การศึกษาแบบย้อนหลังเพื่อศึกษาผลของสมุนไพรหรืออาหารเสริมต่อค่าไอเอ็นอาร์ในผู้ป่วยที่ใช้ยาวาร์ฟาริน ณ โรงพยาบาลพระมงกุฎเกล้า

The Effects of Herbs or Dietary Supplements on International Normalized ratio in Warfarin Users: A Retrospective Study at Phramongkutklao Hospital

นิพนธ์ต้นฉบับ **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลของสมุนไพรหรืออาหารเสริมต่อค่าไอเอ็นอาร์ (INR) ในผู้ป่วยที่ใช้ยาวาร์ฟาริน **วิธีการศึกษา:** การศึกษาแบบย้อนหลัง โดยใช้ข้อมูลในเวชระเบียนและแบบบันทึกข้อมูลผู้ป่วยที่ใช้ยาวาร์ฟาริน ณ คลินิกวาร์ฟาริน โรงพยาบาลพระมงกุฎเกล้า ตั้งแต่วันที่ 1 มกราคม 2556 ถึง 31 ธันวาคม 2557 โดยคัดข้อมูลค่า INR ก่อนและหลังการใช้ผลิตภัณฑ์สมุนไพรหรืออาการเสริม ข้อมูลการใช้ผลิตภัณฑ์ด้านขนาดความแรง ปริมาณและความถี่ และระยะเวลาที่ใช้ พิจารณาแต่ละการใช้ผลิตภัณฑ์เป็นแต่ละรายงาน **ผลการศึกษา:** พบผู้ป่วย 101 รายที่ใช้วาร์ฟาริน มี 30 รายที่ใช้ผลิตภัณฑ์ โดยมีรายงานเหตุการณ์การใช้ 35 ครั้ง โดยพบว่าในรายงาน 35 ครั้ง มี INR หลังการใช้อยู่นอกเป้าหมายถึงร้อยละ 94.3 ผลิตภัณฑ์ที่ใช้มากที่สุด คือ น้ำมันรำข้าว (ร้อยละ 25.7) ขมิ้นชัน (ร้อยละ 11.4) น้ำทับทิมและชาเขียว (ร้อยละ 8.6 เท่ากัน) ตามลำดับ โดยผลิตภัณฑ์ที่ทำให้ INR เพิ่มขึ้นได้แก่ น้ำมันรำข้าว น้ำทับทิม และมะรุม ส่วนที่ทำให้ลดลง ได้แก่ ชาเขียวและวิตามินซี **สรุป:** การใช้ผลิตภัณฑ์สมุนไพรและอาหารเสริมทำให้ค่า INR เปลี่ยนแปลงได้ ในผู้ป่วยที่ใช้ยาวาร์ฟารินควรระมัดระวังการเกิดภาวะเลือดออกผิดปกติหรือภาวะลิ่มเลือดอุดตัน เพื่อป้องกันการเกิดผลข้างเคียงจากภาวะเลือดออกผิดปกติหรือภาวะลิ่มเลือดอุดตัน

คำสำคัญ: วาร์ฟาริน, ไอเอ็นอาร์, สมุนไพร, อาหารเสริม

Abstract

Objective: To evaluate the effects of herb and dietary supplement products on the INR in patients using warfarin. **Methods:** In this retrospective observational study, data from medical records and warfarin clinic form of the patients visiting warfarin clinic of Phramongkutklao Hospital, Bangkok, Thailand, during Jan. 1, 2013, to Dec. 31, 2014, were abstracted. Data regarding the product strength, dosing regimen and duration of use were collected. Each episode of the product use was considered an individual report. **Methods:** Of all 101 patients, 30 patients took the products with 35 individual reports of product use. Of the 35 reports, 94.3% had INR out of the target goal. The most used products were rice bran oil (25.7%), followed by *Curcuma longa* (11.4%), pomegranate juice and *Camellia sinensis* (8.6% each). Products that increased INR included rice bran oil, pomegranate juice and *Moringa oleifera*; while those reducing INR were *Camellia sinensis* and vitamin C. **Conclusion:** The use of herbs and dietary supplement products in patients with warfarin use could cause INR change which could lead to abnormal bleeding or thrombosis.

Keywords: warfarin, INR, herbs, dietary supplements

Introduction

Warfarin therapy is used for prevention of systemic thromboembolism in atrial fibrillation, heart valve replacement, recurrent ischemic stroke, venous thrombo-embolism and other causes of cardioembolism.[1] The International Normalized Ratio (INR) is the most common parameter used to monitor warfarin therapy. Warfarin use is complicated by the difficulty of achieving goals of INR and the maintenance of anticoagulation effects. The goals of INR were between 2.0 - 3.0 in patients with atrial fibrillation and 2.5 - 3.5 in patients with mechanical valve replacement at mitral position.[2] Warfarin is affected by various factors including age, body weight, diet, alcohol intake and drug interaction.[3] Various mechanisms of warfarin interaction with other medications are well known. Absorption of warfarin is inhibited by some medications such as cholestyramine or sucralfate.[4,5] Furthermore, warfarin effect may be decreased by high protein diet.[6,7] Warfarin undergoes approximately 60% oxidative metabolism, primarily by 4 cytochrome P450 (CYP450) isoforms, CYP2C9, CYP1A2, CYP3A4, and to a lesser extent, CYP2C19. Warfarin is inhibited by medications that induced CYP450 such as rifampicin (CYP3A4), phenytoin (CYP2C9) and carbamazepine (CYP2C9). In addition, warfarin also interacts with other medications that

enhance anticoagulation effect, e.g., metronidazole, amiodarone, and ketoconazole.[1]

Warfarin is highly susceptible to interactions with herb and dietary supplement through the effect of enzyme induction or inhibition. In addition, herbs and dietary supplements may also influence the pharmacodynamics of warfarin by inhibiting the synthesis or increasing the clearance of vitamin K-dependent coagulation factors, or interfering with other pathways of hemostasis.[5] Dietary supplement such as fish oil enhanced additional anticoagulation of warfarin by the inhibition of CYP2C9 and CYP3A4.[8] Garlic may affect warfarin by inhibiting platelet aggregation that increases the risk of bleeding.[9] Moreover, there are previous studies about herbs that increase warfarin effect, including dong quai (*Angelica sinensis*)[10], danshen (*Salvia miltiorrhiza*)[11], mango (*Mangifera indica*)[12] and herbs that decrease warfarin effect including Korean ginseng (*Panax ginseng*)[13] and green tea (*Camellia sinensis*).[14] The use of herbs or dietary supplements in patients using warfarin are common. Smith et al. reported that 92.2% of patients who admitted taking herbal medicines while receiving warfarin had not mentioned this use to a conventional healthcare provider.[15] In Thailand, using herbs or dietary supplements is supposed to be more common. Furthermore, clinical significant between warfarin and herbs or dietary supplement interactions can occur. Health care personnel should be educated about the potential risks of bleeding or thromboembolism associated with drug interaction. The aim of the present study was to evaluate the effect of herbal medicines and dietary supplements on the INR in patients taking warfarin at the warfarin clinic of Phramongkutklao hospital.

Materials and Methods

This retrospective observational study included data of all patients taking warfarin at the warfarin clinic, Phramongkutklao hospital, Bangkok, Thailand. Patients' visit data between January 1, 2013 and December 31, 2014 were collected. Ethic approval for the study was obtained from the Ethic Committee of Phramongkutklao College of Medicine, Thailand (IRB/RTA 507/2558, approval date April 9, 2015).

On a given clinic visit date, the patient's information was abstracted from the medical record, and the patient was interviewed using the warfarin clinic data collection form. The data collection form in this study was the one used in daily practice in Phramongkutklao hospital. The form had been developed and modified continuously in the past 13 years of its use at the warfarin clinic of Siriraj Hospital, a leading medical school hospital. The form was divided into 4 parts including 1) characteristics of the patient (such as age, gender, co-morbidities leading to warfarin use and other co-morbidities, history of smoking, alcoholic drinking), 2) history of herb or dietary supplement use, 3) the baseline INR value before the use of herb/dietary supplement and 4) a set of 5 questions inquiring herb/dietary use. The 5 questions asked 1) whether the patient have used or have been using herbs or dietary supplement products, 2) if so, what is the indication the patient have been using the product for, 3) how long the patient have you been using the product, 4) how often the patient have been using the product, and 5) how many tablets/capsules of the product the patient have been taking. With these 5 questions, each herb or dietary supplement was identified for type, dose or amount, and duration of use. If the patient could not remember trade name or type of herb/dietary supplements, the pharmacist helped the patient identify the product by using sample pictures, either with printed pictures or pictures searched by a smart-phone. The process of data collection and product identification was conducted by two pharmacists (first and third authors).

Among patients with herb/dietary supplement product use, their INR values before and after the use were identified. The INR value on that clinic visit was considered the post-use value. We further traced back to the clinic visit date before the use of such product use with the firstly available INR value. This INR value was considered the pre-use value, or baseline value. The target INR range of each patient was identified. For a given patient, more than one episode of herb/dietary supplement use with related INR values was allowed. Each episode was considered independent report. All information gathered was recorded in the same data collection form.

Data analysis

Descriptive statistics, including frequency with percentage, and mean with standard deviation were used as applicable, to report the patient demographic and clinical data, as well as the INR values, i.e., pre- and post-product use INR, and target INR range. For each report of the

product use, the change of INR value was identified based on the pre- and post-product use. The status of the post-use INR value, i.e., either within or out-of INR target range, was also identified. Frequency and percentage of the INR status of all reports were presented. Unit of analysis was based on both individual patients and individual product use reports.

Results

A total of 101 patients in warfarin clinic at Phramongkutklao hospital were included in the present study. About 30% of the patients (n = 30) used herbs or dietary supplement products. Patient characteristics are shown in table 1. The two genders were in equal proportions (51.5% female) with a mean age of 56.9 ± 13.7 years old. Most patients had a written history of denying smoking and alcoholic drinking. The most frequently found indications for warfarin use were mitral valve replacement (63.2%) followed by atrial fibrillation (35.6%), and aortic valve replacement (24.8%). Other co-morbidities were hypertension (24.8%) and dyslipidemia (13.9%).

Table 1 Characteristics of 101 warfarin-treated patients in warfarin clinic.

Parameters	Number (%) among all patients (N = 101)	Number (%) among patients using herbs/dietary supplements (N = 30)
Gender		
Male	49 (48.5)	11 (36.7)
Female	52 (51.5)	19 (63.3)
Age, year (mean ± SD)	56.9 ± 13.7	58.8 ± 10.6
Herbs /dietary supplement use	30 (29.7)	30 (100.0)
Smoking		
Yes	6 (5.9)	1 (3.3)
No	87 (86.1)	27 (90.0)
Not reported	8 (7.9)	2 (6.7)
Alcohol drinking		
Yes	7 (6.9)	1 (3.3)
No	85 (84.2)	26 (86.7)
Not reported	9 (8.9)	3 (10.0)
Co-morbidities*		
Co-morbidities as warfarin indication		
Mitral valve replacement	64 (63.4)	17 (56.7)
Atrial fibrillation	36 (35.6)	15 (50.0)
Aortic valve replacement	25 (24.8)	6 (20.0)
Other co-morbidities		
Hypertension	25 (24.8)	4 (13.3)
Dyslipidemia	14 (13.9)	4 (13.3)
Diabetes mellitus	10 (9.9)	1 (3.3)
Chronic kidney disease	5 (4.9)	1 (3.3)
Heart failure	4 (3.9)	0

* Each patient had 1 or more co-morbidities

Of the 101 patients, 30 patients reported the product use. All 30 patients had INR value at the visit date, i.e., post-use INR value. Pre-use INR values, i.e., baseline value, for all 30 patients were available. Characteristics of 30 patients using herb and dietary supplements concomitantly with warfarin are shown in table 1 while their 35 reports of INR changes and corresponding herb/dietary supplement use, classified by INR status are shown in table 2.

Among 35 reports of INR change with herb/dietary supplement product use (table 2), numbers of reports of patients with INR target ranges of 2.5 – 3.5 and 2.0 - 3.0 were comparable, 18 and 17 reports, respectively. Of the 18 reports with an INR target range of 2.5 – 3.5, all post-use INR values were out of target, where the majority had INR values of 1.5 to 2.5 (8 of 35 reports, or 22.9%) followed by INR ≤ 1.5 (14.3%), and INR of 3.5 to 4.9 (11.4%). Only 1 report (2.9%) was with a post-use INR of ≥ 5.0.

Among the 17 reports with INR target range of 2.0 – 3.0, 5.7% of the post-use INR values (2 of 35 reports) were within target range. The majority of the reports had post-use INR values of 1.5 to 2 (7 of 35 reports, or 20.0%), followed by INR values of ≤ 1.5 (11.4%) and of 3 to 4.9 (11.4%). Only 1 report (2.9%) was with a post-use INR of ≥ 5.0.

Table 2 Number of reports on INR classified by INR target range after the use herb/dietary supplement (30 patients; 35 reports*).

Parameters	N (%) of reports by INR target range	
	Out of target range (n = 35)	Within target range (n = 35)
All patients using herb/dietary supplement	33 (94.3)	2 (5.7)
Target INR of 2.5 - 3.5	18 (51.4)	-
post-use INR ≤ 1.5	5 (14.3)	-
post-use 1.5 < INR < 2.5	8 (22.9)	-
post-use 3.5 < INR ≤ 4.9	4 (11.4)	-
post-use INR ≥ 5	1 (2.9)	-
Target INR of 2 - 3	15 (42.9)	2 (5.7)
post-use INR ≤ 1.5	4 (11.4)	-
post-use 1.5 < INR < 2	7 (20.0)	-
post-use 3 < INR ≤ 4.9	4 (11.4)	-
post-use INR ≥ 5	1 (2.9)	-

* A given patient could have more than 1 report.

Among the 30 patients, the most frequently used herb/dietary supplement was rice bran oil which was used by 25.7% of patients, followed by turmeric *(Curcuma longa*) (11.4%), green tea *(Camellia sinensis)* and pomegranate

juice (8.6% each), and chlorophyll juice and gotu kola *(Centella asiatica*) (5.7% each). Each of the remaining herbs/dietary supplements was used in one patient.

Table 3 Types of herbs and dietary supplements (N = 30).

Herbs and dietary supplement	Frequency (%)
Rice bran oil	9 (25.7)
Turmeric *(Curcuma longa)*	4 (11.4)
Pomegranate juice	3 (8.6)
Green tea *(Camellia sinensis*)	3 (8.6)
Chlorophyll juice	2 (5.7)
Gotu kola *(Centella asiatica*)	2 (5.7)
Moringa *(Moringa oleifera* Lam.*)*	1 (2.9)
Ginkgo *(Ginkgo Biloba*)	1 (2.9)
Andawali *(Tinospora crispa)*	1 (2.9)
Lingzhi (Ganoderma lucidum)	1 (2.9)
Ginger (Zingiber officinale)	1 (2.9)
Black pepper *(Piper nigrum*)	1 (2.9)
Andrographis *(Andrographis paniculata*)	1 (2.9)
Lemon grass *(Cymbopogon citratus)*	1 (2.9)
Gaertner *(Alpinia nigra)*	1 (2.9)
Black thai ginger *(Kaempferia parviflor)*	1 (2.9)
Aloe vera (Aloe barbadenisis)	1 (2.9)
Vitamin C	1 (2.9)

In table 4, changes of INR in individual reports are shown. Of the 9 reports with rice bran oil use, somewhat comparable numbers of reports with an increase and decrease of INR were found (5 and 4 reports, respectively). Among the 4 reports with turmeric use, a decrease of INR was found in the majority of reports (3 or 4). The use of pomegranate juice was associated with a consistent increase of INR values found in all 3 reports. Chlorophyll juice was associated with a decrease of INR values, found in all 2 reports.

All two reports of gotu kola use contained increased INR values; while moringa use was associated with an increased INR as high as 6.4. A report of ginkgo use contained an INR decrease. Three reports of green tea were all associated with the decrease of INR values. Andawali use was associated with an INR increase as seen in one report. Other product uses associated in an increase of INR included ginger, andrographis, and aloe vera; while the ones with an INR decrease included lingzhi, black pepper, lemon grass, gaertner, black Thai ginger and vitamin C, with one report each.

Table 4 Effects of herbs and dietary supplements on INR, classified by number of report (30 patients; 35 reports).

Report No. (n = 35)	Patient No. (n = 30)	Target INR	Pre-use INR	Herbs/dietary supplements	Post-use INR	INR change*
1	1	2.5 - 3.5	3.2	Rice bran oil	3.6	↑
2	2	2.5 - 3.5	1.6	Rice bran oil	5.0	↑
3	3	2.0 - 3.0	2.4	Rice bran oil	4.4	↑
4	4	2.0 - 3.0	1.5	Rice bran oil	2.6	↑
5	5	2.0 - 3.0	1.2	Rice bran oil	1.7	↑
6	6	2.5 - 3.5	2.1	Rice bran oil	1.2	↓
7	7	2.5 - 3.5	3.7	Rice bran oil	2.3	↓
8	8	2.0 - 3.0	1.9	Rice bran oil	1.5	↓
9	9	2.0 - 3.0	2.1	Rice bran oil	1.5	↓
10	10	2.5 - 3.5	5.9	Turmeric *(Curcuma longa)*	3.8	↓
11	11	2.0 - 3.0	2.8	Turmeric *(Curcuma longa)*	1.7	↓
12	12	2.0 - 3.0	1.9	Turmeric *(Curcuma longa)*	1.7	↓
13	13	2.0 - 3.0	1.5	Turmeric *(Curcuma longa)*	1.8	↑
14	14	2.0 - 3.0	2.1	Pomegranate juice	3.2	↑
15	5	2.0 - 3.0	2.5	Pomegranate juice	3.8	↑
16	15	2.5 - 3.5	1.6	Pomegranate juice	1.9	↑
17	16	2.5 - 3.5	1.8	Chlorophyll juice	1.3	↓
18	17	2.5 - 3.5	1.7	Chlorophyll juice	1.2	↓
19	18	2.5 - 3.5	2.9	Gotu kola *(Centella asiatica)*	4.1	↑
20	19	2.5 - 3.5	1.7	Gotu kola *(Centella asiatica)*	2.2	↑
21	20	2.0 - 3.0	1.9	Moringa *(Moringa oleifera)*	6.4	↑
22	21	2.0 - 3.0	1.7	Ginkgo *(Ginkgo biloba*)	1.6	↓
23	22	2.5 - 3.5	2.1	Green tea *(Camellia sinensis)*	1.7	↓
24	23	2.5 - 3.5	3.6	Green tea *(Camellia sinensis)*	1.6	↓
25	24	2.5 - 3.5	2.3	Green tea *(Camellia sinensis)*	1.5	↓
26	25	2.5 - 3.5	1.8	Andawali *(Tinospora crispa)*	4.2	↑
27	*26*	2.0 - 3.0	*2.3*	*Lingzhi (Ganoderma lucidum*)	1.4	↓
28	*27*	2.0 - 3.0	*1.5*	*Ginger (Zingiber officinale*)	1.7	↑
29	28	2.0 - 3.0	1.8	Black pepper *(Piper nigrum*)	1.5	↓
30	12	2.0 - 3.0	1.5	Andrographis *(Andrographis paniculata)*	1.8	↑
31	29	2.5 - 3.5	3.3	Lemon grass *(Cymbopogon citrates)*	1.8	↓
32	29	2.5 - 3.5	1.8	Gaertner *(Alpinia nigra)*	1.6	↓
33	10	2.5 - 3.5	2.1	Black Thai ginger *(Kaempferia parviflora)*	1.6	↓
34	*14*	2.0 - 3.0	1.6	*Aloe vera (Aloe barbadenisis)*	2.0	↑
35	30	2.5 - 3.5	3.9	Vitamin C (Ascorbic acid)	1.5	↓

* ↑ = increase; ↓ = decrease

Discussions and Conclusions

The response to warfarin therapy is associated with many factors. One of them was the use of herbs and dietary supplements. The interactions between herb/dietary supplement and warfarin were attributable to pharmaco-kinetic and pharmacodynamic interactions. The present study showed effect of herbs and dietary supplements on the INR change. The detail of each of the herbs and dietary supplements on potential pharmacodynamic and pharmaco-kinetic interactions are discussed as the following.

Rice bran oil

Rice bran oil and its main components including unsaturated fatty acids, triterpene alcohols, phytosterols, tocotrienols, alpha-tocopherol, and gamma-oryzanol had

demonstrated an ability to reduce plasma cholesterol and triglyceride; it is thus has been used for dyslipidemia.[16,17] Gamma-oryzanol, an antioxidant, is associated with platelet aggregation reduction and inhibiting effects on CYP1A2, CYP2C9 and CYP3A4.[18] INR in the patient using warfarin with rice bran oil should be increased, and lead to a potential for an increased risk of bleeding. However, effects of rice bran oil on warfarin were limited to case reports. In the present study, we found 9 reports of patients who used rice bran oil, 5 reports with increased INR and 4 reports decreased INR. The results of 4 reports with a conflicting decrease of INR could result from the reduction of the warfarin dose on the last visit (2 reports). However, no known causes could be expected in the other 2 reports. With its retrospective nature, specific causes of these decreases could not be verified in this study.

Pomegranate juice

The present study found 3 reports with the use of pomegranate juice. Pomegranate was associated with increased INR in all reports. There have been a limited number of cases on the effect of pomegranate on INR. A previous case report described a 64-year-old woman who used warfarin with a stable dosage of warfarin and had an INR within goal.[19] Her INR rose up after the patient consumed pomegranate juice 2 - 3 times per week. Once stopping drinking the juice, her INRs went down within the therapeutic range.[19] Jarvis et al. reported that a 37-year-old woman consumed pomegranate juice about 3 liters. In a week before hospital admission, her INR value was elevated with hematoma.[20] In addition, Usia et al. reported the effect of *Punica granatum* inhibitory activity against CYP2D6 and CYP3A4[18] which further confirmed that warfarin is metabolized by CYP3A4. Furthermore, pomegranate juice could inhibit platelet aggregation, the first step of coagulation, resulting in an increasing prolonged bleeding time and a higher risk of bleeding.[21]

Turmeric (*Curcuma longa*)

Turmeric is an antioxidant, anti-bacterial and pain reliever. Previous study in animal study has shown an effect of a decreased platelet aggregation and increased bleeding.[22] Moreover, turmeric could also inhibit CYP3A4.[23] In our present study, 3 of 4 reports with turmeric use were associated with a decreased INR. Of the 3 reports, a cause of the decreased INR in 1 report was the decreased dosing of warfarin. Causes of the interaction leading to INR changes in the other cases could not be identified.

Gotu kola (*Centella asiatica*)

Gotu kola (*Centella asiatica*) has been used for many purposes such as healing wounds, improving mental clarity, and curing psoriasis.[24] In two reports in this study, the use of *C. asiatica* was associated with elevated INR level which was in accordance with pharmacokinetic interaction basis. *In vitro* studies, it was found that *C. asiatica* extracts inhibited CYP2C9, CYP2D6 and CYP3A4 activities.[25] This could enhance effect of warfarin. However, previous case reports on the interaction between *C. asiatica* and warfarin have not been reported.

Moringa *(Moringa oleifera)*

M. oleifera is a tropical tree often used as an herbal medicine. Monera et al. found that the extracts of *M. oleifera* on the CYP3A4 possess significant CYP3A4 inhibitory effects.[26] There has been no case report indicating interaction between warfarin and *M. oleifera*. In the present study, one patient taking two capsules per day of *M. oleifera* extract with no known duration of use. The patient's INR was found increasing without abnormal bleeding. The information found in the medical records indicated the patient's good compliance and denied use of other medications. In addition, the patient did not have other conditions, such as heart failure and hyperthyroidism, which may potentially influence the increase of warfarin action.

Ginkgo (*Ginkgo biloba*)

Ginkgo biloba has been well known to increase bleeding.[27] A 78-year-old woman took warfarin with ginkgo and developed a subsequent intracerebral hemorrhage.[28] In addition, a study revealed that ginkgo preparation had demonstrated an antiplatelet activity *in vitro* and may potentially increase bleeding time.[29] Mohutsky et al. reported *G. biloba* extract could inhibit CYP2C9 in an *in vitro* study but no interaction between *G. biloba* with probe for CYP2C9 was found.[30] In contrast, our study showed a decreased INR in patients taking gingko with warfarin. In the patient medical record, we found no specific causes since the patient had a good compliance and used no other medications potentially interfere with warfarin therapy. Other information, such as social history and vegetable consumption, was not recorded.

Green tea *(Camellia sinensis)*

In our present study, all 3 reports had an INR decrease from baseline after the use of green tea. The antagonistic activity of green tea toward warfarin is associated with its high content of vitamin K, about 1,428 microgram per 100 grams.[31] In a previous case report, a 44-year-old man received warfarin for thromboembolic prophylaxis for his mechanical valve replacement (St. Jude) in the aortic position. His INR decreased from 3.79 to 1.14 after taking one-half to one gallon per day of green tea for one week. After discontinuing green tea, the INR increased.[32] In our study, a decrease of INR could also be attributable to the patient's forgetting taking 2 doses of warfarin about a month before the INR measurement.

Andawali *(Tinospora crispa)*

In our study, a patient used *T. crispa* extract for 5 milliliters every day for a month. Her INR level increased from 1.48 to 4.28. As suggested by the medical record, the INR increase could be due to the increased doses of warfarin and an unusual vegetable consumption. Previous cases on interaction between *T. crispa* and warfarin have not been reported. Based on pharmacokinetic basis, Usia et al. reported that more than 70% of the inhibitory effect of *T. crispa* on metabolism of warfarin was mediated by CYP3A4 in an *in vitro* study.[18]

Lingzhi (*Ganoderma lucidum*)

G. lucidum is a popular Asian herb. The health benefits of lingzhi include control of blood glucose level, modulation of the immune system, hepatoprotection, bacteriostasis, and more.[33] A previous report showed the additional effect of warfarin with the use of lingzhi through the increased inhibition of platelet aggregation.[34] This could lead to bleeding but no cases of lingzhi and anticoagulants have been reported. Thus such interaction could not be established up to date.

This present study showed that a single patient taking lingzhi had a decreased INR which was in contrast with the existing knowledge. We could not verify specific cause of this INR decrease because related information was not adequately documented in the medical record. Furthermore, the patient, as suggested by the medical record, had a good compliance to warfarin therapy and did not use other medications which could influence pharmacodynamic interaction with warfarin.

Ginger (*Zingiber officinale*)

This study showed the increase of INR in a patient consuming ginger concomitantly with warfarin. Previously, a case report demonstrated an interaction of ginger and phenprocoumon resulting in an elevated INR with epistaxis.[35] Furthermore, ginger was reported to have antiplatelet effect by inhibiting thromboxane synthetase, as a result, platelet aggregation was decreased.[5,36]

Black pepper (*Piper nigrum*)

Black pepper is widely used in traditional medicines. It shows over 70% inhibitory activity on the metabolism mediated by CYP3A4.[18] Thus black pepper could potentially increase warfarin effect; although not even one incident of interaction between black pepper and warfarin has been reported. Our present study showed that a patient using warfarin with black pepper had a decreased INR level. The cause of INR decrease was verified as non-compliance.

Kariyat *(Andrographis paniculata)*

A. paniculata has been widely used for the prevention and treatment of common cold especially in Asia and Scandinavia. *A. paniculata* may help prevent some cardiovascular disorders, because its active compound (andrographolide) possesses an inhibitory effect on platelet aggregation.[37] Moreover, *A. paniculata* showed an inhibitory activity on the warfarin metabolism mediated by CYP3A4.[18] It thus should be used with caution by patients taking warfarin. Our finding was consistent with such pharmacokinetic interaction basis. A patient had taken kariyat 1 capsule per day about 2 - 3 weeks before the INR increased from 2.8 to 3.2. However, the information documented in the medical record was inadequate to eliminate other possible causes of the increase of INR.

Lemon grass *(Cymbopogon citratus)*

In an animal study, *C. citratus* was hypothesized to have antiplatelet activity.[38] Thus, patients who consume *C. citratus* with warfarin may have an increased risk of bleeding. Our finding pointed to the opposite where a patient using warfarin with *C. citratus* had a reduced INR. However, with a retrospective nature of this study, essential information could

not be retrieved and specific causes of this incident could not be verified.

Black Thai ginger *(Kaempferia parviflora)*

Cases on interaction between *K. parviflora* and warfarin have not been reported. An *in vitro* study showed *K. parviflora* extract had an inhibitory effect on CYP2D6 and CYP1A2 activity.[39] Therefore, patients who consume *K. parviflora* with warfarin may increase the risk of bleeding. With a report of such use in this study, the patient used warfarin with *K. parviflora* had a decreased INR. This effect could be more due to a decreasing dose of warfarin than the use of *K. parviflora*.

Vitamin C (Ascorbic acid)

An interaction between warfarin and vitamin C has been described in case reports.[40] In a study, 5 patients who received warfarin therapy for myocardial infarction were also given 1 gram of ascorbic acid daily for 14 days.[41] The researcher recorded data before and after starting vitamin C. The result showed that while the INR values were reduced, the dose of warfarin was kept at the same level for each patient throughout the six weeks of follow-up. The mechanism of this potential interaction is not clear. A possible explanation for this interaction is the role of vitamin C as a potential chelating agent to decrease warfarin absorption.[41] In our present study, a 56-year-old Thai man patient took warfarin with ascorbic acid (1.5 gram per day), approximately 30 days before the INR measurement. His INR was reduced. We did not find other causes of the decreased INR such as non-compliance or unusual vegetable consumption.

Aloe vera *(Aloe barbadenisi) and gaertner (Alpinia nigra)*

There is a lack of data about effect on warfarin included clinical studies or case report.

Conclusion

The present study showed some conflicting results with the previous studies. The results of the present study could guide the prediction of the warfarin effect when used concomitantly with herbs or dietary supplements, especially those with the lack of evidence about the effects on warfarin. It is also implying that it is possible for pharmacists to prevent the interactions between warfarin and herb/dietary supplement by monitoring the use of all herbs and dietary supplements with documented interactions with warfarin, and more importantly those with a lack of evidence. Studies on the evaluation of the effect of herbs or dietary supplements on warfarin are needed in the near future.

Future researches are needed in part because of the limitations of our study. This study was retrospective in design which could be the source missing data and further to a recall bias. With imperfect data available in the patient medical records, we encourage future research with prospective design. This could help assure the factors potentially affect the change of INR. In addition, more reliable method or algorithm to help evaluate the possibility of the interaction between herb/dietary supplement should be used so that the cause-effect relationship could be established with a greater confidence.

In summary, the present study had identified the possible effects of herbs and dietary supplements on INR, in warfarin users, at Phramongkutklao hospital. Patients on warfarin were specifically advised to avoid taking herbs or dietary supplements or have their INR closely monitored when the use of herbs or dietary supplement product is changed, either by adding the product to the regimen, increasing or decreasing the product dose. Pharmacists should educate the warfarin-taking patients about the possibility and consequence of such interaction, and inquire the use of any herbs or dietary supplements, as well as other alternative medicine products.

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