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Warfarin-herb interactions: a review and study based on assessment of clinical case reports in literature

[Interacciones hierbas-warfarina: una revisión y estudio basado en la evaluación de los reportes de casos clínicos en la literatura]

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Abstract

The potential risk of herb drug interactions is of particular focus today owing to the increasing and inadvertent use of herbs in recent times. It is a major safety concern for the drugs with narrow therapeutic index like warfarin, a most common anticoagulant with the maximum number of interactions reported. The objective of the present study was to conduct a systemic review of literature to consolidate the clinical case reports of warfarin–herb interactions and to assess the report reliabilities. We reviewed the published clinical literature to consolidate and assess the interactions between various herbs and warfarin, based on reported adverse events, descriptions of the clinical case reports and case series using electronic databases as well as hand picked references from the year 1971 to year 2007 and ranked them on likely causality using Naranjo's algorithm. Out of 72 cases of documented case reports of warfarin with various herbs, 84.7% cases were evaluated as possible interactions (61/72) and 15.3% cases (11/72) as probable interactions. Cranberry juice was most commonly involved in interactions with warfarin with 34.7% of cases (25/72) of which 92% cases were possible interactions (23/25) and 8% cases (2/25) were probable interactions. Hence, we conclude that combining anticoagulant medicines with herbs appears to be a risky proposition. The number of herbs reported to interact with warfarin continues to expand. Patients on warfarin are specifically advised to avoid taking herbal medicines or to have their INR measured within two weeks of starting the drug, to be on a safer side. Further, more systematic studies pertaining to warfarin-herb interactions are urgently warranted.

Keywords: Herb-drug interactions, Warfarin, Clinical case series, Clinical assessment, Clinical case reports.

Resumen

El riesgo potencial de las interacciones entre hierbas y fármacos es de particular interés en la actualidad justamente por el incremento del uso de las hierbas. La mayor seguridad radica en el estrecho índice terapéutico de fármacos como la warfarina, un anticoagulante con un número máximo de reportes de interacciones. El objetivo del presente estudio fue conducir una revisión sistemática de la literatura para consolidar los reportes de casos clínicos de interacciones warfarina-hierbas para evaluar las fiabilidades de dichos reportes. Se revisó la literatura clínica publicada para consolidar y evaluar las interacciones entre varias hierbas y la warfarina, basado en los eventos adversos publicados, descripciones de los reportes de casos clínicos y las series de casos mediante las bases de datos electrónicas así como la selección de las referencias desde el año 1971 hasta el 2007 y se alinearon sobre la probable causalidad mediante el algoritmo de Naranjo. Se obtuvieron 72 casos de reportes documentados de interacciones de warfarina con varias hierbas, 84.7% de los casos fueron evaluados como posibles interacciones (61/72) y 15.3% (11/72) como probables interacciones. El jugo de arándano fue el más comúnmente involucrado en las interacciones con warfarina con 34.7% de casos (25/72) de los cuales el 92% fueron interacciones posibles (23/25) y el 8% (2/25) fueron interacciones probables. De estos resultados se concluye que combinar anticoagulantes con hierbas parece ser una proposición arriesgada. El número de reportes de hierbas que actúan recíprocamente con warfarin continúa en aumento. Se aconseja específicamente a los pacientes que toman warfarina que eviten tomar medicinas herbarias o medir su INR a las dos semanas de arranque del fármaco, hacerlo de una forma más segura. De esta forma, se necesitan urgentemente estudios más sistemáticos sobre las interacciones de la warfarina y los productos herbales.

Palabras clave: Interacciones hierba-fármacos, Warfarina, Serie de casos clínicos, Valoración clínica, Reportes de casos clínicos.

INTRODUCTION

These days, millions of people use herbal therapies along with prescription and nonprescription medications (Zhou, 2007). About one third of the adults in developed countries and more than 60% Asians use herb as an alternative medicines (Zhou, 2007; Anonymous, 2006). Despite widespread use of herbal remedies, scientific data about their safety and efficacy are lacking in most cases plus reporting of adverse drug events is currently limited. The lack of available clinical data for many herbal products serves as a barrier for post marketing safety assessment of herbal products (Chavez et al., 2006). Further, the risk of interaction between the herb and the drug increases, causing either potentially dangerous side effects and/or reduced benefits from the medications, and hence, interactions between the two needs to be addressed and reviewed properly (Gohil and Patel, 2007). Concurrent use of herbs may mimic, magnify or oppose the effect of drugs and thus may raise the potential of herb-drug interactions, contrary to the popular belief, that nature is always safe. A major safety concern is the potential interactions of alternative medicinal products with prescription medications like anticoagulants. Herbs that may augment or inhibit the effects of anti-coagulant or antiplatelet therapy are of particular interest because this therapy is so widespread. The issue is especially important with respect to warfarin as it has a narrow therapeutic index and is already known to be associated with numerous food and drug interactions (Saw et al., 2007; Stout, 2006). It becomes imperative to have sufficient knowledge database as a conclusive evidence for herb-warfarin interactions for a very close monitoring of therapy to avoid any potential interactions between the two.

The aim of our present study was to conduct a systemic review of literature to consolidate the clinical case reports on warfarin–herb interactions based on documented clinical evidence and to assess of the reliability of these case reports.

METHODS

A literature survey was carried out to assess the published literature for appraisal of herbal drug interaction information available. As per the guidelines for the use of electronic and internet media (Winker et al., 2000; Wootton 2004; Eysenback and Diepgen, 1998; Silberg et al., 2007) a high quality and reliable medical information from the internet was retrieved only from the Health On Net (HON) conduct certified and accredited websites like Entrez PubMed (Medline), CAM-PubMed, Allied and Complementary Medicine Database, Natural Medicine Comprehensive Database, Embase and Cochrane Library. The databases were searched from the year 1971-2007 using the search terms "herb-drug interactions, anticoagulants, warfarin, adverse drug reactions, herbal medicine, case reports, case series, clinical trials and clinical assessments". Non-English language citations were excluded. The bibliographies of the retrieved articles were checked for any additional pertinent studies. An extensive review of the literature identified reported herb-drug interactions with clinical significance, many of which were in the form of case reports and limited clinical observations. The nature of findings and probability of interactions were then abstracted and compiled in a final report (Table 1).

The probability of interactions were evaluated on a 10 point scoring scale, where each of the case reports received one point for inclusion of following ten evaluating parameters.

- Adequate patient history
- Concurrent diseases, conditions
- Documentation of concomitant medications
- Adequate description of interactions
- Exclusion of obvious alternative explanations
- Complete chronology
- Reasonable time sequence of drug administration to adverse event
- Adequate description of adverse event
- Cessation of event on stopping the drug
- Recurrence of event with a re-challenge

The sum total of all these parameters was calculated and referred as report reliability score as per the criteria mentioned below. The probability of interactions was evaluated independently by 2 raters unaware of the study protocol using Naranjo's algorithm for adverse drug reaction (ADR) causality assessment (Naranjo et al., 1981). The Naranjo's algorithm was used to assess the likelihood that a change in clinical status is the result of an adverse drug reaction rather than the result of other factors such as progression of disease. Each of ten items in the assessment was answered and the values of the answer were entered in the column labeled as Report Reliability Score. The score of ten items were then summed up to determine the total scores and interpretation rules were applied as given below.

Criteria for interpretation of the total score:

- Total scores ≥ 9 suggested that an ADR is highly probable.

- Total Scores between 5 to 8 suggested that an ADR is probable.
- Total Scores between 1 to 4 suggested that an ADR is possible.
- Total Scores of zero or less means that an ADR is doubtful.

RESULTS

A total 72 cases of suspected interactions of warfarin with 21 types of different herbs were consolidated. The interactions were tabulated and categorized by herb, drug, other medications, signs or symptoms of interaction, mechanism, and report reliability score assessed by Naranjo's algorithm (Naranjo et al., 1981) (Table 1). Out of 72 documented case reports of interactions, 84.7% cases (61/72) were classified as possible interactions and 15.3% (11/72) as probable interactions. Cranberry juice was most commonly implicated in interactions with warfarin with 34.7% of cases (25/72) of which 92% cases were evaluated as possible interactions (23/25) and 8% cases (2/25) as probable interactions (Suvarna et al., 2003; Anonymous, 2003; Grant, 2004; Rindone and Murphy, 2006; Walsh, 2005; Jo Yacko, 2006).

Other herbs that have been associated with published case reports of possible or probable interactions with warfarin include Saint John's wort (7 cases) (Yue et al., 2000), birch (5 cases) (Ramanathan, 1995; Joss and Leblond, 2000; Chow et al., 1989; Littleton, 1990), coenzyme Q_{10} (4 cases) (Spigset, 1994; Landbo and Almdal, 1998), danshen (3 cases) (Tam et al., 1995; Yu et al., 1997; Izzat, 1998), garlic (3 cases) (Rose et al., 1990; Sunter, 1991) ginseng (3 cases) (Janetzky and Morreale, 1997; Hopkins et al., 1988; Rosado, 2003), saw palmetto (3 cases) (Yue and Jansson, 2001; Cheema et al., 2001) vitamin C (3 cases) (Rosenthal, 1971), dong qui (2 cases) (Page and Lawrence, 1999; Ellis and Stephens, 1999), ginkgo (2 cases) (Mathews, 1998; Fessenden et al., 2001), green tea (2 cases) (Taylor and Wilt, 1999; Leonard, 2006), papaya extract (2 cases) (Perez-Jáuregui et al., 1995; Shaw et al., 1997), and one case each of devil's claw (Shaw et al., 1997), Chinese herbal tea (*Lycium barbarum*) (Lam et al., 2001), quilinggao (Chinese herbal product) (Wong and Chan, 2003), soy milk (Cambria-Kiely, 2002), royal jelly (Lee and Fermo, 2006), boldo-fenugreek (Lambert, 2001), vitamin E (Corrigan and Marcus, 1974) and chamomile (Segal and Pilote, 2006).

Table 1. Assessment of clinical case reports of herb-warfarin interactions by Naranjo's algorithm.

Sr. No.	Patient Description	Herb *(Latin name)*	Other medications	Signs and symptoms of interaction	Mechanism	Report reliability score
1-12	Case series n=12 (Anonymous, 2004)	Cranberry juice *(Vaccinium macrocarpon, V. oxycoccus*)	Not described	8 cases INR ↑, 3 cases unstable INR, 1 case INR ↓	Not described.	1+2+1+0+0+0+0+0+0+0=4 Possible.
13	A Man in 70s with lethal gastrointestinal, pericardial hemorrhage and chest infection (Suvarna et al., 2003)	Cranberry juice	Cefalaxein, digoxin, phenytoin	INR > 50	Not described.	0+2+0+0+0+0+0+0+0+0=2 Possible
14-21	8 different cases (Anonymous, 2003)	Cranberry juice	Not described	1 case, patient died 4 cases INR ↑ 2 cases unstable INR and 1 case INR ↓	Inhibition of breakdown of warfarin in the body.	1+2+0+0+0+0+0+0+0+0=3 Possible
22	69 year-old man with atrial fibrillation and mitral valve replacement (Grant, 2004)	Cranberry juice	Digoxin, acetaminophen (paracetamol), codeine	INR 12	Not known	0+2+1+0+2+0+0+0+0+0=5 Probable

Table 1. (continued)

Sr. No.	Patient Description	Herb (Latin name)	Other medications	Signs and symptoms of interaction	Mechanism	Report reliability score
23	71-year-old man on Warfarin therapy stroke prophylaxis and symptoms of hemoptysis, hematochezia and shortness of breath (Rindone and Murphy, 2006)	Cranberry juice	None	Profound hypoprothrombinemia and bleeding INR > 18 PT time- 120 sec.	Not described.	1+2+1+0+1+0+0+0+0+0=5 Probable
24	Elderly man with Hypertension and atrial fibrillation (Walsh, 2005)	Cranberry juice	Unknown	INR fluctuates between 1-10	Unknown	1+2+0+0+0+0+0+0+0+0=3 Possible
25.	One patient with no other details (Jo Yacko, 2006)	Cranberry juice	None	INR ↓	Unknown	1+2+1+0+2+0+0+0+0+0=6 Probable
26-32	Case series n=7 75 year old female. Other six cases with no details (Yue et al., 2000)	St. John's wort *(Hypericum perforatum)*		INR ↓	Induction of CYP enzymes	0+2+0+0+0+0+0+0+0+0=2 Possible
33-34.	Two patients using ointment containing birch bark oil (Ramanathan, 1995)	Birch *(Betula pendua, B. alba leaves)*		High INR	Displace warfarin from protein binding sites	0+2+0+0+0+0+0+0+0+0=2 Possible
35.	A 22-year old White woman using topical methyl salicylate gel to both knees for 8 days (Joss and Leblond, 2000)	Birch *(Betula pendua, B. alba leaves)*	-	Elevated INR up to 12.2	Displace warfarin from protein binding sites	0+2+0+0+0+0+0+0+0+0=2 Possible
36.	Patient with arthritic knees using methyl salicylate for two weeks (Chow et al., 1989)	Birch *(Betula pendua, B. alba leaves)*	-	INR = 6.1, Multiple bleeding	Displace warfarin from protein binding sites	0+2+0+0+0+0+0+0+0+0=2 Possible
37.	Patient using large amount of methyl salicylate over arthritic joints (Littleton, 1990)	Birch *(Betula pendua, B. alba leaves)*	-	Bleeding, double prothombin time	Displace warfarin from protein binding sites	0+2+0+0+0+0+0+0+0+0=2 Possible
38.	68 year old man with history of several episodes of pulmonary and cerebrovascular emboli (Spigset, 1994)	CoenzymeQ10 *(Amigo xie)*	-	INR ↓	Herb has procoagulant properties	0+2+1+0+0+0+0+0+0+0=3 Possible
39.	72 year old man with pulmonary embolism (Spigset, 1994)	CoenzymeQ10 *(Amigo xie)*	-	INR ↓	Herb has procoagulant properties	0+2+1+0+0+0+0+0+0+0=3 Possible
40.	70 year old woman with thromboembolic disease (Spigset, 1994)	CoenzymeQ10 *(Amigo xie)*	-	INR ↓	Herb has procoagulant properties t	0+2+1+0+0+0+0+0+0+0=3 Possible
41.	72 year old woman (Landbo and Almdal., 1998)	CoenzymeQ10 *(Amigo xie)*	-	↓ Response to coumadin	Herb has procoagulant properties	1+2+1+0+0+0+0+0+0+0=4 Possible
42.	66-year-old man with bleeding from gastric carcinoma (Tam et al., 1995)	Danshen *(Salvia miltiorrhiza)*	Chinese medicated topical oil containing methyl salicylate	INR ↑	Herb Inhibit platelet aggregation	0+2+1+0+0+0+0+0+0+0=3 Possible

Table 1. (continued)

Sr. No.	Patient Description	Herb (Latin name)	Other medications	Signs and symptoms of interaction	Mechanism	Report reliability score
43.	48-year-old woman with rheumatic heart disease along with atrial fibrillation and mitral stenosis (Yu et al., 1997)	Danshen *(Salvia miltiorrhiza)*	Frusemide, digoxin	INR ↑	Reduce elimination of warfarin	0+2+1+0+2+0+0+ 0+0+0=5 Probable
44.	62-year-old man with mitral valve replacement (Izzat, 1998)	Danshen *(Salvia miltiorrhiza)*	Digoxin, captopril, furosemide	INR ↑	Inhibit platelet aggregation	1+2+1+0+0+0+0+ 0+0+0=4 Possible
45.	A patients, no details provided (Rose et al., 1990)	Garlic *(Allium sativum)*	-	Sponteneous spinal epidural hematoma	Inhibit thromboxane synthesis	0+2+0+0+0+0+0+ 0+0+0=2 Possible
46-47.	Two patients, no details provided (Sunter, 1991)	Garlic *(Allium sativum)*		INR ↑ Prolonged Clotting time with increased post operative bleeding.	Inhibit thromboxane synthesis	0+2+0+0+0+0+0+ 0+0+0=2 Possible
48.	47 year old man with history of heart valve replacement (Janetzky and Morreale, 1997)	Ginseng *(Panax ginseng)*	Diltiazem, nitro-gycerine, salsalate	INR ↓	Reduces the effect of warfarin	0+2+1+0+2+0+0+ 0+0+0=5 Probable
49.	A post menopausal woman (Hopkins et al., 1988)	Ginseng *(Panax ginseng)*	Hormone therapy	Mastalgia and vaginal bleeding	Herb shows estrogen like effect	0+2+1+0+0+0+0+ 0+0+0=3 Possible
50.	A 58-year-old male with mechanical bileaflet aortic valve admitted to hospital with anterospectla MI and diabetic ketoacidosis (Rosado, 2003)	Asian Ginseng *(Panax ginseng)*	-	Unsteady INR	Not known.	0+2+1+0+0+0+0+ 0+0+0=3 Possible
51-52.	2 male patients (Yue and Jansson, 2001)	Saw palmetto *(Serenoa repens)*	Unknown	↑ INR bleeding	Unknown	0+2+0+0+2+0+0+ 0+0+0=4 Possible
53.	A patient with no information (Cheema et al., 2001)	Saw palmetto *(Serenoa repens)*	Unknown	INR ↑	Platelet dysfunction by inhibiting cyclooxygenase enzyme	0+2+0+0+1+0+0+ 0+0+0=1 Possible
54-55.	Two cases (Rosenthal, 1971)	High dose of Vitamin C	-	Reduce blood thining effect of warfarin	Cause diarrhea and reduce absorption of warfarin	0+2+0+0+0+0+0+ 0+0+0=2 Possible
56..	A 52-year-old woman (Rosenthal, 1971)	Unspecified amount of vitamin C	-	Shortening of blood clotting time.	Reduced absorption of warfarin	0+2+1+0+0+0+0+ 0+0+0=3 Possible
57.	46 year old woman with history of stroke, rheumatic heart disease and atrial fibrillation (Page and Lawrence, 1999)	Dong quai *(Angelica sinensis)*	Digoxin, furosemide	INR ↑ PT ↑	Inhibit platelet aggregation	0+2+1+0+2+0+0+ 0+0+0=5 Probable
58.	A woman with history of mitral valve replacement (Ellis and Stephens, 1999)	Dong quai *(Angelica sinensis)*	-	INR=10, Widespread bruising.	Inhibit platelet aggregation	0+2+1+0+0+0+0+ 0+0+0=3 Possible

Table 1. (continued)

Sr. No.	Patient Description	Herb (Latin name)	Other medications	Signs and symptoms of interaction	Mechanism	Report reliability score
59.	70 year old female with history of hypertension, myocardial infarction, atrial fibrillation, coronary bypass and gait disorder (Mathews, 1998)	Ginkgo *(Ginkgo biloba)*	-	PT ↑ Hemorrhage	Antiplatelet activity of herb	0+2+0+0+0+0+0+ 0+0+0=2 Possible
60.	A patient with no other information (Fessenden et al., 2001)	Ginkgo *(Ginkgo biloba)*	-	Post laparoscopic cholecystectomy bleeding	Antiplatelet activity of herb	0+2+0+0+0+0+0+ 0+0+0=2 Possible
61.	44 year old recipient with a mechanical heart valve (Taylor and Wilt, 1999)	Brewed green tea *(Camellia sinensis)*	None	INR ↓	High vitamin K content antagonize warfarin effect	0+2+1+0+2+0+0+ 0+0+0=5 Probable
62.	One man. No other information (Leonard, 2006)	Green tea *(Camellia sinensis)*	None	Thickening of blood	Herb has antagonistic effect	0+2+1+0+0+0+0+ 0+0+0=3 Possible
63.	A woman in Mexico (Perez-Jauregu et al., 1995)[j]	Papaya extract *(Papaya carica)*	-	Prolonged PT time	Potentiate the effect of warfarin	0+2+0+0+0+0+0+ 0+0+0=2 Possible
64.	A male admitted for cardiac surgery (Shaw et al., 1997)	Papaya extract *(Papaya carica*)	-	INR ↑	Potentiate the effect of warfarin	0+2+1+0+0+0+0+ 0+0+0=3 Possible
65.	One case with no other information (Shaw et al., 1997)	Devil's claw *(Harpagophytum procumbens)*	-	Purpura	Inhibit platelet aggregation	0+2+0+0+0+0+0+ 0+0+0=2 Possible
66.	61 year old Chinese woman (Lam et al., 2001)	*Lycium barbarum*	-	INR ↑	Probable no interaction	0+2+1+0+2+0+0+ 0+0+0=5 Probable
67.	61 year old man, no other information (Wong and Chan, 2003)	Quilinggao *(Fritillaria cirrhosa, Paeoniae rubra, Lonicera japonica, Poncirus trifoliata*)	-	Bleeding, epitaxis, skin bruising, ↑ INR	Antiplatelet and/or antithrombotic effects	0+2+1+2+2+0+0+ 0+0+1=8 Probable
68.	70 year old white man (Cambria-Kiely, 2002)	Soy milk	None	INR ↓	Increased metabolism of warfarin	0+2+1+0+2+0+0+ 0+0+0=5 Probable
69.	87 year old man with stage-IV-A follicular non-Hodgkin's lymphoma, atrial fibrillation and hypertension (Lee and Fermo, 2006)	Royal jelly	Felodopine, lisinopril, hydrochlor-thiazide, KCl, diltiazem, oxycodone	↑ INR bleeding	Unknown	0+2+0+0+2+0+0+ 0+0+0=4 Possible

Table 1. (continued)

Sr. No.	Patient Description	Herb (Latin name)	Other medications	Signs and symptoms of interaction	Mechanism	Report reliability score
70.	A 67-year old female with atrial fibrillation (Lambert, 2001)	Boldo-Fenugreek *(Trigonella foenum graceum)*	Metoprolol	INR ↑	Herbs potentiate the effect of warfarin	0+2+1+2+0+0+0+0+0+0=5 Probable
71.	55 year old man (Corrigan and Marcus, 1974)	Vitamin E	-	PT ↑ hematuria	Inhibit oxidation of vitamin K	0+2+1+2+2+0+0+0+0+0=7 Probable
72.	70 year old woman with mechanical mitral valve placement and previous episode of atrial fibrillation (Segal and Pilote, 2006)	Chamomile *(Matricaria recutica)*	Amiodarone, digoxin, symthroid, alendronate, metoprolol, calcium-vitamin-D supplement	Multiple internal hemorrhage	Potentiate the effect of warfarin by inhibition of CYP IA2	0+2+0+0+2+0+0+0+0+0=4 Possible

DISCUSSION

This updated review indicates a significant number of reports of interaction between warfarin and herbs, reaffirming both, the anticoagulant's widespread use and its concomitant use with herbal medicines. Warfarin is the most efficacious oral anticoagulant used for the prevention of thromboembolic events in patients with chronic atrial fibrillation (Albers et al., 2001), prosthetic heart valves (Stein et al., 2001), venous thromboembolism (Hyers et al., 2001) and coronary artery disease (Cairns et al., 2001). The drug is a racemic mixture of 2 optically active isomers, though the S-enantiomer is approximately 5 times more potent than the R-enantiomer (Holbrook et al., 2005). Warfarin interferes in coagulation process by being competitive inhibitor of vitamin K in the biosynthesis of prothrombin and in the process lowering the amount of active vitamin K available for the activation of clotting factors II, VII, IX, and X (Hirsh et al., 2001). A possible interaction refers to the possibility that one substance may alter the bioavailability or clinical effectiveness of another substance when two or more substances are given concurrently. The net result may be an increase or a decrease in effect of one or both substances (Wittkowsky, 2001). Herbs may interact with blood-thinning medications in different ways. Multiple pathways exist for interference with warfarin, and interactions may lead to either hemorrhage or thrombotic episodes by increasing or reducing the effects of this agent. Although the true mechanisms of drug interactions almost always remain unknown, there are several pharmacokinetic and pharmacodynamic factors that could influence warfarin's effect. The more potent warfarin S-isomer is metabolized by cytochrome P-450 (CYP) 2C9. The R-isomer of warfarin is metabolized by CYP 1A2 and CYP 3A4 inhibit CYP 1A2 and CYP 3A4 (Holbrook et al., 1996) while pharmacodynamics of warfarin may be influenced by medications that affect either vitamin K or the coagulation factors (Hirsh et al., 2003). Herbs can affect the response of anticoagulant therapy by increasing or reducing prothrombin time (PT) and International Normalized Ratio (INR). Anticoagulation with warfarin is often difficult to manage and stabilize because of its narrow therapeutic index, high degree of protein binding, its penchant for various food and drug interactions or sudden changes in dietary sources of vitamin K such as leafy greens or a supplemented diet (Ansell et al., 2004). Both effectiveness and safety (primarily risk of bleeding) are related to monitoring INR values and dose adjustments of warfarin influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors.

More number of food and drug interactions has been reported for warfarin than any other prescription medications (Wells et al., 1994). In earlier survey of similar nature, a total of 108 cases of suspected interactions were found and evaluated using 10-point scoring system for assessment of clinical case reports for herb-drug interactions (Fugh-Berman and Ernst, 2001) according to which, warfarin was the most common drug with 18 cases, of which 61.1% cases were evaluated as unevaluable interactions (11/18),

22.2% as possible interactions (4/18) and 16.7% as likely interactions (3/18). St. John's wort was the most common herb interacting with warfarin (07 cases) categorized as "unevaluable" interactions.

In the present study, we have consolidated all cases of herb-warfarin interactions. A total of 72 cases were evaluated using Naranjo's algorithm for adverse drug reaction (ADR) causality assessment, of which 84.7% cases (61/72) were classified as possible interactions and 15.3% cases (11/72) were probable interactions. Cranberry juice was most commonly implicated in interactions with warfarin with 34.7% of cases (25/72) of which 88% cases were evaluated as possible interactions (22/25) and 12% cases (3/25) as probable interactions. Cranberries, a fruit native to North America are primarily cultivated for consumption as food and beverages (Jellin et al., 1999). The juice and concentrated extract from cranberries are increasingly used for the prevention and adjunctive treatment of urinary tract infections (DerMarderosian and Beutler, 2002; Raz et al., 2004). Several case reports published in literature prompted the speculation regarding the interaction between the two. We consolidated total of 25 cases of interactions of warfarin–cranberry juice interactions in this study. Several mechanisms of interaction between cranberry juice and warfarin have been proposed. It is postulated that cranberry juice increases the activity of warfarin possibly by inhibiting the breakdown of warfarin in the body leading to increased INR and excessive thinning of blood resulting in increased risk of bleeding (Anonymous, 2003). Recently, it has been reported that some chemicals in cranberries may interfere with the effects of warfarin. Cranberries contain high percentages of phytochemicals known as flavonoids, which are implicated in modification of various biochemical pathways and modulation of expression of specific CYP-450 enzymes and thus inducing or inhibiting their activities, for example, several flavonoids such as hyperforin and silibinin inhibit the activity of CYP2C9 (Hodek et al., 2002). Another mechanisms implied that the salicylic acid content in cranberry juice might be responsible for exerting antiplatelet effect or a highly protein bound salicylic acid might displaces warfarin from albumin-binding sites and thus increases the risk of bleeding (Wosilait, 1976). Though, some studies have failed to find evidence of such an interaction between the two, (Li et al., 2006; Pham and Pham, 2007) the documented case reports corroborated the possibility of interactions. So it only seems advisable for the patient on warfarin therapy to avoid or limit the intake of large amount of cranberry juice, until more data is available.

Saint John's wort is primarily used for mild to moderate depression (Woelk, 2000). Evidence suggests that St. John's wort might interfere with warfarin, possibly requiring an increased dosage of the drug to maintain the proper therapeutic effects. As certain chemicals found in St. John's wort activate liver enzymes that are involved in the elimination of some drugs including warfarin (Maurer, 1999; Jobst et al., 2000; Jiang et al., 2004; Bressler 2005b). Patients taking warfarin should consult their doctor before taking St. John's wort.

Birch bark oil and leaves (*Betula* species) have been used in folk medicine for centuries as blood purifiers, for gout and rheumatism, for hair loss and dandruff, as flushing-out therapy in bacterial and inflammatory diseases of the urinary tract, and for kidney and bladder stones (Fleming, 1998). It contains high amount of methylsalicylate that is speculated to affect vitamin K metabolism or displacing warfarin from protein binding sites resulting in bleeding events (Beaulieu, 2001).

Coenzyme $Q_{10,}$ also known as ubiquinone or ubidecarenone, has the structure similar to menaquinone and is postulated to have pro-coagulant properties, apart from antioxidant properties (Heck et al., 2000). Coenzyme Q_{10} supplement is primarily promoted to treat a variety of cardiovascular conditions including heart failure, hypertension, stable angina and ventricular arrhythmia. Many patients suffering from these disorders might also be commonly prescribed warfarin (Bonakdar and Guarneri, 2005; Tran et al., 2001), increasing the likelihood of interactions with herbs when ingested simultaneously. The present study consolidated total four cases of interactions between coenzyme Q_{10} and warfarin, assessed as "possible" on Naranjo's scale. Even though evidences are not very consistent, patient receiving concomitant therapy with warfarin and coenzyme Q_{10} should be closely monitored.

The herb danshen, the root of *Salvia miltorrhiza*, is used for treating cardiovascular and cerebro-vascular diseases in traditional Chinese medicine (Zhou et al., 2005). Danshen might increase the risk of bleeding when used with anticoagulants or antiplatelet drugs as it was reported to inhibit platelet aggregation and cause excessive blood-thinning effects in patients taking warfarin (Chan, 2001; Cheng, 1999). Thus preliminary evidence plus the case reports consolidated in the present study suggested that danshen can dangerously increase the effects of warfarin and cause significant bleeding problems and it should only be

used under close medical supervision by patients on warfarin therapy.

Garlic (*Allium sativum*) is another herb, which is thought to provide cardiovascular benefits and utilized to lower cholesterol and blood pressure (Rivlin, 2001, 2006). Garlic oil has been reported to inhibit thromboxane synthesis thereby by inhibiting the platelet aggregation (Gadkari and Joshi, 1991). We assessed three 'possible' cases of interactions by Naranjo's scale in this study. Patients using warfarin are also cautioned regarding possible risk of bleeding with ingestion of garlic.

Three ginseng species -Oriental/Asian ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*) and American ginseng (*Panax quinquefolius*)- are promoted as an adaptogens, a treatment that is said to help the body adapt to stress of all types and also as mood and energy boosters (Ebadi, 2002) the active constituents are ginsenosides that are believed to inhibit the platelet aggregation and inhibit the conversion of fibrinogen to fibrin (Attele et al., 1999). We consolidated three cases for Asian ginseng of which one as probable and two as possible cases of interactions where ginseng antagonizes the anticoagulant effects of warfarin and produce bleeding in patients. Though mechanism is not exactly known and the results of several double blind studies were conflicting (Yuan et al., 2004; Jiang et al., 2005), it is reasonable to recommend the caution while combining ginseng and warfarin.

The herb saw palmetto (*Serenoa repens*) is rich in fatty acids and phytosterols, is shown to be effective in the management of benign prostatic hyperplasia including reduction of urinary frequency, increase in urinary flow and decrease in nocturia (Wilt et al., 1998; Bressler, 2005a). Three 'possible' cases of saw palmetto interaction with warfarin were assessed on Naranjo's scale in this study. Patients taking warfarin should consult their physician before taking saw palmetto because of the risk of increased anti-coagulant effect of drug and the potential bleeding.

Several vitamins may also interfere with the effect with warfarin on concomitant administration (Schrogie, 1975). A high dose of vitamin C (more than 1 000 mg daily) has been reported to reduce the blood-thinning effect of warfarin (Smith et al., 1972). Three cases consolidated in this study were assessed as 'possible' interactions on Naranjo's scale. On the contrast, Vitamin E might add to the effects of warfarin leading to abnormal bleeding (Corrigan and Marcus, 1974; Kim and White, 1996). Though there are no case reports available, it is suggested that vitamin D increases the activity of anticoagulants and that this interaction could prove dangerous. Vitamin A supplements might also increase the blood-thinning effects of warfarin leading to potential risk of abnormal bleeding (Harris, 1995; Pederson et al., 1991; Chow et al., 1990). On the other hand, Vitamin K directly counteracts effect of warfarin since the drug slows blood clotting by interfering with vitamin K activity (Chow et al., 1990). This is true not only for supplemental vitamin K but also for the foods high in vitamin K content. For this reason, eating more vitamin K rich vegetables can decrease the therapeutic effect of warfarin, and eating less of these foods can increase the drug's effect (Pederson et al., 1991; Chow et al., 1990). Either situation is potentially risky. People taking warfarin should consult their physician before taking these vitamin supplements.

The herb dong quai (*Angelica sinensis*) is used for menstrual disorders (Clara et al., 2005; Hirata et al., 1997; Fugh-Berman, 2000). Dong qui might add to the blood-thinning effects of warfarin, thus increasing the risk of abnormal bleeding and if used together requiring caution (Smolinske, 1999).

Ginkgo biloba has been used to Alzheimer's disease, failing memory, age-related dementias, poor cerebral and ocular blood flow, congestive symptoms of premenstrual syndrome, and the prevention of altitude sickness (McKenna et al., 2001; Kleijnen and Knipschild, 1992; Chung et al., 1987). Inconsistent evidences suggest that the active constituent ginkgolide B might inhibit the platelet aggregation possibly, increasing the tendency toward bleeding (Kohler et al., 2004; Kudolo et al., 2002, 2005; Bal et al., 2003; Rosenblatt and Mindel, 1997). These findings raised the concern that ginkgo might add to the blood-thinning effects of warfarin (Vale, 1998) and discretion necessitates physician supervision before combining ginkgo with warfarin therapy.

Green tea (*Camellia sinensis*), also known as Chinese tea is a powerful antioxidant, recently promoted for its anticancer, cardio-protective positive cognitive and gastrointestinal effects (Lifer 2005). It contains significant amount of vitamin K, which directly interferes with warfarin's blood-thinning action (Ali et al., 1990). Therefore, it is suggested that drinking large amounts of green tea simultaneously might reduce the therapeutic effects of the drug. In the present study, we assessed one probable and one possible case of interaction between green tea and warfarin.

We consolidated two documented cases assessed as 'possible' interactions between papain and warfarin

in this study. Papain, an enzyme extract of papaya *(Carica papaya),* which has been used for a variety of ailments: diarrhea, edema, symptoms of herpes zoster and psoriasis was associated with significant increased in INR and potentiation of warfarin effects (Emeruwa, 1982). So it is suggested that patients on warfarin therapy should avoid papain supplements in large amount until further information about this potential interaction becomes available.

The herb devil's claw (*Harpagophytum procumbens*) is promoted for use in treatment of various types of arthritis, gout, myalgia and digestive problems (Brien et al., 2006). The report documented in this study was assessed as 'possible' on Naranjo's scale suggested that the herb might inhibit the platelet aggregation and increase the effect of warfarin resulting in abnormal bleeding. No other details pertaining to other medication taken or duration of warfarin were given in the case, making it difficult to interpret if the alternate causes were responsible but it seem advisable for the patients to avoid devil's claw or do so strictly under medical supervision while on warfarin therapy.

There is one published case report in which ingestion of a Chinese herbal infusion made from *Lycium barbarum* appeared to interfere with the effect of warfarin (Lam et al., 2001). In another published case report, the Chinese herbal product quilinggao (*Fritillaria cirrhosa, Paeoniae rubra, Lonicera japonic*a or *Poncirus trifoliate*) increased the action of warfarin (Wong and Chan, 2003). Both cases were documented as 'probable' on Naranjo's scale in the present study. There are many different brands and compositions of quilinggao. Patients on warfarin therapy should exercise care while using quilinggao product or Chinese herbal infusion and inform the physician about the same to avoid any bleeding episodes.

Another 'probable' interaction assessed in this study was between soy and warfarin indicating that soy milk might decrease warfarin's effectiveness (Cambria-Kiely, 2002). At the same time, a case report assessed as 'possible' interaction in this study indicated that the use of royal jelly can increase the effectiveness of warfarin, creating risk of bleeding (Lee and Fermo, 2006). It may be best to avoid these combinations except under medical supervision.

The herb feverfew is primarily used for the prevention and treatment of migraine headaches, arthritis and various types of allergies (Makheja and Bailey, 1981). Several *in vitro* studies suggested that feverfew thins the blood by interfering with the ability of blood platelets to clump together (Biggs et al., 1982; Loesche et al., 1988; Heptinstall et al., 1987, 1988; Sumner et al., 1992; Groenewegen and Heptinstall, 1990). This raised the concern that feverfew might increase the risk of abnormal bleeding when combined with warfarin. Although there were no isolated cases of feverfew interacting with warfarin in humans, we assessed one case report involving boldo-fenugeek (*Trigonella foenum graceum*) combination (Lambert, 2001), assessed as 'probable' on Naranjo's scale. Patients are advised to be vigilant while using them simultaneously.

The herb chamomile (*Matricaria recutita*), most commonly used as a sedative, antispasmodic, anti-inflammatory and wound-healing agent contains substances in the coumarin family (O'Hara et al., 1998; Shamseer et al., 2006) having blood thinning actions that could interact with warfarin. One interaction between the two was assessed as 'possible' on Naranjo's scale in this study.

Some other herbs thought to contain coumarin or coumarin components include angelica root, arnica flower, anise, asafoetida, celery, horse chestnut, licorice root, lovage root, parsley, passionflower, quassia, red clover, sweet clover and rue (Jellin et al., 1999; Blumenthal et al., 1998; Olin and Hebel, 1999; Miller 1998; Ulubelen et al., 1988). Also, meadowsweet, poplar, and willow bark contain high concentrations of salicylates, while bromelain, clove, onion, have been reported to exhibit antiplatelet activity (Jellin et al., 1999; Blumenthal et al., 1998). Borage seed oil contains glinoleic acid, which may increase coagulation time (Guivernau et al., 1994). Bogbean has been noted to demonstrate hemolytic activity (Kowalak and Mills, 2001), capsicum has been reported to cause hypo-coagulability (Visudhiphan et al., 1982) and turmeric have also been reported to exhibit antiplatelet activity (Lee, 2006). Ginger may decrease thromboxane production and prolong bleeding time (Srivastava, 1984; Lumb, 1994; Afzal et al., 2001). It is suggested that a specific kavalactone, kawain in herb kava-kava may decrease thromboxane 2 production and inhibit cyclooxygenase, indicating that it may have significant inhibitory effect on platelet aggregation (Ulbricht et al., 2005). Grape seed and grape skin extracts might have antiplatelet effects and might prolong PT and INR (Shanmuganayagam et al., 2002). Preliminary evidence suggested that frequent consumption of mango too might interfere with the effect of warfarin (Monterrey-Rodriguez, 2002). There have been no documented case reports of an interaction of warfarin

with any of the above-mentioned herbs and further study is needed to confirm these potential interactions and assess their clinical significance. However, patients taking any products containing these herbs concurrently with medications with anticoagulant effects, such as warfarin, should be closely monitored for signs or symptoms of bleeding.

In the past, very few reports related to herb-drug interactions are reported and many of the reactions could only be explained theoretically. Recently, however, several cases of possible herb drug interactions are reported as the use of herbs is increasing day by day. The shortcomings of many such reported cases of herb drug interactions are lack of proper documentations and incompleteness of reports. For example, in many cases, mechanisms and causality are uncertain and unpredictable, which makes it rather difficult to evaluate the report reliabilities of potential interactions. Also, unlike conventional drugs, herbal products are not regulated for safety, efficacy, purity and potency, and are not subjected to approval process of the FDA. Some of the adverse effects and interactions reported for herbal products could also be caused possibly by impurities like allergens, pollens and spores or batch-to-batch variability (Anonymous, 1994; Angell and Kassirer, 1998). Thus, a lack of adequate information in most cases makes it very difficult to determine whether a particular herb drug interaction has occurred, and may or may not imply the herbs as culprits when co-administered with warfarin. One or two reports may not warrant absolute contraindication to combination of herbs and warfarin but the precautions must be exercised while using herbal products with warfarin to avoid any harm by such potential interactions herbal products should be analyzed to confirm their contents. Patients on warfarin should inform their physicians about any simultaneous herb use. Such patients should be regularly monitored and properly informed by physicians, pharmacists or other health-care providers, about the adverse events that may occur with simultaneous ingestion of herbs and prescription medicines like warfarin. Patients could be advised to avoid herb-warfarin combinations altogether when absolute necessary for which adverse events and interactions are reported frequently. In case, when adequate information is not available then advising them to have a reasonable time period of 2 to 3 hours between administrations of herb in question and warfarin. This should be followed by frequent monitoring of PT time and INR test regularly in patients on warfarin therapy.

Because of widespread use of the herbs today, number of documented case reports of herb drug interactions are rising every year, however, many cases of herb-drug interactions may even go unreported and actual number of cases might be much higher than reported. Despite this, a limited research in this area entails that cases are properly reported, carefully evaluated and constantly reviewed for regular update. More research on warfarin-herb interactions seems to be a matter of urgent concern. The health professionals who suspect any such serious interactions of drugs such as warfarin with any herbal products should be encouraged to report them to local pharmacovigilance center to promote the vigilance in this area.

CONCLUSION

It is difficult to interpret data about interactions between herbs and warfarin as the evidence is mainly based on animal studies or individual cases rather than large-scale human studies. While, the consistency of such reports still needs to be weighed up, the interactions with herbs should be closely monitored. Additional research is urgently needed in order to explore the range of possible effects from herb-warfarin interactions in patients. Nevertheless, combining anticoagulant medicines with herbs appears to be the risky proposition. The number of herbs reported to interact with warfarin continues to expand. Patients on warfarin are specifically advised to avoid taking herbal medicines or to have their INR measured within two weeks of starting the product to be on safer side.

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