INTERACTIONS BETWEEN HERBAL SUPPLEMENTS AND WARFARIN:

A PATIENT TEACHING TOOL

by

Kimberlee Danielle Gilbert

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APPROVAL

of a professional paper submitted by

Kimberlee Danielle Gilbert

This professional paper has been read by each member of the professional paper committee and has been found to be satisfactory regarding content, English usage, format, citation, bibliographic style, and consistency and is ready for submission to The Graduate School.

Dr. Karen Zulkowski

Approved for the College of Nursing

Dr. Donna Williams

Approved for The Graduate School

Dr. Carl A. Fox
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Kimberlee Danielle Gilbert

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Many Americans are using herbal supplements without telling their primary care providers. When a person is taking warfarin, a medication that has a narrow therapeutic window and the potential for interaction with many substances, including food, medications, and supplements, providers must inform them of the risks. A literature review was done to find current literature related to warfarin and herbal interactions. Limited quality data is available, with most literature found being case reports, and small population studies. A patient teaching pamphlet was created and tested using a pre-test/posttest in a convenience sample of 18 patients that use warfarin at an internal medicine clinic in Northern Wyoming. The results showed improvement in posttest scores in 17 of 18 participants. Mean improvement was 10.9%. Providers should include herbal supplements in routine medication history. Providers should teach all patients using warfarin about potential interactions with herbal supplements and about the need to inform their provider about supplements. Lack of standardization of herbal supplements makes it difficult to research the risks and benefits as well as potential interactions. More research is needed to determine risks.
CHAPTER 1

INTRODUCTION

Many Americans use herbal and dietary supplements in combination with prescription medication, including warfarin, which has a narrow therapeutic window and multiple potential interactions. Many people believe that because herbal supplements are sold without a prescription that they are safe and they do not tell their primary care provider about the supplements they are taking. This could lead to interactions with potentially life-threatening results including excessive anticoagulation or clotting from reduced effect of warfarin. A review of the literature was done to examine potential interactions between herbal supplements and warfarin and a patient teaching pamphlet was created as a tool for providers. This teaching pamphlet was tested using a convenience sample of patients who currently take warfarin in an internal medicine clinic in north central Wyoming. It was shown to increase the knowledge of potential interactions between warfarin and herbal supplements.

Problem

Persons taking warfarin do not receive information about potential life-threatening interactions with common herbal supplements.
Purpose

The purpose of this paper is to describe the current literature regarding herb-drug interactions with warfarin and develop an effective teaching pamphlet for patients regarding potential interactions between herbal/dietary supplements and warfarin.

Background

Many Americans are using herbal or dietary supplements. In 2007, 17.7% of adults reported use of non-vitamin, non-mineral, natural products in the past 12 months (Barnes, 2008). Interactions between prescription medications and herbal supplements can occur with potentially deadly side effects (Bush, 2007; Fugh-Berman, 2000). However, patients do not always tell their health care providers about their use of herbal/dietary supplements (Elmer, 2007; Hailemaskel, 2001). One study found that 63% of the patients surveyed did not tell their family physician about their use of alternative therapies (Drivdahl, 1998).

In addition, the Food and Drug Administration (FDA) regulates the uses, doses, and side effects of prescription medications, but not herbal/dietary supplements (FDA, 2003). Herbal supplements are not required to have dosage, efficacy, or safety testing. Many patients believe that because the term “natural” is used to describe herbs, that they are safe (Hailemaskel, 2001). Very little is known about the safety of herbal supplements (Elmer, 2007).

Warfarin is the most prescribed anticoagulant in North America. It is the preferred drug in long-term anticoagulation therapy. The anticoagulation effect of warfarin is
created by inhibition of enzymes responsible for cyclic interconversion of Vitamin K in the liver. There are certain Vitamin K dependent clotting factors, specifically II (prothrombin), VII, IX, and X, as well as endogenous anticoagulant proteins C and S.

Warfarin acts by inhibiting the supply of Vitamin K which serves as a cofactor in the making of these proteins, therefore decreasing the rate of clotting by decreasing the amount of clotting factors. Warfarin has no effect on already existing clotting factors or clots (Dipiro, 2008). The major risk factor in patients using warfarin therapy is bleeding, and this can range in severity from minor to life-threatening. Warfarin has a narrow therapeutic index, and its therapeutic effects may be changed by dietary and herbal supplements.

Patients using warfarin are monitored closely for change in response to warfarin to minimize adverse events and maximize therapeutic effect. Routine prothrombin time (PT), which measures clotting time, is drawn on each patient with frequency based on their condition, changes in medication, or response to warfarin. Internationalized Normalized Ratio (INR) is used to remove variability issues that prothrombin time has. INR is used to determine whether the patient is therapeutic, subtherapeutic, or overanticoagulated. Therapeutic INR is based on the condition of the patient being treated, but is usually 2.5, or a range from 2-3. There are certain conditions that goal INR is 3.0, and the acceptable range is 2.5-3.5 (Dipiro, 2008)

Patients may be unaware of the risk of taking herbal supplements while taking warfarin. In persons using warfarin, more than two-thirds used herbal and dietary supplements, 47% did not view herbal supplements as drugs, and 63% said they would
not consult with their pharmacist or provider before using a supplement (American Heart Association, 2010). A communication gap between providers and patients can lead to severe and even life-threatening events when patients use warfarin therapy for anticoagulation and they do not understand the risks of taking herbal supplements.

**Definitions**

**Herbal/Dietary Supplements**

This paper frequently refers to herbal and dietary supplements. These terms describe complementary and alternative medicine, or CAM, which is defined by the U.S. National Center for Complementary and Alternative Medicine as “a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine” (2007). CAM in oral forms may be called herbal, botanical, supplements, vitamins, minerals and natural products.

**Interactions**

The definition of interaction for the purpose of this paper is a change in the pharmacologic action or effect of a medication through multiple potential mechanisms, including absorption, distribution, metabolism, excretion, or bioavailability (Philp, 2004).
CHAPTER 2

LITERATURE REVIEW

The purpose of this literature review is to describe the current literature relevant to herb-drug interactions and warfarin to create an evidence-based teaching tool for patients.

Literature Search

A literature search was done in CINAHL (Cumulative Index for Nursing and Allied Health) and Medline using the search terms herb-drug interactions, warfarin, boldo, chamomile, coenzyme Q10, cranberry, curcumin, danshen, dong quai, Echinacea, fenugreek, fish oil, garlic, ginger, ginkgo, ginseng, green tea, maitake, omega 3 fatty acid, policosanol, saw palmetto, soy milk, and St. John’s wort to find the most current data available on the topic of herb-drug interactions with warfarin. Search terms were used together and separately. References of the articles found in the search were scanned and relevant articles were found to use in the review. Two reference books were found to use in the review (Philp, 2004; Stargrove, 2008)

Not all articles found in the search were included in the review. To find the most relevant literature for this review and project, exclusion criteria were set. These criteria included: pediatric, reproductive health, oncology, nursing curricula, general complementary and alternative medicine (CAM) use, nephrology, general cardiovascular effects of herbal supplements, diabetes, perioperative considerations, animal studies, uses
for herbs, prescription medication interaction with warfarin, general use of warfarin, non-
English articles, and drug development.

**Results**

After the thorough literature search, the data was gathered and organized into a table to determine the relevance of the evidence (Appendix A). The results of the literature search were analyzed and evidence was reviewed. Numerous case studies were found regarding single incidence of increased bleeding or decreased anticoagulant effect while using herbals and warfarin together but causal relationship cannot be determined in a case study. Few studies have been done to determine causal relationships. In the studies found the population sizes were small in all the studies and most were done on healthy volunteers. Multiple literature reviews have been done to look at the evidence of interactions between herbal supplements and prescription drugs and the consensus in the review literature is that lack of regulation of herbal supplements creates a difficult time for researchers to prove causal relationships and make recommendations about what supplements are safe or unsafe to take with prescription drugs (Basila, 2005; Boullata, 2005; Chavez, 2006; Cheng, 2003; Cranwell-Bruce, 2008; Gardiner, 2008; Greenblatt, 2005; Heck, 2000; Hu, 2005; Izzo, 2004; Izzo, 2005; Izzo, 2001; Izzo, 2009; Mills, 2005; Saw, 2006; Vaes, 2000; Wittkowsky, 2005; Yarnell, 2002; Zarowitz, 2010).

**Herbs that May Cause Bleeding**

**Boldo**  Boldo is a coumarin containing herb with a potential for increasing the action of warfarin (Izzo, 2004). There is one case study that described a patient taking a
product of boldo and fenugreek that increased a patient’s INR. The INR normalized after discontinuing the product and increased on rechallenge (Lambert, 2001).

**Chamomile** Some forms of chamomile, like Roman chamomile, may contain coumarin and give it a theoretical increased risk of bleeding when given with warfarin (Philp, 2004)

A case report was found of a 70 year old female who was stable on long term warfarin after a valve replacement 30 years prior to this event having an elevated INR (7.9) and bleeding (retroperitoneal hematoma and hemoglobin of 8) after using chamomile tea (4-5 cups per day) and lotion to relieve respiratory symptoms. Her INR had been 3.6 five days earlier when she was treated for the upper respiratory infection (Segal, 2006).

**Cranberry** Multiple case studies report incidences of increased bleeding when taking warfarin and cranberry products together. One patient died of a gastrointestinal and pericardial hemorrhage after being admitted to the hospital with an INR of >50. He had recently been ill with a chest cold and reported having a poor appetite and only taking his regular medications and cranberry juice for 6 weeks. His regular medications included warfarin, phenytoin, and digoxin. It was reported that his INR had been controlled prior to his illness (Suvarna, 2003). One 69 year old patient who had been stable on warfarin for atrial fibrillation was admitted to the hospital for surgery. He had an admission INR of 12, which returned to 2 after Vitamin K was given. When warfarin was started after surgery, his INR quickly rose to 8 and then 11. He did have hematuria. The patient had been drinking approximately 2 liters of cranberry juice per day because
of chronic urinary tract infections. He was advised to stop drinking cranberry juice and within 3 days of stopping, his INR was 3 (Grant, 2004). One case study reported that after a year of having a stable INR with atrial fibrillation, a 75 year old man had an elevated INR (4.8) after ingesting cranberry sauce for one week (Mergenhagen, 2008).

Three small studies have been done testing the effects of cranberry juice on warfarin with varying results. Mohammed Abdul (2008) found that cranberry altered the pharmacodynamics of warfarin and may increase the anticoagulant effect using an open-label, three treatment, crossover randomized clinical trial (N=12). Ansell (2009) found that no significant different occurred between placebo group or cranberry juice group (240mL daily over a 2 week period) in S- or R- warfarin plasma levels in a randomized, double-blind, placebo controlled trial (N=30). Mellen (2010) found no significant different in placebo versus cranberry juice group (240mL twice per day for 7 days) at baseline, days, 2, 6, and 8 in a prospective, open-labeled study (N=10).

**Curbicin** Curbicin is a product that contains saw palmetto, pumpkin, and Vitamin E. One case study reported that a 73-year-old male had an INR of 2.1 after taking Curbicin for greater than one year while not taking any anticoagulation therapy and with a normal albumin (Yue, 2001). His INR decreased with Vitamin K to 1.3-1.4, but did not return to normal (1.0) until the man discontinued Curbicin. Another case report involved a 61-year-old man who was stable on warfarin (INR 2.4). He started taking Curbicin for micturation difficulties, and his INR increased to 3.4. His INR returned to previous level after discontinuing Curbicin (Yue, 2001).
Danshen (Salvia Miltiorrhiza) Danshen has anticoagulant qualities and contains coumarin which gives it a theoretical increased risk for bleeding when taken with or without an anticoagulant (Izzo, 2004; Fugh-Berman, 2001; Philp, 2004).

There are multiple case reports of bleeding in patients taking Danshen while taking warfarin. A 62 year old male with a history of a mitral valve replacement on long term warfarin was reported to have an increased INR of 8.4 and bleeding into the pleural and pericardial spaces when he consumed Danshen (Izzat, 1998). A 66 year old male on warfarin with a history of atrial fibrillation, rheumatic mitral stenosis, cerebral embolus, and gastric adenocarcinoma had an increased INR and gastric bleeding after taking Danshen (Tam, 1995). A 48 year old female on warfarin with a history of rheumatic heart disease, mitral stenosis, and atrial fibrillation had increased INR when taking Danshen (Yu, 1997).

Dong Quai (Danggui, A. Sinensis) Dong Quai is a coumarin containing herb giving it a theoretical risk for increased bleeding when taken with or without an anticoagulant (Izzo, 2004). Two case studies were found describing potential interactions between Dong Quai and warfarin. One report described a 46 year old African American female stabilized on warfarin for atrial fibrillation that had a greater than two fold increase in PT/INR after taking Dong Quai for 4 weeks (Page, 1999). Another report described a patient stable on warfarin for 10 years presented with widespread bruising and an elevated INR of 10 one month after starting Dong Quai for menopausal symptoms (Ellis, 1999). She was hospitalized for 6 days.
Fenugreek  Fenugreek contains coumarin and theoretically carries a risk for increased anticoagulant effect or bleeding (Izzo, 2004). A case study discussed previously under the Boldo heading described a patient taking a product of boldo and fenugreek that increased a patient’s INR. The INR normalized after discontinuing the product and increased on rechallenge (Lambert, 2001).

Garlic (Allium Sativum) Multiple sources describe an increased risk of bleeding from ingestion of garlic (Awang, 2002; Hu, 2005). Garlic decreases platelet aggregation which increases the risk of bleeding (Izzo, 2004). Spontaneous bleeding has been documented in persons taking garlic (Awang, 2002). Two patients were reported to have increased INR while taking garlic and warfarin (Sunter, 1991).

Three studies were found testing interactions between garlic and warfarin. One studied the pharmacokinetics and pharmacodynamics of warfarin when taken with garlic in an open-label, three-treatment, crossover randomized clinical trial of 12 healthy volunteers and found no significant alteration in pharmacokinetics or pharmacodynamics of warfarin (Mohammed Abdul, 2008). One double-blind, randomized, placebo controlled pilot study found no significant differences in bleeding events between the group that took aged garlic extract (AGE)(N=22) or placebo (N=26)(Macan, 2006). One double-blind, placebo-controlled study found no significant effect on platelet aggregation in 14 males (Morris, 1995).

Ginger  Ginger has been reported to have antiplatelet characteristics (Heck, 2000). One case report was found describing epistaxis and an increased INR after a 76 year old
female who was taking phenprocoumon (an anticoagulant) in addition to an unspecified amount of ginger (Kruth, 2004).

Three studies were found testing interactions between warfarin and ginger. One study found no significant effects on clotting status, pharmacokinetics, or pharmacodynamics of warfarin in an open-labeled, three-way, randomized crossover study of 12 healthy volunteers (Jiang, 2005). In another study done by Jiang (2006), ginger did not affect the pharmacokinetics of warfarin in a randomized, open-label, placebo-controlled, 3-treatment, 3-sequence crossover studies with 14 day washout between. One prospective, longitudinal study over 16 weeks with 171 participants found ginger to be associated with self-reported bleeding events when other risk factors were accounted for (Shalansky, 2007).

Ginkgo (Ginkgo Biloba) Ginkgo, also known as ginkgo biloba, has antiplatelet properties and may increase the risk for bleeding independent of other factors (Izzo, 2004). One case report was found describing a 78 year old female stabilized on warfarin for 5 years that had a left parietal hemorrhage with significant cognitive impairment 2 months after starting ginkgo biloba. Cognitive function improved after 1 month of rehabilitation and discontinuing ginkgo biloba (Matthews, 1998).

Two studies were found testing interactions between ginkgo biloba and warfarin. One randomized, double-blind, placebo controlled study found no change in INR over 4 weeks of ingestion of ginkgo and warfarin in 24 subjects (Engelsen, 2002). Another study found no changes in pharmacokinetics of warfarin when taken with ginkgo in 12 healthy volunteers (Jiang, 2005).
Maitake

There is one case report of a potential interaction with maitake extract. A 79 year old with atrial fibrillation and bladder cancer who was stable on warfarin (INR 2-3) for 2 months took maitake and had an INR of 5.1. The patient did not discontinue maitake so his warfarin was decreased by 11% of his previous dose while monitoring his INR (Hanselin, 2010).

Omega 3 Fatty Acid (Fish Oil)

One case report was found describing an increased INR when a 67 year old female previously stable on warfarin 1.5mg daily (INR 2.8) and fish oil (1gm per day) increased her dose of fish oil to 2gm daily. Her INR then increased to 4.3. When she decreased her dose of fish oil to 1gm daily her INR became subtherapeutic with 1mg warfarin daily and the dose was then increased to 1.5mg daily and her INR then became therapeutic again (Buckley, 2004).

Policosanol

Policosanol may have properties that decrease platelet aggregation. A clinical trial was done using an open-label, randomized, three treatment, crossover method testing the pharmacokinetics and pharmacodynamics of warfarin when policosanol was given concomitantly in 12 healthy adults. It showed no significant effect on pharmacokinetic or warfarin response (Mohammed Abdul, 2010).

Saw Palmetto

There was one case study with a report of intraoperative hemorrhage during a surgical resection of a brain tumor in a 53 year old male with a normal INR and PTT preoperatively. He was not taking warfarin or other anticoagulants but had been taking saw palmetto. He did not stop the saw palmetto preoperatively (Cheema, 2001).
Other Herbs with Potential to Cause Bleeding Reports of potential or theoretical risks of bleeding were based on known pharmacologic mechanisms of the herb. Herbs that may cause bleeding because they contained coumarin or coumarin-like substances include: angelica root, anise, arnica flower, asafetida, Bai zhi (angelica root), celery, horse chestnut, licorice root, lovage root, parsley, passionflower, Pau d’arco, Quassia, red clover, rue, and sweet clover (Philp, 2004). Herbs that may cause bleeding because of antiplatelet activity or because they have salicylates include: bromelain, clove, feverfew, meadowsweet, motherwort, onion, poplar, tamarind, and willow bark (Philp, 2004). Herbs that may cause bleeding from unknown mechanism include: bogbean, borage seed oil, capsicum, devil’s claw, ginsana, papain, and papaya extract (Philp, 2004).

Herbs that May Reduce the Effectiveness of Warfarin

Coenzyme Q10 Coenzyme Q10 is structurally related to Vitamin K, which decreases the effect of warfarin (Shalansky, 2007). Case reports have shown decreased effectiveness of warfarin from concomitant use of Coenzyme Q10 with warfarin (Philp, 2004).

Two studies were looking at interactions between Coenzyme Q10 and warfarin. Shalansky (2007) found Coenzyme Q10 to increase the risk of bleeding in a prospective, longitudinal study of 171 participants over 16 weeks. This was, according to the author, the only documented case of an increased risk of bleeding from Coenzyme Q10. One placebo-controlled, double-blind study found no effect on the INR of 24 patients on long-term warfarin taking 100mg of Coenzyme Q10 (Engelsen, 2002).
**Echinacea**  An open-label, randomized, three treatment, crossover, clinical trial testing the pharmacokinetics and pharmacodynamics of Echinacea was done in 12 healthy adults. It showed an increased clearance of s-warfarin when Echinacea was given with warfarin, but there was no significant change in INR (Mohammed Abdul, 2010).

**Ginseng (Panax Ginseng, P. Quinquefolium, Korean Red)** There are multiple forms of ginseng. This section includes literature found on all types of ginseng. Some of the articles specified the type, while others did not. Two case reports were found describing potential interactions between warfarin and ginseng, both describing decreased anticoagulant effect or subtherapeutic INR. One case reports a 47 year old man stable on warfarin for 5 years (INR 3.0-4.0) who had a decreased INR (1.5) two weeks after initiating ginseng on his own to boost his “energy”. His INR returned to 3.3 two weeks after discontinuing ginseng (Janetzky, 1997). Another case report describes a 58 year old with a subtherapeutic INR (1.4) and thrombosis on a mechanical valve after taking a ginseng product (Rosado, 2003).

Four studies were found that looked at interactions between ginseng and warfarin. Yuan (2004) found in a randomized, double-blind, placebo-controlled trial with 20 healthy volunteers that American ginseng significantly reduced the INR, C\text{max} and area under curve (AUC) of warfarin. Jiang (2004) found no effect on pharmacokinetics or pharmacodynamics of warfarin when ginseng was given in 12 healthy patients in an open-label, three-way, crossover randomized study. In a randomized, open-label, placebo-controlled study study of 25 patients with ischemic stroke, there was no significant difference in INR between warfarin group and warfarin and ginseng group.
A study of Asian ginseng in 24 healthy volunteers found an increase in clearance of s-warfarin, but no clinical significance (Jiang, 2006). A study done on 25 patients with cardiac valve replacement using Korean red ginseng found a decrease in INR compared to placebo (Lee, 2010).

**Green Tea** Green tea contains Vitamin K and therefore has a theoretical risk for decreased anticoagulant effect of warfarin (Taylor, 1999). One case report was found describing a subtherapeutic INR in a 44 year old patient who had been stabilized on warfarin previously after he began drinking one-half to one gallon of green tea per day. His INR increased to 2.55 after he stopped drinking green tea (Taylor, 1999).

**Soy Milk** One case report describes a subtherapeutic INR in a 70 year old male taking warfarin for atrial fibrillation after he ingested soy milk. His INR returned to therapeutic range after discontinuing soy milk (Cambria-Kiely, 2002).

**St. John’s Wort (Hypericum Perforatum)** There were three literature reviews specifically related to interactions of St. John’s wort with prescription medications (Bressler, 2005; Henderson, 2002; McIntyre, 2000). These discussed the potential for interaction with warfarin based on induction of CYP2C9 enzyme and/or decreased gastrointestinal absorption.

Yue (2000) reports seven cases of decreased INR with concomitant use of warfarin and St. John’s wort. The ages of patients reporting were 56-85, 4 were female, 3 were male. Some patients increased their dose of warfarin while others stopped St. John’s wort to return their INR to therapeutic range (Yue, 2000). One case report was found that
described a bleeding episode and elevated INR with concomitant use of warfarin and St. John’s wort (Bayramicli, 2011). These case reports are contradictory to each other.

Two studies were found testing effects of St. John’s wort on warfarin. Jiang (2004) found that St. John’s wort significantly increased the clearance of both s-warfarin and r-warfarin, which resulted in a significant reduction in the pharmacologic effect of rac-warfarin in an open-label, three-way, crossover, randomized study of 12 healthy volunteers. In another study done by Jiang (2006), 24 volunteers participated in a randomized, open-label, controlled, 3-treatment, 3-sequence crossover study. This showed when the patients were pretreated with St. John’s wort, the clearance of a single dose of warfarin (25mg) was increased.

Other Herbs that May Reduce the Effect of Warfarin Goldenseal may reduce anticoagulant effect of warfarin but the mechanism of the interaction is unknown (Philp, 2004). No articles were found in CINAHL or Medline related to interactions between goldenseal and warfarin.

Limitations

The large amount of poor quality data regarding interactions between warfarin and herbal supplement interactions may limit understanding of each of the potential interactions. Future research may be done to gain additional insight into specific herbs and the mechanisms behind the interaction. The data found is limited in quality. Case studies and small sample sized studies are not sufficient data to make generalizations about safety. More research is needed to ensure safety before concomitant use of warfarin
with any herbal supplement is recommended. Lack of regulation of herbal supplements makes research difficult, if not impossible.

Many limitations exist when looking at data regarding herbal supplements. Lack of standards in the industry and lack of regulation makes research difficult and creates a difficult presentation to patients by health care providers in recommendations of supplement use (Philp, 2004). Ultimately, patients on warfarin should be monitored closely using regular INR checks and providers should educate patients on the need to share all medications and herbal supplements they may be taking, to ensure safe monitoring when changes occur.
CHAPTER 3

METHODS

Preparation of the Patient Teaching Pamphlet

After the literature review was performed, the data was gathered to create a pamphlet that could be used as a tool for providers to teach patients about potential risks of taking herbal supplements while taking warfarin. The pamphlet was created using Microsoft Word and was created as a trifold double sided paper. It tested at an 11th grade reading level when tested for readability (Simpson, 2009).

Teaching about Coumadin

Background information was written about warfarin to inform the patients what the uses and risks are of taking the medication. This information was taken from the U.S. full prescribing information (Bristol-Myers Squibb, 2011). Included in this were reasons for taking warfarin, risks of bleeding that are associated with warfarin, risks of interactions associated with warfarin, and a brief description of how warfarin effectiveness is monitored.

Teaching about Taking Herbal Supplements with Coumadin

It is important to teach patients the risks associated in taking herbal supplements while taking warfarin. Information was given in the pamphlet that described the difficulties in understanding all the effects of herbal supplements including lack of
standardization in dosage and content of herbal supplements, and lack of regulation by the FDA.

Supplements that Have Potential to Cause Interaction

Information gained from the data in the literature review was provided in this section of the pamphlet. The types of interactions were divided by potential to cause bleeding based on case reports or theoretical risks and the potential to decrease the effects of warfarin.

Important Information

Additional information was included at the end of the pamphlet with a summary of how to use the information in the pamphlet. The pamphlet advises patients to discuss all herbal supplements with their primary care provider and any person that prescribes them medication. It also discusses the importance of watching for signs and symptoms of bleeding or clotting which may occur as a result of increased or decreased effect of warfarin.

Testing the Pamphlet

A pilot study of 18 participants was used to test the effectiveness of the pamphlet. Originally 20 participants were tested but 2 participants failed to complete the survey and the testing data was not used so that the demographic data would be accurate. A pre-test/posttest format was used to gain understanding of knowledge acquired by reading the pamphlet.
Pre-post Test

A test was created to test knowledge pre and post intervention (pamphlet). This test included 6 questions, 5 true/false testing general principles and 1 multiple choice testing knowledge of interactions between specific herbal supplements and warfarin. The questions were created to test basic knowledge and included only information provided in the pamphlet. The test is shown in Table 2.

1. All herbal supplements are natural and safe.
   True or False

2. Herbal supplements are regulated by the Food and Drug Adminstration (FDA).
   True or False

3. Coumadin (warfarin) can interact with drugs, food, and herbal supplements.
   True or False

4. Which of the following herbal supplements could interact with Coumadin (warfarin)?
   a. Ginseng
   b. St. John’s wort
   c. Danshen
   d. None of the above
   e. All of the above

5. A patient taking Coumadin does not have to tell their provider if they are taking herbal supplements.
   True or False

6. Changes in the effects of Coumadin could cause serious problems, like bleeding or clotting.
   True or False

Figure 1: Sample Pre-Post Test
Creating a Survey

A survey was created using a likert-type scale to test appearance, content, understanding, and effectiveness of the pamphlet. The purpose of the survey was to evaluate the opinions and prior knowledge of the participants and to provide an opportunity to give suggestions for improvement of the pamphlet. There were 9 questions on the survey. The responses were numbered 1 (strongly disagree), 2 (disagree), 3 (neither), 4 (agree), and 5 (strongly agree). The survey also included questions about age, gender, and length of time using warfarin.

Sampling

A convenience sample of 20 participants was used to test the pamphlet. Patients coming to an internal medicine clinic in Northern Wyoming clinic for routine INR testing for management of their warfarin were approached by a nurse and asked to participate in the study. Each participant was given a packet that included informed consent, pre-test, patient teaching pamphlet, posttest, and survey. They completed the form within 15 minutes and returned it to the nurse that provided INR testing. Consent was given by completing the test and survey. No identifying information was used in the testing of the pamphlet.

Institutional Review Board

The study of the patient teaching tool, including pamphlet, pre-test, posttest, informed consent, and survey, were submitted to the Institutional Review Board at Montana State University and was given exempt status (Appendix C).
CHAPTER 4

RESULTS

The pamphlet created was tested using a convenience sample of 20 patients at an internal medicine clinic in Northern Wyoming. Two of the participants’ data were not used because the survey was not completed. The data was analyzed to assess effectiveness of the teaching pamphlet by pre-test and posttest. The participants were also asked to evaluate the pamphlet using a likert-type survey with questions used to assess opinions of the survey and prior knowledge of the subject matter.

Demographic

The mean age of participants was 66.9 years with a standard deviation of 14.5. The youngest participant was 25, the oldest was 84. There were 10 females and 8 males that participated in the pilot testing of the pamphlet. There was large variation of length of time the participants used warfarin. The average length of time using warfarin was 60.6 months with a standard deviation of 65.82. The shortest length of time using warfarin was 4 months and the longest was 228 months (19 years).

Pre-post Test Results

The results of the pre-post testing showed improvement or no change on 17 of 18 participants. One posttest showed a decline in score. The mean pre-test score was 80.1% with a standard deviation of 19.9. The mean posttest score was 91% with a standard
deviation of 10.6. The average overall change was 10.9% with a standard deviation of 18.7.

<table>
<thead>
<tr>
<th>Pre-test</th>
<th>Posttest</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>83</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>83</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>0</td>
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<tr>
<td>100</td>
<td>83</td>
<td>-17</td>
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<tr>
<td>66</td>
<td>83</td>
<td>17</td>
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<td>83</td>
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<td>83</td>
<td>100</td>
<td>17</td>
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<tr>
<td>83</td>
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<td>0</td>
</tr>
<tr>
<td>66</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>33</td>
<td>83</td>
<td>50</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>66</td>
<td>66</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean 80.11765 91 10.88235
SD 19.90252 10.61249 18.68784

Table 1. Pre-test/Posttest Results

The pre-posttest shows overall improvement in knowledge about interactions between herbal supplements and warfarin. 5 participants answered all questions correctly on both the pre-test and posttest. One question was frequently answered incorrectly and review of the question shows it may be difficult for the population at hand. Question #4 on the pre-post test included multiple choices also including options “none of the above” and “all of the above”. Of the 18 completed tests, 33% (6) were answered incorrectly on the posttest, and 50% (9) were answered incorrectly on the pre-test for question #4. One
participant clarified his answer to question #5 answering incorrectly “true” and stating that the patient does not have to “but should” tell their provider if they are taking herbal supplements.

Survey Results

Participants were asked to submit the likert-type survey with responses that included their age, gender, length of time taking Coumadin (warfarin), and answers to questions about appearance, readability, prior knowledge, and helpfulness of the pamphlet. The responses were numbered 1 through 5 as follows 1 (strongly disagree), 2 (disagree), 3 (neither), 4 (agree), and 5 (strongly agree). The results of the survey are shown in Table 2. The survey showed the participants liked the way the pamphlet looked,

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I liked the way the pamphlet looked.</td>
<td>4.32</td>
<td>1.00</td>
</tr>
<tr>
<td>The pamphlet was easy to read.</td>
<td>4.47</td>
<td>.84</td>
</tr>
<tr>
<td>The pamphlet was easy to understand.</td>
<td>4.68</td>
<td>.58</td>
</tr>
<tr>
<td>The pamphlet had helpful information.</td>
<td>4.74</td>
<td>.45</td>
</tr>
<tr>
<td>I was previously aware of the potential interactions mentioned in the pamphlet.</td>
<td>3.73</td>
<td>1.09</td>
</tr>
<tr>
<td>I knew the risks associated with Coumadin before reading this pamphlet.</td>
<td>3.89</td>
<td>1.37</td>
</tr>
<tr>
<td>I knew the risks associated with interactions with Coumadin before reading this pamphlet.</td>
<td>3.63</td>
<td>1.57</td>
</tr>
<tr>
<td>I learned valuable information from the pamphlet.</td>
<td>4.32</td>
<td>1.42</td>
</tr>
<tr>
<td>I would recommend this pamphlet to a friend, family member, or patient if they used Coumadin.</td>
<td>4.95</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Table 2: Survey Results

found it easy to read, easy to understand and that it had helpful information. Looking at prior knowledge of the subject matter showed a variety of answers, with some having
prior knowledge and some not having prior knowledge. The survey shows that most would recommend this pamphlet to a friend or family member who uses Coumadin.

The form also provided a space for participants to write in additional comments or suggestions. Comments were helpful and will be taken into consideration when evaluating and making changes to the pamphlet. The comments provided are included in Table 3.

<table>
<thead>
<tr>
<th>Comment provided</th>
<th>Age/Gender</th>
<th>Time using warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Pamphlet provides valuable information for new patients. (It is) a good reminder for patients taking warfarin for months-or years”</td>
<td>62/male</td>
<td>11 months</td>
</tr>
<tr>
<td>“Clarify signs and symptoms (change in mental status?)(fatigue or weakness?). Also give pamphlets to health food store and other places that sell supplements.”</td>
<td>62/female</td>
<td>5 months</td>
</tr>
<tr>
<td>“Maybe a bit more eye-catching picture or print would help”</td>
<td>25/male</td>
<td>10 years</td>
</tr>
<tr>
<td>“I am somewhat of a reading nut so I had read quite a bit about Coumadin when I started”</td>
<td>75/male</td>
<td>13 months</td>
</tr>
<tr>
<td>“Although I was aware of the information in the pamphlet, it is always helpful to refresh your memory”</td>
<td>57/male</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Table 3: Additional Comments or Suggestions from Survey

Based on the results of the pre-test/posttest and survey results, the patient teaching tool was successful in increasing the knowledge the participants have. The tool may be an effective way for providers to teach patients about potential interactions between herbal supplements and warfarin.
Patients may be unaware of potentially dangerous interactions between warfarin and herbal supplements. Many patients do not inform their health care providers about herbal supplements they are taking (Elmer, 2007; Hailemaskel, 2001). Health care providers must provide information and resources for patients taking warfarin about the potential for life-threatening interactions. Finding effective ways to educate patients that take warfarin about the risks, signs and symptoms of adverse effects may reduce the risk of life-threatening side effects or interactions.

The patient teaching pamphlet created from the literature review was effective in teaching a small group of patients that presently use warfarin about potential interactions between herbal supplements and warfarin based on a small pilot study of the pamphlet. Based on both pre-test/posttest results and feedback given in the survey used in this project, the pamphlet is a useful tool in teaching patients about potential interactions between warfarin and herbal supplements.

Changes could be made to clarify what signs and symptoms to watch for, emphasizing risks of bleeding or clotting to those patients taking warfarin. Testing the validity of the pre-test and posttest and would increase the usefulness of this patient teaching pamphlet. Increasing the population size and using different locations, such as urban, community health centers, or various other locations that would provide access to
participants with different backgrounds and exposure to education would help to see if the tool would be useful in different settings.

**Limitations**

There are many limitations in this study. The quality of literature regarding interactions between warfarin and herbal supplements is poor. The majority of the data found were case reports or case studies. These show potential for interaction but no causal relationship. The studies that were done to show a causal relationship were very small in population size. Clinical trials are needed with standardized dosages of herbal supplements to show a more accurate relationship between warfarin and herbal supplements. The potential for mild to severe interactions between warfarin and multiple herbal supplements exists, but the scientific basis for the relationship is lacking.

The lack of regulation of herbal supplements plays a role in the difficulty testing for interactions between herbal supplements and prescription medication. As herbal supplements are sold and marketed in various forms and dosages with no regulation by federal agencies, it is difficult to assess safety and effectiveness of any supplements. As long as herbal supplements go unregulated, the findings of research in the field may not be generalized due to unknown content of products. Products that are verified by the U.S. Pharmacopeial Convention (USP verified) are the most likely to be standardized dosages and labeled appropriately.

The population size of the pilot study and lack of standardization of the testing tools used to test the patient teaching pamphlet may lead to inaccurate conclusions from the data. The purpose was to create a tool to help providers teach patients, but the
conclusion that the tool was effective cannot be drawn from this study, due to the size, convenience sampling method, unvalidated tests, and collection methods. These factors may contribute to bias in the test results.

Recommndations

Health care providers that treat patients who take warfarin should always take a thorough medication history that includes herbal/dietary supplements and over-the-counter medications. Using open-ended questions to obtain this information may be helpful such as “What supplements, vitamins, or natural products do you use?” (Gardiner, 2008). Using a non-judgmental approach may increase the likelihood that patients will disclose information regarding supplement use. Providers should have discussions with patients regarding risk versus benefit of using herbal supplements when they are using medications with high potential for interaction or narrow therapeutic windows.

When patients that take warfarin initiate or discontinue an herbal supplement, they should be monitored diligently for a change in INR (Fugh-Berman, 2001). Providers should be alert for the possibility that an interaction between herbal supplements and warfarin may be responsible for adverse events, should they occur. Documentation of use of herbal supplements in a patient’s medical record may help alert the provider if a patient using warfarin has an adverse event.

Using reliable sources, such as the Natural Medicines Comprehensive Database, to gain the most current information regarding interactions between supplements and warfarin may be helpful tool for a provider. Pharmacists may be used as references to gain further understanding of interactions when questions arise. More research is needed
in the area of herbal supplements and interactions with prescription medications, especially those with narrow therapeutic index and those medications that have high potential to interact with other substances.
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drugs: A systematic review. *Drugs*, 61(15), 2163-2175.


APPENDICES
APPENDIX A

TABLE WITH LITERATURE REVIEW RESULTS
<table>
<thead>
<tr>
<th>Source</th>
<th>Herb causing interaction</th>
<th>Type of interaction</th>
<th>Type of evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boldo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Izzo (2004)</td>
<td>Boldo</td>
<td>Coumarin containing herb</td>
<td>Theoretical</td>
<td></td>
</tr>
<tr>
<td>Lambert</td>
<td>Boldo-fenugreek</td>
<td>Patient treated with warfarin for a fib had an increased INR after taking a boldo and fenugreek. The INR normalized after discontinuation and increased again with rechallenge</td>
<td>Case study</td>
<td>Providers be vigilant with patients taking anticoagulants and herbal supplements</td>
</tr>
<tr>
<td><strong>Chamomile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segal (2006)</td>
<td>Chamomile (matricaria chamomilla)</td>
<td>A 70 year old female with an elevated INR (7.9) and bleeding (retroperitoneal hematoma and hbg 8) after using chamomile tea (4-5 cups per day) and lotion to relieve respiratory symptoms. Her INR had been 3.6 five days earlier.</td>
<td>Case report</td>
<td>Patients should be cautioned about use of chamomile and warfarin together</td>
</tr>
<tr>
<td><strong>Coenzyme Q10</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philp (2004)</td>
<td>Coenzyme Q10</td>
<td>Structurally related to Vitamin K</td>
<td>Theoretical</td>
<td>May have procoagulant properties when taken with warfarin</td>
</tr>
<tr>
<td>Engelsen</td>
<td>Coenzyme Q10</td>
<td>100mg of coenzyme Q10 daily had no effect on the INR of patients receiving long-term warfarin</td>
<td>Placebo-controlled, double-blind, crossover study (N=24)</td>
<td></td>
</tr>
<tr>
<td>Shalansky</td>
<td>Coenzyme Q10</td>
<td>Coenzyme Q10 was associated with bleeding and supratherapeutic INR independent of other risk factors</td>
<td>Prospective, longitudinal study (16 weeks)(N=171)</td>
<td>Coenzyme Q10 should be avoided in those patients taking warfarin</td>
</tr>
<tr>
<td><strong>Cranberry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdul (2008)</td>
<td>Cranberry</td>
<td>Alters the pharmacodynamics of warfarin and may increase anticoagulant effects significantly</td>
<td>Open-label, three treatment, crossover randomized clinical trial (N=12)</td>
<td>Concomitant use should be discouraged and if occurs requires careful monitoring</td>
</tr>
<tr>
<td>Ansell (2009)</td>
<td>Cranberry juice</td>
<td>No significant difference between placebo group and cranberry juice (240mL/day for 2 weeks) group in S- or R- warfarin plasma levels, a one-time elevation of INR occurred in the CJ group at day 12 of the intervention</td>
<td>Randomized, double-blind, placebo controlled trial (N=30)</td>
<td>Small amounts of cranberry juice does not affect the anticoagulant effect of warfarin, more information is needed</td>
</tr>
<tr>
<td>Mellon (2010)</td>
<td>Cranberry juice</td>
<td>No significant difference in prothrombin time in 10 male patients taking stable doses of warfarin taking cranberry juice (240mL BID x7days) between baseline and at days 2, 6, and 8</td>
<td>Prospective, open-labeled study (N=10)</td>
<td>Cranberry juice did not alter pharmacodynamics of warfarin in this small population</td>
</tr>
<tr>
<td>Suvarna (2003)</td>
<td>Cranberry juice</td>
<td>Man in his 70’s was admitted to the hospital with an INR of &gt;50, with prior control. He had a history of a poor appetite, and had only been drinking cranberry juice x6 weeks and taking his regular medication, which included warfarin, phenytoin,</td>
<td>Case study</td>
<td>Caution should be taken with cranberry juice for those patients taking warfarin</td>
</tr>
<tr>
<td>Reference</td>
<td>Herb/Complementary Medicine</td>
<td>Description</td>
<td>Type</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------</td>
<td>-------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Grant (2004)</td>
<td>Cranberry juice</td>
<td>69 year old male on long term warfarin with a fib and prosthetic mitral valve had an elevated INR (12 on admission, 10 days later, and return to 2 with Vitamin K) during hospital stay for surgery after drinking approximately 2L cranberry juice per day for chronic UTI</td>
<td>Case study</td>
<td>Patients taking warfarin should limit their cranberry juice consumption</td>
</tr>
<tr>
<td>Mergenhagen (2008)</td>
<td>Cranberry sauce</td>
<td>75 year old male with history of atrial fibrillation who had been stable on warfarin x 1 year had an elevated INR (4.8) after one week of ingesting cranberry sauce.</td>
<td>Case report</td>
<td>Cranberry sauce may increase INR if taken with warfarin</td>
</tr>
<tr>
<td>Yue (2001)</td>
<td>Curbicin (saw palmetto, pumpkin, Vitamin E)</td>
<td>73 year old man taking Curbicin for &gt;1 year had INR 2.1 in spite of no anticoagulation and normal albumin, improved with Vitamin K (1.3-1.4), but did not return to normal (1.0) until after discontinuing Curbicin 61 year old man had been stable on warfarin (INR 2.4), started Curbicin for micturation difficulties, 6 days later his INR was 3.4, INR returned to previous level after discontinuing Curbicin</td>
<td>Case report x2</td>
<td>More information needed</td>
</tr>
<tr>
<td>Izzat (1998)</td>
<td>Danshen (salvia miltiorrhiza)</td>
<td>Increased INR (8.4) and bleeding (pleural effusion) when patient on long term warfarin consumed danshen (62 year old male with mitral valve replacement)</td>
<td>Case reports</td>
<td>Danshen may increase the risk of bleeding</td>
</tr>
<tr>
<td>Tam et al. (1995)</td>
<td>Danshen</td>
<td>66 year old man with a-fib, rheumatic mitral stenosis, cerebral embolus, gastric adenocarcinoma had increased INR and gastric bleeding after taking danshen and warfarin</td>
<td>Case report</td>
<td>Danshen may increase the risk of bleeding</td>
</tr>
<tr>
<td>Yu et al. (1997)</td>
<td>Danshen</td>
<td>48 year old female with history of rheumatic heart disease, mitral stenosis, and a-fib had increased INR when taking Danshen and warfarin</td>
<td>Case report</td>
<td>Danshen may increase the risk of bleeding</td>
</tr>
<tr>
<td>Dong Quai</td>
<td>Dong Quai (Danggui, A. sinensis)</td>
<td>46 year-old African American female with a-fib who was stabilized on warfarin had a &gt;2 fold increase in PT and INR after taking Dong Quai for 4 weeks</td>
<td>Case report</td>
<td>Precautionary advice should be given, concurrent use should be avoided</td>
</tr>
<tr>
<td>Ellis (1999)</td>
<td>Dong Quai</td>
<td>Patient stable on warfarin for 10 years presented with widespread bruising and INR of 10 one month after starting Dong Quai for menopause symptoms. She was hospitalized for 6 days.</td>
<td>Case report</td>
<td>Potential interaction between Dong Quai and warfarin</td>
</tr>
<tr>
<td>Author</td>
<td>Treatment</td>
<td>Description</td>
<td>Study Design</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Izzo (2004)</td>
<td>Dong Quai</td>
<td>Coumarin containing herb</td>
<td>Theoretical</td>
<td>Dong Quai may increase the risk of bleeding</td>
</tr>
<tr>
<td>Mohammed Abdul (2010)</td>
<td>Echinacea</td>
<td>Echinacea reduced plasma concentration of S-warfarin but did not show significant changes in INR</td>
<td>Open-label, randomized, three treatment, crossover, clinical trial (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Izzo (2004)</td>
<td>Fenugreek</td>
<td>Coumarin containing herb</td>
<td>Theoretical</td>
<td>Fenugreek may increase the risk of bleeding</td>
</tr>
<tr>
<td>Lambert (2001)</td>
<td>Boldo- fenugreek</td>
<td>Patient treated with warfarin for a fib had an increased INR after taking a boldo and fenugreek. The INR normalized after discontinuation and increased again with rechallenge</td>
<td>Case study</td>
<td>Providers be vigilant with patients taking anticoagulants and herbal supplements</td>
</tr>
<tr>
<td>Hu (2005) Awang (2002)</td>
<td>Garlic (allium sativum)</td>
<td>Increased clotting time and increased INR Increased postoperative bleeding Spontaneous epidural hematoma</td>
<td>Case reports x 2</td>
<td>Precautionary advice should be given</td>
</tr>
<tr>
<td>Mohammed Abdul (2008)</td>
<td>Garlic</td>
<td>Did not significantly alter the pharmacokinetics or pharmacodynamics of warfarin</td>
<td>Open-label, three treatment, crossover randomized clinical trial (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Macan (2006)</td>
<td>Aged garlic extract (AGE)</td>
<td>No significant difference in hemorrhagic events versus placebo</td>
<td>Double-blind, randomized, placebo controlled pilot study (N=48)</td>
<td>Aged garlic extract may be safe for patients taking warfarin</td>
</tr>
<tr>
<td>Izzo (2004)</td>
<td>Garlic</td>
<td>Antiplatelet herb</td>
<td>Theoretical</td>
<td>Garlic may cause bleeding</td>
</tr>
<tr>
<td>Morris (1995)</td>
<td>Garlic</td>
<td>No significant effect on platelet aggregation</td>
<td>Double-blind, placebo-controlled study (N=14)</td>
<td></td>
</tr>
<tr>
<td>Sunter (1991)</td>
<td>Garlic</td>
<td>Two patients with increased INR who were previously stabilized on warfarin</td>
<td>Case studies</td>
<td>Garlic may increase bleeding risk</td>
</tr>
<tr>
<td>Kruth (2004)</td>
<td>Ginger</td>
<td>76 year old female taking phenprocoumon (anticoagulant) with an increase in INR after ingesting unspecified amounts of ginger, with epistaxis</td>
<td>Case report</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Jiang (2005)</td>
<td>Ginger</td>
<td>Did not significantly affect clotting status, the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects</td>
<td>Open-label, three-way crossover randomized study (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Jiang (2006)</td>
<td>Ginger</td>
<td>Ginger did not affect pharmacokinetics of warfarin in healthy volunteers</td>
<td>Randomized, open-label, controlled, 3-treatment, 3-sequence crossover</td>
<td>More research is needed</td>
</tr>
<tr>
<td>Author</td>
<td>Herb</td>
<td>Effect</td>
<td>Study Design</td>
<td>Conclusion</td>
</tr>
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<tr>
<td>Shalansky</td>
<td>Ginger</td>
<td>Ginger was associated with self-reported bleeding events independent of other risk factors</td>
<td>Prospective, longitudinal study (16 weeks)(N=171)</td>
<td>Ginger may increase the risk of bleeding when taken with warfarin</td>
</tr>
<tr>
<td>Izzo</td>
<td>Ginkgo</td>
<td>Did not significantly affect clotting status, the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects when taken with ginkgo</td>
<td>Open-label, three-way crossover randomized study (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Matthews</td>
<td>Ginkgo</td>
<td>78-year-old female stabilized on warfarin for 5 years following CABG suffered left parietal hemorrhage 2 months after initiation of ginkgo biloba. Cognitive function improved following 1 month of rehab and discontinuing ginkgo biloba</td>
<td>Case report</td>
<td>Precautionary advice should be given, more research needed</td>
</tr>
<tr>
<td>Engelsen</td>
<td>Ginkgo</td>
<td>No change of INR over 4 weeks of ingestion of ginkgo while using warfarin</td>
<td>Randomized, double-blind, placebo-controlled (N=24)</td>
<td></td>
</tr>
<tr>
<td>Jiang</td>
<td>Ginkgo</td>
<td>Ginkgo did not affect the pharmacokinetics of warfarin in 12 healthy volunteers</td>
<td>Randomized, open-label, controlled, 3-treatment, 3-sequence crossover studies with 14 day washout between (N=24)</td>
<td>More research is needed</td>
</tr>
<tr>
<td>Jiang</td>
<td>Ginseng</td>
<td>No effect on the pharmacodynamic or pharmacokinetic effect of warfarin in 12 healthy patients</td>
<td>Open-label, three-way crossover randomized study (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Janetzky</td>
<td>Ginseng</td>
<td>47 year old with a mechanical heart valve on stable on warfarin for 5 years with decreased INR two weeks after patient started taking ginseng (INR 3.1→1.5). His INR returned to 3.3 2 weeks after discontinuing ginseng.</td>
<td>Case report</td>
<td>Precautionary advice should be given</td>
</tr>
<tr>
<td>Yuan</td>
<td>American ginseng (P. quinquefolium)</td>
<td>Treatment with American ginseng at 1.0gm/day for 3 weeks significantly reduced INR, Cmax, and AUC of warfarin in healthy volunteers</td>
<td>Randomized, double-blind, placebo-controlled trial (N=20)</td>
<td>American ginseng reduces warfarin’s anticoagulant effect, those taking warfarin should avoid taking American ginseng, precautionary advice should be given</td>
</tr>
<tr>
<td>Authors</td>
<td>Herb</td>
<td>Description</td>
<td>Study Type</td>
<td>Conclusion</td>
</tr>
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</tr>
<tr>
<td>Lee (2008)</td>
<td>Panax ginseng</td>
<td>No significant difference in INR between patients with ischemic stroke given warfarin and ginseng and warfarin alone.</td>
<td>Randomized, open-label, controlled study (N=25)</td>
<td>Coadministration of P. ginseng and warfarin in ischemic stroke patients does not influence the pharmacologic action of warfarin</td>
</tr>
<tr>
<td>Rosado (2003)</td>
<td>Ginseng (unknown type)</td>
<td>58 year old with a thrombosis on a mechanical bileaflet aortic valve prosthesis after taking ginseng product with subtherapeutic anticoagulation (INR 1.4)</td>
<td>Case study</td>
<td>Ginseng may cause warfarin to be less effective, physicians must be aware of herbal supplements patients are taking, and educate patients about the risks.</td>
</tr>
<tr>
<td>Jiang (2006)</td>
<td>Ginseng (Asian, panax ginseng)</td>
<td>Coadministration of Asian ginseng and warfarin did increase the clearance of s-warfarin but did not reach clinical significance</td>
<td>Randomized, open-label, controlled, 3-treatment, 3-sequence crossover studies with 14 day washout between (N=24)</td>
<td>Asian ginseng may decrease the effectiveness of warfarin, more research is needed.</td>
</tr>
<tr>
<td>Lee (2010)</td>
<td>Korean red ginseng</td>
<td>Korean red ginseng decreased INR compared to placebo in patients with cardiac valve replacement</td>
<td>Prospective, double-blind, randomized, two-period crossover study (N=24)</td>
<td>Patients that take warfarin and Korean red ginseng concomitantly should be monitored closely</td>
</tr>
<tr>
<td>Green Tea</td>
<td></td>
<td>Vitamin K containing herb</td>
<td>Theoretical</td>
<td>May antagonize the effects of warfarin</td>
</tr>
<tr>
<td>Izzo (2004)</td>
<td>Green Tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor (1999)</td>
<td>Green Tea</td>
<td>44 year old male with subtherapeutic INR (1.14) after previously being stable on warfarin (3.2-3.79) after consuming ½ to 1 gallon of green tea per day. His INR increased to 2.55 after discontinuing green tea</td>
<td>Case report</td>
<td>Large amounts of green tea may be a significant source of Vitamin K and reduce the effects of warfarin.</td>
</tr>
<tr>
<td>Maitake</td>
<td>Maitake extract</td>
<td>79 year old with a fib and bladder cancer was stable on warfarin for 2 months (INR 2-3), after taking maitake extract for one week his INR was 5.1, the patient did not want to discontinue maitake, so his warfarin was decreased by 11% of previous dose through monitoring INR</td>
<td>Case report</td>
<td>Close monitoring of INR should be done for any patient on warfarin and maitake extract</td>
</tr>
<tr>
<td>Buckley (2004)</td>
<td>Omega 3 fatty acid (fish oil supplement)</td>
<td>67 year old female that was previously stable (INR 2.8) on 1.5mg warfarin while taking 1 gm of fish oil per day for 5 months had and</td>
<td>Case report</td>
<td>Close monitoring of INR when taking fish oil with warfarin</td>
</tr>
<tr>
<td>Study</td>
<td>Herbal</td>
<td>Intervention</td>
<td>Clinical Trial Design/Inclusion Criteria</td>
<td>Summary of Findings</td>
</tr>
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</tr>
<tr>
<td>Bender (1998)</td>
<td>Fish oil</td>
<td>Increased INR (4.3) after increasing her dose of fish oil to 2gm daily. She decreased the fish oil and her INR decreased.</td>
<td>Placebo-controlled, randomized, double-blind, parallel study (N=16)</td>
<td>No significant change in INR in 16 patients on stable warfarin therapy that took 3gm to 6gm of fish oil daily</td>
</tr>
<tr>
<td>Policosanol</td>
<td>Policosanol</td>
<td>Did not significantly affect pharmacokinetics or warfarin response</td>
<td>Open-label, randomized, three treatment, crossover, clinical trial (N=16)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Mohammed Abdul (2010)</td>
<td>Saw palmetto</td>
<td>53 year old white male intraoperative hemorrhage during surgical resection of brain tumor in a patient taking saw palmetto, with normal INR and PTT preoperatively</td>
<td>Case report</td>
<td>Saw palmetto may increase risk for bleeding</td>
</tr>
<tr>
<td>Soley</td>
<td>Soy milk</td>
<td>70 year old male on warfarin for a fib had subtherapeutic INR after ingesting soy milk, his INR returned to therapeutic range after discontinuing soy milk, no other factors were present that would cause a decrease in INR</td>
<td>Case report</td>
<td>Providers should be aware of potential food drug interactions with warfarin</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>St. John’s Wort</td>
<td>May decrease plasma levels and anticoagulant effect stimulating CYP2C9 or decreasing GI absorption</td>
<td>Theoretical</td>
<td>Recommend patients not use St. John’s Wort with warfarin or monitor INR closely</td>
</tr>
<tr>
<td>Hu (2005)</td>
<td>St. John’s Wort (hypericum perforatum)</td>
<td>Unstable INR (mostly decreased), decreased anticoagulant effect</td>
<td>Case reports</td>
<td>Precautionary advice should be given</td>
</tr>
<tr>
<td>Jiang (2004)</td>
<td>St. John’s Wort</td>
<td>Significantly increased the clearance of both S-warfarin and R-warfarin, which resulted in a significant reduction in the pharmacologic effect of rac-warfarin</td>
<td>Open-label, three-way crossover randomized study (N=12)</td>
<td>Close monitoring of INR should be done in patients that take herbal supplements and warfarin</td>
</tr>
<tr>
<td>Jiang (2006)</td>
<td>St. John’s Wort</td>
<td>St. John’s wort increased the clearance of warfarin when given one dose of warfarin (25mg) in 24 healthy volunteers but did not significantly affect the pharmacodynamics of warfarin.</td>
<td>Randomized, open-label, controlled, 3-treatment, 3-sequence crossover studies with 14 day washout between (N=24)</td>
<td>St. John’s Wort may interact with warfarin in a clinically significant way with a decrease in INR.</td>
</tr>
<tr>
<td>Yue (2000)</td>
<td>St. John’s</td>
<td>7 different case reports with</td>
<td>Case reports</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Bayramicli (2011)</td>
<td>St. John’s wort</td>
<td>85 year old patient with a fib on warfarin for 1 year started taking St. John’s wort, presented to ER with upper GI bleed, INR 6.2, Hbg 7.9, hct 23%.</td>
<td>Case report</td>
<td>May interact with warfarin</td>
</tr>
</tbody>
</table>
APPENDIX B

PATIENT TEACHING PAMPHLET
What should you do with this information if you take Coumadin® (warfarin)?

- Tell your primary care provider and any person prescribing medications for you if you are taking herbal supplements.
- Never add anything to your supplement regimen before checking with your primary care provider or pharmacist.
- Always watch for signs or symptoms of bleeding
  - Bruising
  - Nosebleeds
  - Bleeding gums
  - Coughing up blood
  - Vomiting blood
  - Blood in your urine
  - Blood in your stool
  - Change in mental status
  - Fatigue or weakness
- Always watch for signs or symptoms of blood clots
  - Pain or swelling in your legs or arms
  - Chest pain
  - Shortness of breath
  - Change in mental status
- Tell your primary care provider right away if any of the above symptoms occur or call 911

Potential Interactions Between Herbal Supplements and Coumadin® (warfarin): What You Need to Know

For more information:
health.nih.gov/topic/herbalMedicine
nccam.nih.gov/health/supplements/nihes1.htm
www.coumadin.com

What is Coumadin® (warfarin)?

Coumadin®, also known as warfarin, is a medicine given to prevent blood clots from forming. When taking Coumadin®, a person must be closely monitored to make sure the medicine is working correctly.

It is very important to keep your blood at a safe level. Your doctor will do this by checking your blood periodically and adjusting your Coumadin® dose.

Coumadin® can interact with many things, including prescription drugs, food, or herbal supplements. The risks of these interactions can include bleeding (from mild to life-threatening) or decreasing the effects of the Coumadin® (which can cause blood clots). Some supplements may increase the risk of bleeding with or without a blood thinning medication.

What about taking herbal supplements while taking Coumadin® (warfarin)?

There are many herbal supplements on the market. Many people believe that because a product is sold over-the-counter, or without a prescription from a doctor, that it is safe. Because the Food and Drug Administration (FDA) does not regulate herbal supplements, very little is known about the safety or effectiveness of herbal supplements or the interactions they may have with prescribed medicines.

Included in this pamphlet is a list of herbal supplements that may interact with your Coumadin®.

Herbal supplements that may cause bleeding or increase the effects of Coumadin® (warfarin):

- Angelica root
- Arnica flower
- Bai shao
- Boldo
- Bromelain
- Calendula
- Clove
- Curcumin
- Devil's claw
- Echinacea
- Garlic
- Gingko biloba
- Horse chestnut
- Hawthorn
- Meadowweet
- Onion
- Papaya extract
- Passionflower
- Poplar
- Red clover
- Saw palmetto
- Tamarind
- Willow bark

Herbal supplements that may decrease the effects of Coumadin® (warfarin):

- Coenzyme Q10
- Ginseng
- Green tea
- St. John's wort

- Echinacea
- Goldenseal
- Soy milk
APPENDIX C

INSTITUTIONAL REVIEW BOARD EXEMPTION
INSTITUTIONAL REVIEW BOARD
For the Protection of Human Subjects
FWA 00000165

MEMORANDUM

TO: Kimberlee Gilbert
FROM: Mark Quinn, Chair
DATE: January 19, 2012

RE: "Interactions between Herbal Supplements and Warfarin: A Patient Teaching Tool" [KG011912-EX]

The above research, described in your submission of January 19, 2012, is exempt from the requirement of review by the Institutional Review Board in accordance with the Code of Federal regulations, Part 46, section 101. The specific paragraph which applies to your research is:

(b) (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(b) (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation.

(b) (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(b) (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that the subjects cannot be identified, directly or through identifiers linked to the subjects.

(b) (5) Research and demonstration projects, which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(b) (6) Taste and food quality evaluation and consumer acceptance studies, if wholesome foods without additives are consumed, or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA, or approved by the EPA, or the Food Safety and Inspection Service of the USDA.

Although review by the Institutional Review Board is not required for the above research, the Committee will be glad to review it. If you wish a review and committee approval, please submit 3 copies of the usual application form and it will be processed by expedited review.