlic, ginkgo, and saw palmetto); whereas others have been found to demonstrate a clinically significant increase (e.g. glucosamine / chondroitin, essential fatty acids, multi-herb products, evening primrose oil) or decrease (e.g. coenzyme Q10, soy, melatonin, ginseng, St. John's wort) in prothrombin time and required warfarin dose adjustments or vitamin K administration.

Conclusions:
Of the most commonly used herbal and nonherbal supplements, the majority impacted prothrombin times and 26% significantly impacted warfarin therapy safety or efficacy. The combined use of herbal-warfarin products has the potential to result in significant bleeding or thrombotic sequelae complicating the management of an already high-risk medication. Medical providers must be proactive in asking about supplement use and then discussing the risks of herbal-warfarin interactions with their patients.

List of Figures

Review of Literature

Warfarin

Warfarin sodium, commonly known under the brand name Coumadin, is a popular anticoagulant drug. It is the most widely prescribed oral anticoagulant in North America and has been proven effective in the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves, venous thromboembolism, and coronary artery disease (1). Coumarins or vitamin K antagonists (VKAs) have been the foundation of oral anticoagulant therapy for more than 50 years (2).

Atrial Fibrillation

Atrial fibrillation (AF) is a cardiac arrhythmia affecting an estimated in 2.2 million people in America and 4.5 million in the European Union (3). In some cases, AF can cause chest pain or heart failure, especially when the heart rhythm is very rapid (4). Frequently, people who have AF are asymptomatic. However, even if asymptomatic, AF can increase the risk of stroke (4). About 15 percent of patients with AF have experienced a stroke (5).

Clinical risk factors for AF include advanced age, diabetes, hypertension, congestive heart failure, rheumatic and nonrheumatic valve disease, and myocardial infarction (6). Three to five percent of people older than 65 years have atrial fibrillation (5). To reduce stroke risk in patients with AF, anticoagulant and antiplatelet medications are used to thin the blood reducing risk for emboli (5). Warfarin is the anticoagulant most frequently used for this purpose, and aspirin is the antiplatelet drug most often used (5). Long-term use of warfarin in patients with AF and other stroke risk factors can reduce stroke by 68 percent (5).

Use of HDS in the US

In 1994, the Dietary Supplement Health & Education Act (DSHEA) was passed that defines a supplement as: a product other than tobacco, is intended to supplement the diet, contains one or more dietary ingredients, intended to be taken by mouth, and labeled as being a dietary supplement (7). In 2004, dietary supplement sales exceeded $20 billion (8). According to the National Center for Complementary and Alternative Medicine (NCCAM), "a national survey conducted in 2007 found that 17.7 percent of American adults had used "natural products" (i.e., dietary supplements other than vitamins and minerals) in the past 12 months (9). The most popular products used by adults for health reasons in the past 30 days were fish oil/omega 3/DHA (37.4%), glucosamine (19.9%), echinacea (19.8%), flaxseed oil or pills (15.9%), and ginseng (14.1%)" as seen in figure 1 (10).

Table 3. Frequencies and age-adjusted percentages of adults 18 years and over who used selected types of nonvitamin, nonmineral, natural products for health reasons in the past 30 days, by type of product used: United States, 2007

Nonvitamin, nonmineral, natural products	Used selected nonvitamin, nonmineral, natural products[1]	
	Number in thousands	Percent[2] (standard error)
Fish oil or omega 3 or DHA	10,923	37.4 (1.13)
Glucosamine	6,132	19.9 (0.91)
Echinacea	4,848	19.8 (1.01)
Flaxseed oil or pills	4,416	15.9 (0.87)
Ginseng	3,345	14.1 (0.87)
Combination herb pill	3,446	13.0 (0.83)
Ginkgo biloba	2,977	11.3 (0.88)
Chondroitin	3,390	11.2 (0.82)
Garlic supplements	3,278	11.0 (0.66)
Coenzyme Q-10	2,691	8.7 (0.60)
Fiber or psyllium	1,791	6.6 (0.61)
Green tea pills	1,528	6.3 (0.65)
Cranberry (pills, gelcaps)	1,560	6.0 (0.63)
Saw palmetto	1,682	5.1 (0.46)
Soy supplements or isofavones	1,363	5.0 (0.53)
Melatonin	1,296	4.6 (0.48)
Grape seed extract	1,214	4.3 (0.43)
MSM (methysulfonylmethane)	1,312	4.1 (0.37)
Milk thistle	1,001	3.7 (0.49)
Lutein	1,047	3.4 (0.38)

[1]Respondents may have used more than one nonvitamin, nonmineral, natural product.
[2]The denominator used in the calculation of percentages was the number of adults who used nonvitamin, nonmineral, natural products within the past 30 days, excluding persons with unknown information for usage of the specified nonvitamin, nonmineral, natural product.

NOTE: Estimates were age adjusted using the projected 2000 U.S. population as the standard population and using four age groups: 18–24 years, 25–44 years, 45–64 years, and 65 years and over.

DATA SOURCE: CDC/NCHS, National Health Interview Survey, 2007. Estimates are based on household interviews of a sample of the civilian, noninstitutionalized population.

Figure 1: Frequencies and age-adjusted percentages of adults ≥18 yrs old who used nonvitamin, nonmineral, natural products for health reasons in the past 30 days.

Use of VKAs

In clinical practice, the use of VKAs is complicated. First, they have a limited therapeutic window. Second, they exhibit substantial variability in dose response among subjects. Third, they are susceptible to interactions with drugs and diet. Fourth, they have laboratory control that can be difficult to standardize. Lastly, there are difficulties in dosing as a consequence of patient nonadherence and miscommunication between the physician and patient (2). Warfarin use is somewhat restricted by a justifiable fear of bleeding as well as drug and food interactions that are frequently cited as causes of adverse events with warfarin. Noting this challenging situation in the utilization of warfarin, safety must be carefully practiced while taking it.

Mechanism of Warfarin

The effects of warfarin occur due to interference with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the carboxylation of glutamate residues to γ-carboxyglutamates (Gla) on the N-terminal regions of vitamin K-dependent proteins (11). These proteins include coagulation factors II, VII, IX, and X, and require vitamin K for γ-carboxylation for biological activity. By inhibiting the vitamin K conversion cycle, warfarin stimulates hepatic production of partially decarboxylated proteins with decreased coagulant activity (11).

Carboxylation supports binding of the vitamin K-dependent coagulation factors to phospholipid surfaces, thus increasing blood coagulation (11). In order for γ-carboxylation to work effectively, the reduced form of vitamin K (vitamin KH_2) is required. Coumarins block the formation of vitamin KH_2 by inhibiting the enzyme vitamin K epoxide reductase, thereby restricting the γ-carboxylation of the vitamin K-dependent coagulant proteins (11). The vitamin

K antagonists also inhibit carboxylation of the regulatory anticoagulant proteins C and S. Low doses of vitamin K_1 (phytonadione) are capable of aiding in overcoming the anticoagulant effect of coumarins because vitamin K_1 bypasses vitamin K epoxide reductase (11). Subjects treated with large doses of vitamin K_1 (usually greater than five mg) can be unaffected by warfarin for up to a week because vitamin K_1 accumulating in the liver is available to bypass vitamin K epoxide reductase (11). Figure 2 depicts warfarin interaction in the vitamin K cycle (12).

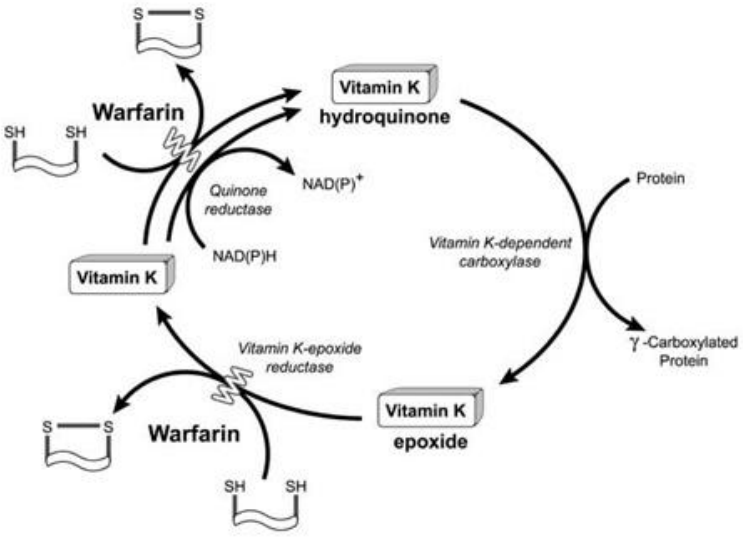


Figure 2: Warfarin Interaction in the Vitamin K Cycle

Factors Influencing Warfarin's Effects

The anticoagulant response to warfarin is affected by pharmacokinetic factors, including drug and herbal/nonherbal supplement interactions that affect its absorption or metabolic clearance, genetic factors such as hereditary resistance to warfarin, and food interactions such as dietary vitamin K intake (11). Warfarin requires monitoring and frequent dose adjustment to maintain the desired therapeutic action and minimize adverse bleeding events. A thrombosis is a result of underanticoagulation, which can be fatal. A hemorrhage is a result of over-anticoagulation, which can also be life-threatening. Length of treatment varies, from 6 weeks to

6 months for venous thrombosis, to life-long treatment for cardiac indications or repeated thrombosis (13).

Patients taking oral anticoagulant drugs, such as warfarin, must regulate their international normalized ratio (INR) measured routinely with appropriate anticoagulant dose adjustment. Some patients are particularly sensitive to oral anticoagulants and, in such individuals, small increases in dose, or introduction or discontinuation of interacting medicines, herbal preparations and certain foods can cause significant changes in the anticoagulant effect (13). Polypharmacy is not uncommon, which complicates the efficacy of warfarin. Patients taking warfarin should be aware of the risks of taking other prescribed or purchased medicines, herbal products and specific foods without first discussing it with their physician.

Dietary Interactions with Warfarin

As previously stated, warfarin use is subject to dangerous interactions with other medications as well as some food products. Due to the actions of warfarin interfering with the vitamin K conversion cycle, dietary vitamin K intake must remain consistent on a daily basis to reduce the risk of hemorrhage or thrombosis. Persons on long-term warfarin therapy are vulnerable to fluctuating levels of dietary vitamin K, which is obtained predominantly from phylloquinones found in plant foods (11).

Phylloquinones inhibit the anticoagulant effect of warfarin because they are reduced to vitamin KH_2 through the warfarin-insensitive pathway (11). Significant fluctuations in vitamin K intake occur in both healthy and sick individuals. Increased intake of dietary vitamin K sufficient to lessen the anticoagulant effect of warfarin occurs in patients consuming green vegetables or vitamin K-containing supplements while following weight-reduction diets as well as in patients supplementing with intravenous vitamin K (11). Reduced dietary vitamin K intake has the

potential to affect warfarin efficacy in sick patients treated with antibiotics and intravenous fluids without vitamin K supplementation and in circumstances of fat malabsorption (11).

Medicinal Interactions with Warfarin

Warfarin also interacts with some common drugs such as aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and penicillins in high doses (11). These drugs inhibit platelet function and thus increase the risk of warfarin-associated bleeding. Of these, aspirin is the most critical because of its universal use and drawn out effect. Aspirin and nonsteroidal antiinflammatory drugs can also increase the risk of upper gastrointestinal bleeding as a result of them producing gastric erosions (11). The risk of clinically significant bleeding is amplified when elevated amounts of aspirin are taken throughout high-intensity warfarin therapy (11).

Herbal and Nonherbal Dietary Supplement Interactions with Warfarin

Warfarin has been documented to interact with herbal and nonherbal dietary supplements (HDS) (11). However, little is known about the great extent to which some of the most commonly used HDS may impact warfarin safety and efficacy. Although herbal remedies are perceived as being natural and therefore safe, many have adverse effects that can sometimes produce life-threatening consequences.

It is important to determine the degree to which HDS can interfere with warfarin because of the rapidly growing dietary supplement market and consumer demand in the United States. According to the research completed through this thesis, the top five products in Figure 1 (fish oil, flaxseed oil, glucosamine, echinacea, and ginseng) were shown to have an interaction with warfarin. Also, as documented in the manuscript portion of this thesis, garlic (37-45), ginkgo (49, 52-56) and St. John's wort (80-84) should be avoided while taking warfarin. Because of the

high risk of adverse effects while concurrently taking these common HDS and warfarin, a brief review of each HDS will follow.

Fish Oil and Flaxseed Oil

Fish oil and flaxseed oil both had minor interactions, mainly with platelets (35-36). Many people consume fish and flax seed oils because of the purported health benefits of the omega-3 fatty acids they contain. Omega-3 fatty acids have been thought to reduce the risk for cardiovascular disease and some cancers, as well as improve brain health. Some research has shown that the omega-3 component of fish oils may suppress thromboxane A2 synthesis. This may intensify the effects of warfarin, thus increasing the chances of bleeding. Conflicting research has suggested that fish oil does not have an additive effect with aspirin. Data does suggest that 3-6g/day does not affect INR (35-36).

Ginseng

The source of the ginseng root and its method of extraction can result in a wide array of ginseng products. Ginseng is touted as an immune system stimulant that increases vigor, sexual potency, and longevity, and for use as an antidiabetes agent (14). It is also used as medicine in Chinese culture for congestive heart failure (CHF), myocardial infarction, and angina pectoris (14). Ginseng use should be avoided while taking warfarin (76-78). Ginseng may inhibit platelet aggregation consequently decreasing the effects of warfarin. A recent study inspecting the effect of 3 weeks of American ginseng on the effect of warfarin in healthy volunteers found a statistically significant but quantitatively small decrease in INR of 0.19, as well as a decrease in warfarin plasma area under the curve (AUC) (15). These results imply that this specific ginseng preparation may produce a minor reduction in the efficacy of warfarin, perhaps by way of accelerated clearance.

Glucosamine

Glucosamine is recommended to be used with caution while taking warfarin although the exact mechanism of the interaction is unknown (2-4). Glucosamine is a chemical component of heparin, a widely used injectable anticoagulant (16). It is possible that the combining of warfarin with higher-dose glucosamine and chondroitin might have had an additive pharmacodynamic effect on coagulation (16). At the usual dosages of glucosamine (1500 mg) and chondroitin (1200 mg) used on a daily basis, these supplements alone or in combination do not appear to cause a clinically significant interaction with warfarin (16). Nevertheless, it is advised to monitor for INR changes in patients taking warfarin and beginning a supplement or drug that has not been thoroughly investigated for its effect on warfarin.

Echinacea

Echinacea is commonly thought to stimulate the immune system and therefore prevent infections. It has been shown to have minor interactions with warfarin. Flavonoids from echinacea may inhibit or induce cytochrome P450 enzymes, depending on their structure and assay conditions (14). A minor impact of CYP function was established through in vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: citrus aurantium, echincea purpurea, milk thistle, and saw palmetto.

Garlic

Garlic is often used by patients for remedy of infectious conditions because of its presumed antimicrobial and immune-boosting activity. Garlic has been considered to have cholesterol-lowering and other antiatherosclerotic and antihypertensive properties and is used in the prevention of cardiovascular disease (14). It has been shown to increase fibrinolytic activity,

and may inhibit platelet aggregation by reducing thromboxane B2 thereby, increasing risk for bleeding.

Garlic's active component, ajoene inhibits collagen-induced platelet aggregation; thus, patients with cardiovascular disease often use garlic for its antiplatelet and fibrinolytic effects (14). Nevertheless, the risk of bleeding in patients using warfarin increases, so its concomitant use should be avoided. It is worthy to note that not all garlic products contain the constituents that possess "antiplatelet properties". It has been advised that garlic supplements be discontinued ten days prior to surgery to prevent excessive bleeding. Ingestion of normal amounts of dietary garlic should not affect bleeding times (37-45).

Ginkgo

Ginkgo is a popular HDS and is one of the bestselling herbal remedies in the United States for cognitive impairment (14). Ginkgo biloba beginnings date back centuries to the Permian period, making it one of the world's oldest living tree species (14). The main implications for ginkgo use are peripheral vascular disease such as intermittent claudication and, more chiefly, "cerebral insufficiency" (17). It has been documented to increase the risk of bleeding while taking warfarin. This is thought probable by inhibition of cytochrome P450 2C9 by ginkgo. Also, ginkgo is thought to displace platelet activating factor (PAF), inhibiting PAF-induced platelet aggregation.

St. John's Wort

St. John's wort is frequently used to treat depression, anxiety, sleep disorders, the common cold, herpes, and the human immunodeficiency virus (HIV) (14). It acts as a hepatic cytochrome P450 enzyme inducer (CYP2C9, CYP1A, CYP3A4). Simultaneous use of St. John's wort with warfarin reduces prothrombin time, which may produce subtherapeutic

anticoagulation and increase the risk of thromboembolism (14). Patients with a history of stroke, thrombosis, atrial fibrillation, or prosthetic cardiac valves should avoid the use of St. John's wort while taking warfarin (14).

Conclusion

From this evidence alone, there are major risks when using HDS and warfarin concomitantly. Steps must be taken to bridge the communication gap that exists between physicians and patients with regard to supplement use. To ensure that patients are taking warfarin safely, physicians must be aware of the risks HDS pose with concomitant use of warfarin. Physicians must be proactive in asking their patients about such use and discussing the risks involved to aid in preventing serious complications with an already high risk medication.

References

1. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, Wells PS. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165:1095-1106.

2. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3):2045-2335.

3. Fuster V, Ryden LE, Cannon DS, Crijns Hj, Curtis AB, Ellenbogen KA, Halperin JL, Heuzey J-YL, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL,Wann S. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. *Circulation.* 2006;114:e257-e354.

4. National Heart, Lung and Blood Institute. Atrial Fibrillation. Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html. Accessed April 15, 2010.

5. American Heart Association. Atrial Fibrillation. Available at: http://www.americanheart.org/presenter.jhtml?identifier=4451. Accessed April 15, 2010.

6. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. *Circulation*. 1998;98(10):946-952.

7. Saldanha LG. *Opening Comments: What are Dietary Supplements? Introduction.* American Dietetic Association's Food & Nutrition Conference & Expo (FNCE). 2005;Session 250.

8. Picciano MF. *Who Is Using Dietary Supplements and What are They Using?* American Dietetic Association's Food & Nutrition Conference & Expo (FNCE). 2005;Session 250.

9. National Center for Complementary and Alternative Medicine. Get the Facts: Using Dietary Supplements Wisely. Available at: http://nccam.nih.gov/health/supplements/wiseuse.htm. Accessed March 30, 2010.

10. Barnes PM, Bloom B, Nahin R. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. *National Health Statistics Reports.* 2008:12;1-24.

11. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2003;41:1633-1652.

12. Linus Pauling Institute of Medicine. The Vitamin K Cycle. Available at: http://lpi.oregonstate.edu/infocenter/vitamins/vitaminK/kcycle.html. Accessed April 21, 2010.

13. Baglin TP, Cousins D, Keeling DM, Perry DJ, Watson HG. Recommendations from the British Committee for Standards in Haematology and National Patient Safety Agency. *Br J Haematol*. 2006;136(1):26-29.

14. Greenblatt DJ, von Moltke LL. Interaction of Warfarin with Drugs, Natural Substances, and Foods. *J Clin Pharmacol.* 2005;45:127-132.

15. Tachjian A, Maria V, Jahangir A. Use of Herbal Products and Potential Interactions in Patients with Cardiovascular Diseases. *J Am Coll Cardiol*. 2010;55:515-525.

16. Scott GN. Interaction of Warfarin with Glucosamine—Chondroitin. *Am J Health-Syst Pharm*. 2004;61:1186.

17. Kleijnen J, Knipschild P. Ginkgo Biloba. *Lancet*. 1992;340(1136):4p.

Manuscript

Significant interactions with the most commonly used herbal and nonherbal supplements impact warfarin safety and efficacy

Jennifer Strohecker[1], Megan B. Smith[2], Nedra Christensen2, Brittany Sagers[2], John D. Day[3], J. Peter Weiss[3], Brian G. Crandall[3], Jeffrey S. Osborn[3], Jeffrey L. Anderson[3], Brent Muhlestein[3], Donald L. Lappe[3], T. Jared Bunch[2,3]

[1] Intermoumtain Medical Center, Murray, Utah

[2] Department of Nutrition and Food Sciences, Utah State University, Logan, Utah

[3] Department of Cardiology, Intermountain Medical Center, Murray, Utah

Address for correspondence: T. Jared Bunch, M.D.

Intermountain Heart Rhythm Specialists,

Intermountain Medical Center

Eccles Outpatient Care Center

5169 Cottonwood St, Suite 510

Murray, Utah, 84107

Fax: 801-507-3584

E-mail: Thomas.bunch@imail.org

Introduction:

For centuries, botanicals and their derivatives have been utilized for prevention and treatment of disease. Indeed, even today, due to extensive availability and widespread acceptance, herbal and dietary supplement (HDS) use has become commonplace. One out of five American's reports using at least one HDS in the last twelve months, a trend that has continued to gain momentum over the last decade (1). Growing concern for patient safety has driven international and national groups in efforts towards regulation of the herbal supplement industry, but with limited success. In the present day era of patient guided research, selection and self-treatment with supplements, it is imperative that medical providers be proactive in inquiry about HDS use and provide relevant guidance in efforts to minimize potential adverse events. When combined with prescription drugs, herbal-drug interactions are of great concern because they may lead to unexpected, serious patient harm.

The supplement industry is the fastest growing share of the US pharmaceutical industry, with annual earnings approaching 24 billion dollars in 2007 (2). Today, greater than 1500 products claiming "functional support" of the bodies various organ systems line the shelves of pharmacies and health food stores, easily accessible to an often uneducated consumer. Ironically, HDS are not considered "drugs" by the Food and Drug Administration (FDA), and are therefore free from the safety and regulatory standards set in place by the FDA for other over the counter and prescription products. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was passed and outlines the US regulations set in place for herbal and nonherbal supplements: *the manufacturer is to ensure that the product is safe and labeling must include product ingredients* (3). As a food source the preparation, packing, and holding of HDS are governed by the FDA's 'Good Manufacturing Practices' (4). In June of 2007, the FDA

established regulations to require current 'Good Manufacturing Practices" for dietary supplements that require dietary supplement manufacturers to evaluate the identity, purity, strength, and composition of their dietary supplements (5). Although these measures may help, the quandary with HDS continues to be, that the pharmacologic effects of these products are undefined, unpredictable, and potentially unsafe, yet the well-intended consumer has little knowledge of this. This can present the greatest risk to patients with multiple medical co-morbidities, fragile end organ function, and those on complicated drug regimens. In 2002, the World Health Organization launched a global strategy with end goals of promoting consumer safety through industry regulation and standardization (6). Clearly, the unregulated use of HDS is not just a national, but an international concern.

The introduction of warfarin sodium in 1954 revolutionized the prophylaxis and treatment of thromboembolic disorders, and remains the gold standard oral anticoagulant. More than 22 million prescriptions for warfarin were filled in 2008, and enormous health care resources are dedicated to its management. In spite of efforts to achieve tight control of the international normalized ratio (INR), warfarin accounts for more emergency room visits than any other drug excluding insulin. In 2009, the Joint Commission of Healthcare Accreditation made the appropriate use of warfarin a National Patient Safety Goal (7). As part of this effort, it is crucial to understand the influence that HDS use may have on INR variability when taken concomitantly with warfarin. Such an understanding must be constantly reappraised as the kinds of HDS used varies as well as their relative frequency and quantify of use.

Methods:

The authors determined the top 20 herbal and 20 nonherbal supplements used by Americans using sales data from 2008 and each product was reviewed for its potential to interact

with warfarin (8). Electronic searches were conducted using the Natural Medicines Comprehensive Database, AltMedDex (Micromedex) and Natural Standard databases. Search terms included common herbal names, warfarin, and anticoagulants, and drug-drug interactions. Databases were reviewed for herb-drug interactions with warfarin. Databases were searched for relevant case reports and any clinical trials which documented an herbal/supplement – drug interaction with reported changes in INR, bleed risks, or thromboembolic events. Collected data was limited to English only reports and those with a documented human interaction. Supplements with a purported *theoretical* interaction only were excluded from the analysis.

Results:

Of the 40 most commonly used herbal and nonherbal supplements, more than half demonstrate an indirect or direct drug interaction with warfarin therapy. Of the top 10 most commonly used supplements, 80% have been reported to interact with warfarin therapy. Overall, 14 of 40 were associated with a clinically significant change in INR. Specifically, 9 of 14 were found to potentiate a bleeding risk, and 5 of 14 were found to decrease the effectiveness of warfarin. Documented bleeding events have been linked to the use of some of these products (e.g. cranberry, garlic, ginkgo, and saw palmetto); whereas others have been found to demonstrate a clinically significant increase (e.g. glucosamine / chondroitin, essential fatty acids, multi-herb products, evening primrose oil) or decrease (e.g. coenzyme Q10, soy, melatonin, ginseng, St. Johns's wort) in prothrombin time thus necessitate warfarin dose adjustments or vitamin K administration.

Discussion:

The HDS industry has experienced enormous growth with extensive consumer acceptance and trust. A survey of 100 patients with CV disease on warfarin showed that many patients do

not view HDS as drugs, and most do not consult with their pharmacist/physician before taking a HDS (9). More than 2/3 of patients who use HDS fail to communicate use to their physicians/pharmacists, and physicians often fail to ask patients about HDS consumption as well (5, 9). The reasons for the communication gap are many: patients believe that health care professionals lack knowledge of or acceptance for HDS, patients perceive HDS as "natural" and do not relate their use to drug interaction (9), and medical providers may fail to ask about HDS use due to a lack of knowledge, confidence, or comfort with the subject matter (10). Addressing these issues will be paramount as clinicians seek to bridge this gap in order to improve safety outcomes, particularly in high-risk patient groups.

A survey of the literature shows that anticoagulant/antiplatelet therapies are among the drug classes most likely to interact with HDS (11). Of the 40 most commonly used HDS, more than half demonstrated a clinically significant change in INR values, and the majority were associated with a bleeding event or thromboembolic complication. While most of these reports are cited as individual case reports, the true level (degree/risk) of harm for warfarin-treated patients may actually be greater than is documented. Pharmacokinetic properties and toxicity parameters of individual herbs are not well studied, and drug-drug, drug-disease interactions are largely unknown. Additionally, a vast number of supplements are not marketed as “single-entity” products, but rather a potpourri of dozens or hundreds of individual ingredients. The new FDA regulation should impact quality of supplements. Unfortunately, companies have to be compliant to the new regulation by supplement June 2008, 2009, or 2010, depending on the number of personnel employed at the company. This will continue to impact the consistency of HDS in the marketplace. Without prior study it is completely unclear if the enhanced quality

which may provide relatively higher or lower HDS concentrations with favorability or unfavorability impact the many drug-HDS interactions.

Development, implementation, and adherence to a comprehensive management program that outlines standards of care have been shown to improve safety outcomes in anticoagulated patients. As such, inquiry and recommendation about herbal supplement use is an essential part of such a program. Important aspects to incorporate may be the following: proactive inquiry about herbal or supplement use separately from prescription or over the counter drug use; documentation of use in the medical record; active education of known risks/interactions between the specified herbal product and warfarin; and more frequent INR monitoring if necessary. Other valuable education points for patients who use HDS may be: encourage dialogue *before* use with physician/pharmacist; take the product consistently to achieve a more predictable effect on INR; to purchase the same brand of product to minimize constituent variability; follow up with routine testing as instructed; bring the HDS with them to all scheduled appointments; report any adverse events to their medical provider immediately. Additionally, encourage selection of supplements that are verified by the United States Pharmacopeia (USP).

Likewise, physicians and other medical providers must acknowledge a "communication gap" exists with their patients and make efforts to minimize this barrier. Self-education is critical, so that a knowledgeable exchange about the supplement industry, including DHSEA and rationale for safety risks, can be undertaken with patients. Physicians must recognize that HDS use is common and underreported, and therefore must be proactive and specific in patient interview. It is essential to be forthright with regard to the risks/benefits of using supplements, so that the patient can make an informed and educated decision. Likewise, it is imperative that

the physician be familiar with on-line herbal databases, such as AltMedDex (Micromedex), and utilizes them to search for herbal information, such as herbal-warfarin interactions.

Steps must be taken to bridge the communication gap that exists between physicians and patients with regard to supplement use. While warfarin remains the gold standard anticoagulant drug therapy for long-term management of patients at risk for thromboembolism, its safe use can be compromised by many factors, including HDS consumption. Our data shows that of the most commonly used HDS, warfarin-related drug interactions are very common and have been associated with bleeding. This risk is greatest in the 10 most commonly used herbal supplements, where 8 of 10 have demonstrated an HDS-warfarin interaction. Our research highlights/emphasizes the widespread risk that warfarin-treated patients are exposed to when self-medicating with HDS. It is imperative that action be taken to address communication-related barriers with regard to HDS use, and should include the steps outlined above. As hospitals seek to achieve compliance with the Joint Commission's 2009 National Patient Safety Goals of medication reconciliation and appropriate anticoagulant management, this creates a perfect opportunity/forum for HDS-focused education. Future research should be aimed at "bridging the gap" through the development and implementation of both physician-focused and patient-focused educational tools.

Manuscript References

1. Barnes PM, Bloom B, Nahin RL. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. Advance Data from Vital and Health Statistics

2. Picciano MF. *Who Is Using Dietary Supplements and What are They Using?* American Dietetic Association's Food & Nutrition Conference & Expo (FNCE). 2005;Session 250.

3. US Food and Drug Administration. Overview of dietary supplements. Available at: www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm. Accessed June 11, 2009.

4. FDA/CFSAN. Dietary Supplement Health and Education Act of 1994. US Food and Drug Administration Center for Food Safety and Applied Nutrition, December 1, 1995. Available at: http://www.cfsan.fda.gov/~dms/dietsupp.html. Accessed June 2009.

5. US Food and Drug Administration. FDA issues dietary supplements final rule. FDA News. Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01657.html. Accessed June 2009.

6. World Health Organization. WHO launches the first global strategy on traditional and alternative medicine. Available at: www.who.int/mediacentre/news/releases/release38 /en/print.html. Accessed June 11, 2009.

7. Joint Commission. 2009 National Patient Safety Goals 03.05.01. The Joint Commission on Accreditation of Healthcare Organizations. 2008;p.10.

8. Natural Foods Merchandiser. 2008 Herbal and Nonherbal Supplement Sales. Available at: http://naturalfoodsmerchandiser.com/portals/0/pdfs/supps.pdf. Accessed June 11, 2009.

9. Smith MB, Christensen N, Wang S, Strohecker J, Anderson JL, Horne BD, Day JD, Weiss JP, Crandall BG, Osborn JS, JB Muhlestein, Lappe DL, Moss H, Oliver J, Viau K, Bunch JB. Atrial fibrillation patients at the highest risk of thromboembolism have very poor knowledge of warfarin use. *Cardiology*. (in press).

10. Kemper KJ, Gardiner P, Gobble J, Woods C. Expertise about herbs and dietary supplements among diverse health professionals. *BMC Complement Altern Med.* 2006,6(15):9.

11. Sood A, Sood R, Brinker FJ, et al. Potential for interactions between dietary supplements and prescription medications. *Am J Med*. 2008;121(3):207-11.

Warfarin/HDS Interaction Table

Supplement	*Recommendation for Management*	*Warfarin Interaction*	*Platelet Interaction*	*Mechanism*	*Patient Information*
CAM therapies that may increase the risk of bleeding					
Chondroitin sulfate (2-4)	!	+		Chondroitin is a small component of a heparinoid and might have weak anticoagulant activity	
Cod liver oil-Essential Fatty Acids (5-9)	⇔			Cod liver oil contains omega-3 fatty acids, which may interfere with the ?????	
Cranberry (10-22)	!	+		Unknown mechanism: One proposed mechanism is that flavanoids in cranberry may interfere with the P450 2C9 metabolism of warfarin, thus prolonging its effects. Another hypothesis is that cranberry may increase the sensitivity of clotting factors to the effects of warfarin	-Avoid drinking in large quantities -Have INR checked more frequently with chronic consumption
Evening primrose oil (31)	!		+	Primrose oil contains gamma-linolenic acid which has been show to inhibit thromboxane B2 production and increase prostacyclin production	
Fish oil-Essential Fatty Acids (35,36)	⇔		+	Some research shows that the omega-3 component of fish oil may suppress thromboxane A2 synthesis. Conflicting research suggests that fish oil does not have an additive effect with aspirin	Data does suggest that 3-6g/day does not affect INR
Garlic (37-45)	∅		+	Garlic has been shown to increase fibrinolytic	-Not all garlic products contain the constituents that possess

Supplement	Recommendation for Management	Warfarin Interaction	Platelet Interaction	Mechanism	Patient Information
				activity, and may inhibit platelet aggregation by reducing thromboxane B2	"antiplatelet properties" -Garlic supplements should be stopped 10 days prior to surgery -Ingestion of normal amounts of dietary garlic should not affect bleeding times
Ginger (34,46-51)	⇔		+	Mixed results in studies: one suggests a significant inhibition of platelet aggregation, where two others showed no affect on platelet function	-Caution with intake exceeding 4 grams of dried or 15 grams of raw ginger daily
Ginkgo biloba (49, 52-56)	∅	+	+	Probable cytochrome P450 2C9 inhibition by ginkgo. Also, ginkgo is thought to displace platelet activating factor (PAF), inhibiting PAF-induced platelet aggregation	
Glucosamine (2-4)	!		+	May have antiplatelet activity	
Melatonin (62)	!			Unknown mechanism	
Saw palmetto (63, 64)	!		+	Saw palmetto may inhibiti cyclooxygenase, leading to increased risk of bleed	
CAM therapies that may decrease the effects of warfarin					
Coenzyme Q10 (72-74)					
Ginseng (American) (76-78)	∅		+	May inhibit platelet aggregation	
Ginseng	∅		+	May inhibit platelet	

Supplement	Recommendation for Management	Warfarin Interaction	Platelet Interaction	Mechanism	Patient Information
(Panax) (76-78)				aggregation	
Soy (79)	⇔	+		Soy isoflavones may alter warfarin drug absorption, metabolism or biliary excretion. They may also have antiplatelet effect	
St. John's wort (80-84)	∅	+		St. John's wort is a cytochrome P450 enzyme inducer (CYP2C9, CYP1A2, CYP3A4)	

Table References:

1. Lambert J, Cormier J. Potential interaction between warfarin and boldo-fenugreek. *Pharmacotherapy*. 2001;21:509-12.
2. Knudsen J, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: Case report and review of the literature and MedWatch database. *Pharmacotherapy*. 2008;28:540-8.
3. Rozenfeld V, Crain JL, Callahan AK. Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health Syst Pharm.* 2004;61:306-307.
4. Yue QY, Strandell J, Myrberg O. Concomitant use of glucosamine may potential the effect of warfarin. The Uppsala Monitoring Centre. Available at: www.who-umc.org/graphics/9722.pdf. Accessed 28 April 2008.
5. Knudsen JF, et al. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy*. 2008;28(4):540-548.
6. Landymore RW, Kinley CE, Cooper JH, et al. Cod-liver oil in the prevention of intimal hyperplasia in autogenous vein grafts used for arterial bypass. *J Thorac Cardiovasc Surg*. 1985;89:351-7.
7. Jensen T, Stender S, Goldstein K, et al. Partial normalization by dietary cod-liver oil of increased microvascular albumin leakage in patients with insulin-dependent diabetes and albuminuria. *N Engl J Med*. 1989;321:1572-7.
8. Landymore RW, MacAulay M, Sheridan B, Cameron C. Comparison of cod-liver oil and aspirin-dipyridamole for the prevention of intimal hyperplasia in autologous vein grafts. *Ann Thorac Surg*. 1986;41:54-7.
9. Brox JH, Killie JE, Gunnes S, Nordoy A. The effect of cod liver oil and corn oil on platelets and vessel wall in man. *Thromb Haemost*. 1981;46:604-11.
10. Hansen JB, Olsen JO, Wilsgard L, Osterud B. Effects of dietary supplementation with cod liver oil on monocyte thromboplastin synthesis, coagulation and fibrinolysis. *J Intern Med Suppl*. 1989;225:133-9.
11. Anon. Possible interaction between warfarin and cranberry juice. *Current Problems in Pharmacovigilance*. 2003;29:8.
12. Grant P. Warfarin and cranberry juice: An interaction? *J Heart Valve Dis*. 2004;13:25-6.
13. Suvarna R, Pirmohamed M, Henderson L. Possible interaction between warfarin and cranberry juice. *BMJ*. 2003;327:1454.
14. Hodek P, Trefil P, Stiborova M. Flavonoids-potent and versatile biologically active compounds interacting with cytochromes P450. *Chem Biol Interact*. 2002;139:1-21.
15. Li Z, Seeram NP, Carpenter CL, et al. Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc*. 2006;106:2057-61.
16. Greenblatt DJ, von Moltke LL, Perloff ES, et al. Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: in vitro and clinical studies. *Clin Pharmacol Ther.* 2006;79:125-33.
17. Lilja JJ, Backman JT, Neuvonen PJ. Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam - probes of CYP2C9, CYP1A2 and CYP3A4. *Clin Pharmacol The*. 2007:81:833-9.

18. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. *J Urol*. 2008;180:1367-72.
19. Committee on Safety of Medicines : Possible interaction between warfarin and cranberry juice. *Curr Prob Pharmacovigilance*. 2003;29(8):8-8.
20. Griffiths AP: Fatal haemopericardium and gastrointestinal haemorrhage due to possible interaction of cranberry juice with warfarin. *J R Soc Health*. 2008;128(6):324-326.
21. Mergenhagen KA: Elevated International Normalized Ratio after concurrent ingestion of cranberry sauce and warfarin. *Am J Health-System Pharm*. 2008;65(22):2113-2116.
22. Paeng CH: Interaction between warfarin and cranberry juice. *Clin Ther*. 2007;29(8):1730-1735.
23. Rindone JP: Warfarin-cranberry juice interaction resulting in profound hypoprothrombinemia and bleeding. *Am J Ther*. 2006;13(3):283-284.
24. Izzat MB, Yim APC & El-Zufari H: A taste of Chinese medicine. *Ann Thorac Surg*. 1998;66:941-942.
25. Yu CM, Chan JCN & Sanderson JE: Chinese herbs and warfarin potentiation by danshen. *J Intern Med*. 1997;241(4):337-339.
26. Tam L, Chan T, Leung W et al: Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust NZ J Med*. 1995;25(3):258.
27. Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements: a 5-year toxicological study (1991-1995). *Drug Saf*. 1997;17:342-56.
28. Ellis GR & Stephens MR: Minerva. *BMJ*. 1999;319:650.
29. Junjie T & Huaijun H: Effects of Radix Angelicae Sinensis on hemorrheology in patients with acute ischemic stroke. *J Tradit Chin Med.* 1984;4:225-228.
30. Ko FN, Wu TS, Liou MJ et al: Inhibition of platelet thromboxane formation and phosphoionsitides breakdown by osthole from Angelica pubescens. *Thromb Haemost.* 1989;62:996-999.
31. Page RL & Lawrence JD: Potentiation of warfarin by dong quai. *Pharmacotherapy*. 1999;19:870-876.
32. Guivernau M, Meza N, Barja P et al: Clinical and experimental study on the longer-term effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation, thromboxane formation, and prostacycline production. *Prostaglandins Leukot Essent Fatty Acids*. 1994;51:311-316.
33. Lambert JP, et al. Potential interaction between warfarin and boldo-fenugreek. *Pharmacotherapy*. 2001;21:509-512.
34. Bordia A, Verma SK, Srivastava KC. Effect of ginger (Zingiber officinale Rosc.) and fenugreek (Trigonella foenumgraecum L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins Leukot Essent Fatty Acids*. 1997;56:379-84
35.
36. Buckley MS, Goff AD & Knapp W: Fish oil interaction with warfarin. *Ann Pharmacother*. 2004;38:50-53.
37. Svaneborg N, Kristensen SD, Hansen LM, et al. The acute and short-time effect of supplementation with the combination of n-3 fatty acids and acetylsalicylic acid on platelet function and plasma lipids. *Thromb Res*. 2002;105:311-6.

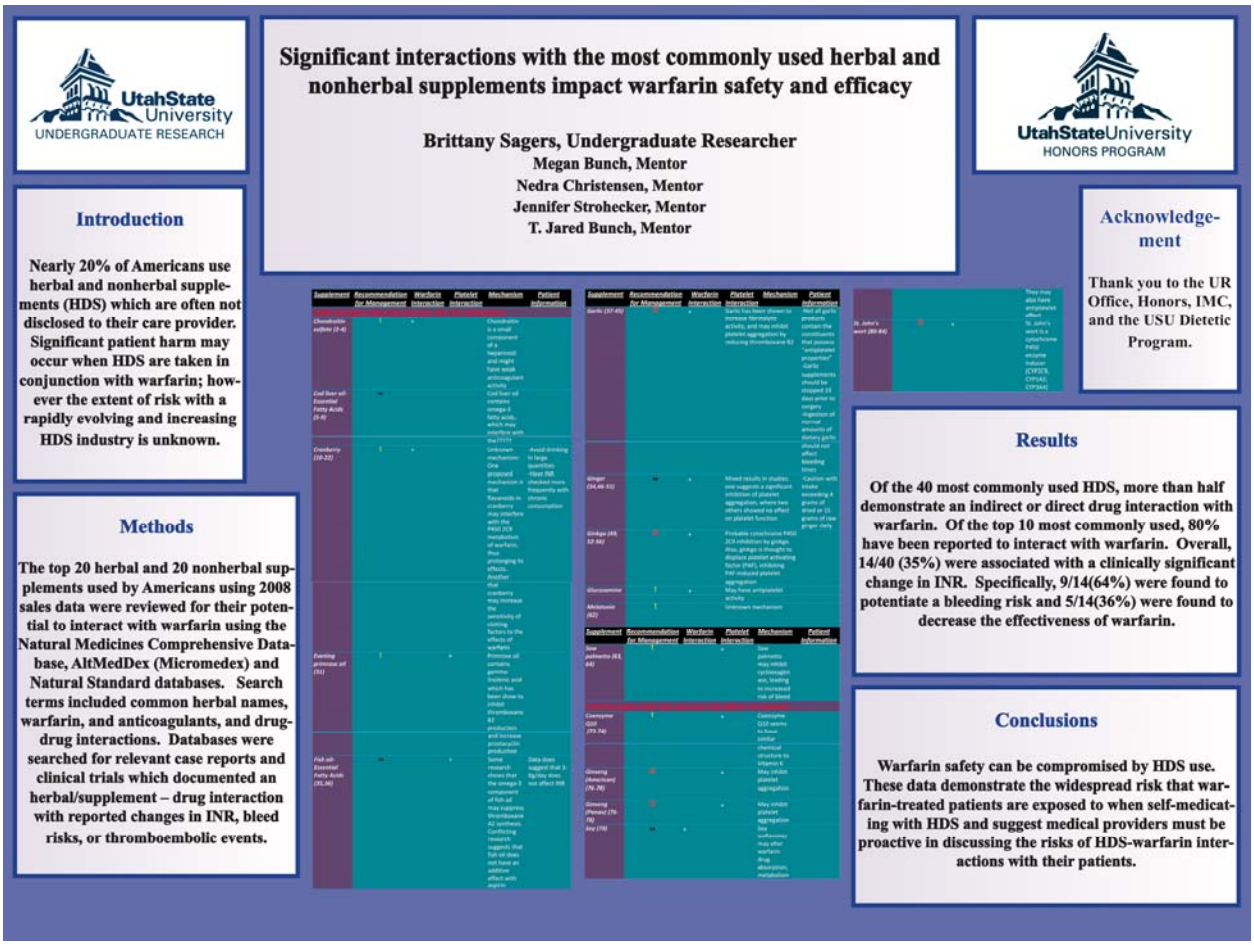
38. Burnham BE: Garlic as a possible risk for postoperative bleeding (letter). *Plast Reconstr Surg*. 1995;95(1):213.
39. German K, Kumar U & Blackford HN: Garlic and the risk of TURP bleeding. *Br J Urol*. 1995;76(4):518.
40. Kiesewetter H, Jung F, Jung EM et al: Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *Eur J Clin Pharmacol*. 1993a;45(4):333-336.
41. Harenberg J, Giese C & Zimmermann R: Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia. *Atherosclerosis*. 1988;74(3):247-249.
42. Legnani C, Frascaro M, Gauzzaloca G et al: Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. *Arzneimittelforschung*. 1993;43(2):119-122.
43. Rose KD, Croissant PD, Parliament CF et al: Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery*. 1990;26:880-882.
44. Sunter W: Warfarin and garlic. *Pharm J*. 1991;246:722.
45. Rahman K, Billington D. Dietary supplementation with aged garlic extract inhibits ADP-induced platelet aggregation in humans. *J Nutr*. 2000;130:2662-5.
46. Kruth P, Brosi E, Fux R et al: Ginger-associated overanticoagulation by phenprocoumon. *Ann Pharmacother*. 2004;38:257-260.
47. Janssen PL, Meyboom S, van Staveren WA et al: Consumption of ginger (Zingiber Officinale Roscoe) does not affect ex vivo platelet thromboxane production in humans. *Eur J Clin Nutr*. 1996;50(11):772-774.
48. Lumb AB: Effect of dried ginger on human platelet function. *Thromb Haemost*. 1994;71(1):110-111.
49. Jiang X, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol*. 2005;59:425-432.
50. Thomson M, Al-Qattan KK, Al-Sawan SM, et al. The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent. *Prostaglandins Leukot Essent Fatty Acids.* 2002;67:475-8.
51. Dorso CR, et al. Chinese food and platelets. *N Engl J Med*. 1980;303:756-757.
52. Matthews MK Jr. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology*. 1998;50:1933-1934.
53. Engelsen J, et al. Effect of coenzyme Q10 and Ginkgo biloba on warfarin dosage in stable, long-term warfarin treated outpatients. A randomised, double blind, placebo-crossover trial. *Thromb Haemost*. 2002;87:1075-1076.
54. Rowin J, et al. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. *Neurology*. 1996;46:1775-1776.
55. Gilbert GJ. Ginkgo biloba. *Neurology*. 1997;48:1137.
56. Gaudineau C, Beckerman R, Welbourn S, Auclair K. Inhibition of human P450 enzymes by multiple constituents of the Ginkgo biloba extract. *Biochem Biophys Res Comm*. 2004;318:1072–8.
57. Sullivan DM, Ford MA, Boyden TW. Grapefruit juice and the response to warfarin. *Am J Health-Syst Pharm. 1998;55:1581-3*.

58. Bachmann HU, Hoffmann A. Interaction of food supplement L-carnitine with oral anticoagulant acenocoumarol. *Swiss Med Wkly*. 2004;134:385.
59. Martinez E, Domingo P & Roca-Cusachs A: Potentiation of acenocoumarol action by L-carnitine (letter). *J Intern Med*. 1993; 233:94.
60. Lam AY, Elmer GW, Mohutsky MA. Possible interaction between warfarin and Lycium Barbarum. *Ann Pharmacother*. 2001;35:1199-201.
61. 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.
62. Herxheimer A & Petrie KJ: Melatonin for the prevention and treatment of jet lag (Cochrane Review). In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software.
63. Yue QY & Jansson K: Herbal drug curbicin and anticoagulant effect with and without warfarin: possibly related to the vitamin E component. *J Am Geriatr Soc*. 2001;49(6):838.
64. Cheema P, El-Mefty O & Jazieh AR: Intraoperative haemorrhage associated with the use of extract of Saw Palmetto herb: a case report and review of literature. *J Intern Med*. 2001;250(2):167-169.
65. Hansten PD: Effects of vitamins on drug action. Drug Interactions Newsletter. Applied Therapeutics, Inc, San Francisco, CA, 1981; 1:35-38.
66. Hardman JG, Limbird LL, Molinoff PB, eds. Goodman and Gillman's The Pharmacological Basis of Therapeutics, 9th ed. New York, NY: McGraw-Hill, 1996.
67. Shinn AS (ed): Evaluations of Drug Interactions. CV Mosby Company, St Louis, MO, USA, 1985.
68. Corrigan JJ Jr & Ulfers LL: Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. *Am J Clin Nutr*. 1981;34(9):1701-1705.
69. Littleton F. Warfarin and topical salicylates. *JAMA*. 1990;263:2888.
70. Tam LS, et al. Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med*. 1995;25:258.
71. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother*. 2000;34:729-33.
72. Engelsen J, Nielsen JD & Hansen KF: Effect of coenzyme Q10 and gingko biloba on warfarin dosage in patients on long-term warfarin treatment. A randomized, double-blind, placebo-controlled cross-over trial (Abstract-Article in Danish). *Ugeskr Laeger*. 2003;165(18):1868-1871.
73. Spigset O: Reduced effect of warfarin caused by ubidecarenone. *Lancet*. 1994;344:1372-1373.
74. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health Syst Pharm*. 2000;57:1221-7.
75. Grebe HB, Gregory PJ. Inhibition of warfarin anticoagulation associated with chelation therapy. *Pharmacotherapy*. 2002;22:1067-9.
76. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health Syst Pharm*. 1997;54:692-3.
77. Yuan CS, Wei G, Dey L, et al. American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med*. 2004;141:23-7.
78. Rosado MF: Thrombosis of a prosthetic aortic valve disclosing a hazardous interaction between warfarin and a commercial ginseng product. *Cardiology*. 2003;99(2):111.

79. Cambria-Kiely JA: Effect of soy milk on warfarin efficacy. *Ann Pharmacother*. 2002;36(12):1893-1896.
80. Jiang X, Williams KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol*. 2004;57:592-9.
81. Jiang X, Blair EY, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. *J Clin Pharmacol*. 2006;46:1370-8
82. Yue QY, Bergquist C, Gerden B. Safety of St. John's wort (Hypericum perforatum). *Lancet.* 2000;355:576-7.
83. Groning R, Breitkreutz J, Muller RS. Physico-chemical interactions between extracts of Hypericum perforatum L. and drugs. *Eur J Pharm Biopharm*. 2003;56:231-6.
84. Maurer A, et al. Interaction of St. John's wort extract with phenprocoumon. *Eur J Clin Pharmacol.* 1999;55:A22.
85. McKevoy GK, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 1998.
86. Lubetsky A, Dekel-Stern E, Chetrit A et al: Vitamin K intake and sensitivity to warfarin in patients consuming regular diets. *Thromb Haemost*. 1999;81:396-399.

Appendix

Research Poster



Acknowledgments

Thank you to the Utah State University Undergraduate Research Office, Honors program and Dietetic program, and Intermountain Medical Center.

Author Biography

Brittany Jean Sagers was born in Salt Lake City, Utah. She was raised in Grantsville, Utah and graduated from Grantsville High School in 2005. She then attended Snow College in Ephraim, Utah as an Academic Excellence Scholar and graduated Magna Cum Laude with her Associate of Science degree in the spring of 2007. Brittany then transferred to Utah State University as a Dean's Scholar to pursue her education in dietetics. She will graduate with her Bachelor of Science degree in Nutrition, Dietetics and Food Sciences with an emphasis in Dietetics in the spring of 2010.

During her career at Utah State, Brittany was a member of the Golden Key International Honor Society, the USU Honors Program and the USU Dietetics Club, as well as a student member of USU's Undergraduate Research Advisory Board, representing the College of Agriculture for the 2009-2010 academic year.

Her future plans are to complete a dietetic internship through Utah State University in 2010-2011. After becoming a Registered Dietitian she is planning on achieving a Master of Dietetic Administration from Utah State University.