

Interaction between warfarin and Chinese herbal medicines

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ABSTRACT In traditional Chinese medicine (TCM), the human body is divided into *Yin* and *Yang*. Diseases occur when the *Yin* and *Yang* balance is disrupted. Different herbs are used to restore this balance, achieving the goal of treatment. However, inherent difficulties in designing experimental trials have left much of TCM yet to be substantiated by science. Despite that, TCM not only remains a popular form of medical treatment among the Chinese, but is also gaining popularity in the West. This phenomenon has brought along with it increasing reports on herb-drug interactions, beckoning the attention of Western physicians, who will find it increasingly difficult to ignore the impact of TCM on Western therapies. This paper aims to facilitate the education of Western physicians on common Chinese herbs and raise awareness about potential interactions between these herbs and warfarin, a drug that is especially susceptible to herb-drug interactions due to its narrow therapeutic range.

Keywords: drugs, herbs, interaction, traditional Chinese medicine, warfarin

INTRODUCTION

Warfarin is an anticoagulant that is widely prescribed for chronic atrial fibrillation, mechanical valves, deep vein thrombosis and recurrent stroke.^(1,2) Patients on warfarin are often maintained on long-term therapy; hence, a substantial number turn concurrently to traditional Chinese medicine (TCM) for synergistic effects. This, coupled with the narrow therapeutic range of warfarin, renders these patients particularly susceptible to adverse outcomes from herb-warfarin interactions. Patients on warfarin are regularly monitored using the international normalised ratio (INR), of which a target between 2.0 and 3.5 is desired, depending on its indications. While the role of dietary changes in causing INR fluctuations is often discussed, little attention has been paid to the role of herbal medicines in altering the effects of warfarin.

The problem of herb-drug interaction is one that is pertinent. Firstly, TCM use is prevalent. A survey of a Singapore housing estate in 2005 showed that 76% used complementary medicine over the past year, of which TCM was the most common.⁽³⁾ Secondly, a significant proportion, estimated at 26.0% and 23.5% in Hong Kong and Italy, respectively, co-ingest warfarin and Chinese herbs.^(4,5) Thirdly, there is widespread undisclosed use of complementary medicine among Western doctors, which studies in Singapore and Italy have estimated at rates of 75.4% to more than 90.0%.^(3,4) Therefore, there is a need for practitioners to recognise the need to actively elicit the use of complementary medications from patients. This is especially important as most over-the-counter herbs,⁽³⁾ the commonest mode of complementary medicine use, do not contain key safety messages, such as that of herbal interaction with Western medications.⁽⁶⁾

Warfarin works by inhibiting vitamin K epoxide reductase, preventing the recycling of vitamin K, which is needed to activate clotting factors II, VII, IX and X. These clotting factors are required for the formation of fibrin.^(1,2) Warfarin is orally administered in

the form of R- and S-warfarin, of which S-warfarin is 3–5 times more active than R-warfarin. S-warfarin is mainly metabolised by CYP2C9; other enzymes include CYP2C8, CYP2C18 and CYP2C19. R-warfarin is mainly metabolised by CYP1A2 and CYP3A4; other enzymes include CYP1A1, CYP2C8, CYP2C18, CYP2C19 and CYP3A5.⁽²⁾

Interaction between warfarin and Chinese herbs can be classified into pharmacokinetic or pharmacodynamic interactions. Pharmacokinetic interactions affect the absorption, distribution, metabolism or elimination of a drug. Pharmacodynamic interactions result from synergistic or antagonistic effects of herbs on drugs.⁽⁷⁾ This paper aims to consolidate the available literature for and against the interactions between commonly used Chinese herbs and warfarin. This can, firstly, serve as a resource to help guide medical practitioners in counselling patients on the use of warfarin, and secondly, identify gaps in existing evidence.

METHODS

A recently published review article⁽⁸⁾ was consulted for a list of Chinese herbs with known or potential interaction with antiplatelets or anticoagulants, with the addition of other herbs known in TCM to invigorate blood circulation and stop bleeding. Of these, 44 Chinese herbs and supplements commonly used in Singapore were included in our study. A search was conducted in both English (PubMed) and Chinese (Wanfang Med Online) databases. Wanfang Med online is an established database that displays selected top Chinese medical journals in China. The MeSH headings and keywords were: warfarin *or* antiplatelet *or* anticoagulant *or* cytochrome P450, *and* the English, Chinese or Latin names of each Chinese herb. Bibliographies of the papers were also referred to for other relevant studies. All studies with relevant titles were retrieved and selected based on their abstracts. In view of the limited research papers in this area, all forms of

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publications, including randomised controlled trials, crossover studies, case reports, animal studies and *in vitro* studies, were selected. Studies involving herbal formulae were excluded. Studies over a 30-year period from 1983 to 2014 were included. Only articles involving warfarin were selected, with the exception of herbs that yielded no articles on interaction with warfarin. In such cases, interaction of the herb with other antiplatelets or anticoagulants was included in view of possible extrapolations, and such cases were highlighted.

Articles were selected independently by two authors based on title and abstract. The selected articles were approved by the two senior authors (an experienced TCM physician and an established Western physician with special interest in TCM) before the results were consolidated. The articles were analysed and the data was organised into an excel document for easy reference. Relevant data extracted included the study methodology, evidence and mechanism of interaction, and other information such as plant parts as well as herb and warfarin dosages, if available. The results were continually reviewed by the two senior authors and two other non-authors (an established Western practitioner and a senior Chinese physician) during meetings.

A total of 107 articles were selected based on title and abstract. Of these, only articles with full texts available were selected. A total of 77 articles were included: 13 case reports, 14 human studies, 21 animal studies and 29 *in vitro* studies. Of the human studies, two were randomised controlled studies and six were crossover studies. Given the limited number of randomised controlled studies available in this area, other articles (case reports, human studies, animal studies and *in vitro* studies) had to be included in the data analysis. The type of study from which each piece of evidence was obtained was included in the collated table of results for the reader's reference.

RESULTS

The information gathered from the search has been classified into four tables for easy reference. Table I contains the existing evidence and mechanism of herb-warfarin interactions of herbs with the greatest evidence of interaction with warfarin, ordered based on decreasing evidence. Table II describes other herb-warfarin interactions based solely on experimental studies. Table III lists other common Chinese herbs with no published studies on their interaction with Warfarin. Table IV contains common indications of the 11 herbs found to have the greatest evidence of interaction with warfarin.

DISCUSSION

This review has evaluated the current published evidence regarding the herb-warfarin interactions of 44 commonly used Chinese herbal products in Singapore. Of these, 11 herbs (danshen, ginkgo, dong quai, American ginseng, safflower, peach kernel, licorice, Asian ginseng, lycium, ginger and notoginseng) were found to have the strongest evidence of potential interaction with warfarin. Expounded below is a discussion of published studies regarding the interactions of the aforementioned herbs as well as the evidence of their interactions with warfarin. Refer

to the appendix for further information regarding the proposed mechanism of herb-warfarin interactions.

Danshen 丹参 (*Salvia miltiorrhiza* Bge.)

Published case reports have pointed to over-anticoagulation associated with concomitant danshen and warfarin use.^(9,10) A 62-year-old man developed haemothorax two weeks after daily consumption of a danshen decoction (INR > 8.4). Dechallenge of danshen with reintroduction of warfarin at original dosage returned his INR to therapeutic range.⁽⁹⁾ In addition, a controlled clinical trial (n = 40) concluded that concomitant administration of two weeks of danshen with warfarin significantly prolonged prothrombin time (PT) and INR, as compared to those in the control group.⁽¹¹⁾

Ginkgo 银杏, 白果 (*Ginkgo biloba* L.)

Numerous case reports of spontaneous bleeding with warfarin have been published. From 1966 to October 2004, 15 case reports were published describing the temporal association of ginkgo with bleeding.⁽¹²⁾ There was a single case report of a 78-year-old patient on warfarin who, following ginkgo consumption, developed intracerebral bleeding, which stopped with the discontinuation of ginkgo.⁽¹³⁾

However, clinical trials conducted have not substantiated these reports. A randomised, double-blind, placebo-crossover trial (n = 24) of patients who were stable on warfarin concluded that consumption of daily *Ginkgo biloba* 100 mg for four weeks had no significant influence on warfarin response.⁽¹⁴⁾ Similarly, an open-label crossover study (n = 12) concluded that ginkgo at recommended doses did not significantly affect the pharmacokinetics or pharmacodynamics of a single 25 mg dose of warfarin in healthy subjects.⁽¹⁵⁾

Dong quai 当归 (*Angelica sinensis* [Oliv] Diel)

A case report illustrated a 46-year-old woman on warfarin 5 mg/day who developed two episodes of raised INR of 4.05 and 4.90, related to oral dong quai administration of 565 mg 1–2 times daily. A month after dong quai was discontinued, with warfarin dose maintained, her INR dropped to 2.48.⁽¹⁶⁾

American ginseng 西洋参 (*Panax quinquefolius* L.)

A randomised, double-blind, placebo-controlled trial of healthy patients (n = 20) concluded that two weeks of American ginseng 1.0 g twice daily significantly reduced peak INR, peak plasma warfarin and warfarin area under the curve.⁽¹⁷⁾ However, experimental studies have yielded conflicting results. A study by Li et al found that *Panax quinquefolius* significantly extended activated partial thromboplastin time, PT and thrombin time in human plasma *in vitro*.⁽¹⁸⁾

Safflower 红花 (*Carthamus tinctorius* L.)

A case report depicted bleeding and raised INR associated with safflower use.⁽³³⁾ A 74-year-old man on warfarin 1.25 mg/day with therapeutic INR developed haematuria after 14 days of consumption of safflower 20 g (INR 5.31). When he was subsequently restarted on the same dose of warfarin

Table I. Summary of existing evidence of the interaction between warfarin and Chinese herbal medicines.

Chinese herb Scientific name Chinese name	Potentiates warfarin (evidence)	Potentiates warfarin (mechanism)	Antagonises warfarin (evidence)	Antagonises warfarin (mechanism)	No interaction (evidence)
Danshen <i>Salvia miltiorrhiza</i> Root: 丹参	Case report ^(9,10) <i>In vitro</i> study ^(34,36) Animal study ⁽³⁵⁾ Clinical study ⁽¹¹⁾	- CYP1A1, 2C6, 2C11 inhibitor ⁽³⁵⁾ - Displaces warfarin from HSA-warfarin ⁽³⁶⁾ - Antiplatelet effect ⁽³⁴⁾ - Coumarin-containing ⁽³³⁾	Clinical study ⁽³⁷⁾ Animal study ⁽³⁸⁾	- CYP3A4 inducer ⁽³⁷⁾ - CYP1A, 2C, 3A inducer ⁽³⁸⁾	-
Ginkgo <i>Ginkgo biloba</i> Leaf: 银杏; Fruit: 白果	Case report ^(12,13) <i>In vitro</i> study ^(41,42) Clinical study ⁽³⁹⁾	- Antiplatelet effect ⁽³⁹⁾ - CYP1A2, 2C9, 2C19, 2E1, 3A4 inhibitor ^(41,42)	Animal study ⁽⁴³⁾	- CYP1A1, CYP1A2, CYP2B, CYP2C, CYP3A inducer ⁽⁴³⁾	Clinical study ^(14,15,40) <i>In vitro</i> study ⁽⁴⁴⁾
Dong quai <i>Angelica sinensis</i> Root: 当归	Case report ⁽¹⁶⁾ Animal study ⁽⁴⁵⁾	- Coumarin-containing ⁽³³⁾	-	-	-
American ginseng <i>Panax quinquefolius</i> Root: 西洋参	<i>In vitro</i> study ⁽¹⁸⁾	- Anticoagulant effect ⁽¹⁸⁾	Clinical study ⁽¹⁷⁾	-	-
Safflower <i>Carthamus tinctorius</i> Flower: 红花	Case report ⁽¹⁹⁾ Clinical study ⁽⁴⁶⁾	- Antiplatelet effect ⁽⁴⁶⁾	-	-	-
Peach kernel <i>Prunus persica</i> , <i>Semen persicae</i> Seed: 桃仁	Case report ⁽²⁰⁾ Animal study ⁽⁴⁷⁾	- Antiplatelet effect ⁽⁴⁷⁾ - Anticoagulant effect ⁽⁴⁷⁾	-	-	-
Licorice <i>Glycyrrhiza uralensis</i> , <i>Glycyrrhiza inflata</i> , <i>Glycyrrhiza glabra</i> Root, rhizome: 甘草	Case report ⁽²¹⁾ <i>In vitro</i> study ⁽⁴⁸⁾ Animal study ⁽⁴⁹⁾	- CYP3A4, 2B6, 2C9 inhibitor ⁽⁴⁸⁾ - Antiplatelet effect ^(49,50)	Animal study ⁽⁵¹⁾	- Activates pregnane X receptor ⁽⁵¹⁾	-
Asian ginseng <i>Panax ginseng</i> Root: 人参	<i>In vitro</i> study ^(52,53,59) Animal study ^(54,57,58)	- CYP3A4, 2C9, 2C19, 2D6 inhibitor ⁽⁵²⁻⁵⁴⁾ - Antiplatelet effect ⁽⁵⁷⁻⁵⁹⁾ - Anticoagulant effect ^(18,58)	Case report ^(25,26)	-	Clinical study ⁽²⁷⁾
Lycium <i>Lycium barbarum</i> Dried ripe fruit: 枸杞子	Case report ^(28,29)	-	-	-	-
Ginger <i>Zingiber officinale</i> Fresh: 生姜, Dried: 干姜	Clinical study ^(30,63,64) <i>In vitro</i> study ⁽⁶²⁾	- Antiplatelet effect ^(62,64) - Fibrinolytic effect ⁽⁶³⁾	-	-	Clinical study ⁽¹⁵⁾
Notoginseng <i>Panax notoginseng</i> Root: 三七	Animal study ^(32,65,66)	- Increases half-life of warfarin ⁽³²⁾ - Antiplatelet effect ^(65,66)	-	-	-

HSA: human serum albumin

without safflower use, his INR dropped to 1.64–2.57. However, it was highlighted that at 20 g, the patient had exceeded the recommended safflower daily dosage of 10 g.⁽¹⁹⁾

Peach kernel 桃仁 (*Prunus persica* [L.] Batsch, *Semen persicae*)

A case report illustrated a 54-year-old woman on stable warfarin (INR 2.0–2.5) who experienced an isolated episode of INR at 5.5, related to daily consumption of peach kernel. Dechallenge of peach kernel with original warfarin dose resulted in normalisation of INR to 2.1.⁽²⁰⁾

Licorice 甘草 (*Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., *Glycyrrhiza glabra* L.)

A case report described an 80-year-old woman on stable warfarin who developed two episodes of melaena (INR 9.1 and 5.5)

associated with ingestion of a pound of black licorice.⁽²¹⁾ After dechallenge of licorice, her INR normalised to 1.2 two weeks later.

Asian ginseng 人参 (*Panax ginseng*)

The effect of ginseng on warfarin has not been established due to abundant conflicting results. Ginseng has been associated with a few episodes of spontaneous bleeding,⁽²²⁻²⁴⁾ but have also been associated with reports of subtherapeutic INR and thrombosis in patients previously stable on warfarin.^(25,26)

The effect of ginseng on warfarin has not been replicated in clinical trials. A randomised, open-label, controlled study of newly diagnosed ischaemic stroke patients (n = 35) found that two weeks of concomitant use of *Panax ginseng* extract 1.5 g with warfarin did not significantly affect peak values, INR and PT area under the curve, thus concluding that *Panax ginseng* did not influence the pharmacological action of warfarin.⁽²⁷⁾

Table II. Proposed mechanism of interaction between warfarin and other Chinese herbal medicines.

Mechanism	Herb	Scientific name	Chinese name
Pharmacodynamic interaction via antiplatelet effects	Motherwort ⁽⁶⁷⁾	<i>Leonurus japonicus</i>	益母草, Seed: 茺蔚子
	Danshen ⁽⁶⁸⁾	<i>Codonopsis pilosula</i> , <i>Codonopsis pilosula</i> , <i>Codonopsis tangshen</i>	Root: 党参
	Reishi/Lingzhi ^(69,70)	<i>Ganoderma lucidum</i>	Sporophore: 灵芝
	Dandelion ⁽⁷¹⁾	<i>Taraxacum mongolicum</i> , <i>Taraxacum sinicum</i> , <i>Taraxacum officinale</i>	Whole plant: 蒲公英
	Cassia ⁽⁷²⁾	<i>Cassia obtusifolia</i> , <i>Cassia tora</i>	Dried ripe seed: 决明子
	Burdock ⁽⁷³⁾	<i>Arctium lappa</i>	Ripe fruit: 牛蒡子
	Coltsfoot ⁽⁷⁴⁾	<i>Tussilago farfara</i>	Flower: 款冬花
	Hawthorn ⁽⁷⁵⁾	<i>Crateagus pinnatifida</i>	Fruit: 山楂
Pharmacokinetic interaction via CYP450 inhibition	Turmeric ⁽⁷⁶⁾	<i>Curcuma longa</i>	Rhizome: 姜黄
	Astragalus ⁽⁷⁷⁾	<i>Astragalus membranaceus</i> , <i>Astragalus membranaceus</i>	Root: 黄芪
	Bitter orange/sour orange ^(78,79)	<i>Citrus aurantium</i> , <i>Citrus sinensis</i>	Unripe fruit: 枳实; Ripe fruit peel: 枳壳
	Skullcap ⁽⁷⁷⁾	<i>Scutellaria baicalensis</i>	Root: 黄芩
	Coptis Rhizome ⁽⁸⁰⁾	<i>Coptis chinensis</i> , <i>Coptis deltoidea</i> , <i>Coptis teeta</i>	黄连
	Cat's claw ⁽⁸¹⁾	<i>Ranunculus ternatus</i> , <i>Uncaria tomentosa</i>	Tuberous root: 猫爪草
	Angelica ⁽⁸²⁾	<i>Angelica dahurica</i>	Root: 白芷
	Notopterygium root ⁽⁸²⁾	<i>Notopterygium incisum</i> , <i>Notopterygium forbesii</i>	羌活
Antiplatelet effects + CYP450 inhibition	Saposhnikovia root ⁽⁸²⁾	<i>Saposhnikovia divaricata</i>	防风
	Peony ^(77,83,84)	<i>Paeonia suffruticosa</i> , <i>Paeonia lactiflora</i>	Root cortex: 牡丹皮 Root: 芍药, 赤芍, 白芍
	Pubescent angelica ^(82,85)	<i>Angelica pubescens</i>	Root: 独活
	Andrographis ⁽⁸⁶⁻⁹⁰⁾	<i>Andrographis paniculata</i>	Whole plant: 穿心莲
	Kudzu ⁽⁹¹⁻⁹⁴⁾	<i>Pueraria lobata</i>	Root: 葛根

Table III. Chinese herbs (scientific and Chinese names) with no evidence of interaction with warfarin.

Chinese Herb	Scientific name	Chinese name
Corydalis yanhusuo	<i>Corydalis yanhusuo</i>	Tuber: 延胡索
Glehnia	<i>Glehnia littoralis</i>	Root: 北沙参
Aloe vera	<i>Aloe barbadensis</i> , <i>Aloe ferox</i>	Concentrated juice: 芦荟
Chrysanthemum	<i>Chrysanthemum morifolium</i>	Flower: 菊花
Siberian cork-tree bark	<i>Phellodendron chinense</i>	黄柏
Artemisia	<i>Artemisia annua</i>	青蒿
Schisandra fruit	<i>Schisandra chinensis</i>	五味子
Kelp	<i>Sargassum pallidum</i> , <i>Sargassum fusiforme</i>	Fronde: 海藻
Da huang	<i>Rheum palmatum</i> , <i>Rheum tanguticum</i> , <i>Rheum officinale</i>	Root and tuber: 大黄
Magnolia bark	<i>Magnolia officinalis</i> , <i>Magnolia officinalis</i>	Bark: 厚朴
Plantain	<i>Plantago asiatica</i> , <i>Plantago depressa</i>	Seed: 车前子 Whole plant: 车前草
Rhodiola	<i>Rhodiola rosea</i> , <i>Rhodiola euryphylla</i>	Rhizome: 红景天

Lycium 枸杞子 (*Lycium barbarum* L.)

There has been evidence of potentiation of warfarin linked to the consumption of this Chinese herb, as published in case reports of raised INR and bleeding associated with concomitant use of warfarin and lycium. A 71-year-old woman developed epistaxis, ecchymosis and haematochezia (INR of indeterminate level)⁽²⁸⁾ and an 80-year-old woman on warfarin (weekly dosage 15.5–16.5 mg) with therapeutic INR developed two episodes of raised INR (4.97 and 3.86) associated with the consumption of concentrated herbal tea containing *Lycium barbarum* (estimated dosage 20–40 g/day) for 1–2 days prior

to blood-taking.⁽²⁹⁾ Avoidance of the herbal tea returned INR to therapeutic range.

Ginger 生姜, 干姜 (*Zingiber officinale* Rosc.)

A prospective longitudinal study of patients on warfarin (n = 171) found that ginger was independently associated with increased risk of self-reported bleeding.⁽³⁰⁾ Although studies on interaction between ginger and warfarin were not found, a case report illustrated an over-anticoagulatory effect of ginger on phenprocoumon, a coumarin derivative.⁽³¹⁾ A 76-year-old woman on long-term phenprocoumon with stable INR within therapeutic

Table IV. Common traditional Chinese medicine (TCM) uses of the Chinese herbs with the greatest evidence of interaction with warfarin.

Herb	Function in TCM	Common indications for use
Danshen	<ul style="list-style-type: none"> - Invigorates blood circulation - Soothes irritability - Regulates menstruation 	<ul style="list-style-type: none"> - Cardiovascular disease, palpitations - Abdominal masses, traumatic injury, arthralgia from wind-dampness, boils and abscesses, febrile diseases, insomnia - Menstrual abnormalities (irregularity, amenorrhoea, dysmenorrhoea), postpartum abdominal pain
Ginkgo	<ul style="list-style-type: none"> - Preserves lungs' <i>Qi</i> (fruit and leaf) - Invigorates blood circulation (leaf) - Reduces urination (fruit) 	<ul style="list-style-type: none"> - Cough, angina, hyperlipidaemia, hypertension, cerebral vasospasm (leaf) - Excess phlegm, enuresis (fruit)
Dong quai	<ul style="list-style-type: none"> - Tonifies the blood - Relieves pain - Regulates menstruation 	<ul style="list-style-type: none"> - Blood deficiency, dizziness, palpitations - Arthralgia from wind-dampness, traumatic injury, boils and abscesses - Menstrual abnormalities (irregularity, amenorrhoea, dysmenorrhoea), abdominal pain due to deficiency in cold
American ginseng	<ul style="list-style-type: none"> - Tonifies <i>Qi</i> and nourishes <i>Yin</i> - Clears heat 	<ul style="list-style-type: none"> - Dyspnoeic cough with bloody sputum - Tiredness due to deficiency in heat, diabetes mellitus, dry throat
Safflower	<ul style="list-style-type: none"> - Invigorates blood circulation - Regulates menstruation 	<ul style="list-style-type: none"> - Abdominal masses, traumatic injury, painful ecchymoses - Menstrual abnormalities (amenorrhoea, dysmenorrhoea), postpartum abdominal pain
Peach kernel	<ul style="list-style-type: none"> - Invigorates blood circulation - Promotes menstruation - Promotes bowel movement 	<ul style="list-style-type: none"> - Impeded blood circulation from blood stasis, dyspnoeic cough, - Intestinal and lung abscesses, constipation
Licorice	<ul style="list-style-type: none"> - Tonifies spleen <i>Qi</i> - Clears heat and relieves fire toxicity - Relieves spasm and pain 	<ul style="list-style-type: none"> - Weakness, palpitations, cough with profuse sputum - Alleviation of drug toxicity - Pain in the stomach and limbs, boils and abscess
Asian ginseng	<ul style="list-style-type: none"> - Augments <i>Qi</i> - Tonifies the spleen and lungs - Improves mental function 	<ul style="list-style-type: none"> - Prostration syndrome (of primary <i>Qi</i>) - <i>Yin</i> impairment in febrile disease - Diabetes mellitus
Lycium	<ul style="list-style-type: none"> - Tonifies liver and kidney <i>Yin</i> essence - Improves eyesight 	<ul style="list-style-type: none"> - <i>Yin</i> deficiency in liver and kidney - Progeria
Ginger	<ul style="list-style-type: none"> - Dispels exterior cold - Warms the stomach - Warms the lungs 	<ul style="list-style-type: none"> - Vomiting due to stomach-cold, cough due to lung-cold - Abdominal pain - Dyspnoea and cough due to cold
Notoginseng	<ul style="list-style-type: none"> - Eliminates blood stasis - Arrests bleeding 	<ul style="list-style-type: none"> - Haemorrhage, traumatic injury, painful ecchymoses - Restoration of <i>Qi</i>

range developed epistaxis (INR > 10), related to several weeks of regular ginger intake in the form of dried ginger and tea from ginger powder. Discontinuation of ginger and resumption of phenprocoumon at previous dose returned INR to therapeutic range. The Naranjo probability scale scored ginger as a probable cause of the over-anticoagulation.

Notoginseng 三七 (*Panax notoginseng* [Burk.])

Clinical studies or case reports on interaction between Notoginseng and warfarin were not located. However, experimental studies conducted in rats found that administration of notoginseng 20 mg/kg/day for five weeks increased the T_{max} , half-life and area under the curve of warfarin.⁽³²⁾

It is acknowledged that this review has some limitations. Firstly, the use of only two databases may have limited the papers retrieved; however, both selected databases are established ones, with PubMed displaying over 25,000 journals and Wanfang, about 200 selected Chinese medical journals. Secondly, the list of 40 potential herb-warfarin interactions is not exhaustive. Also, data processing was complicated by the exclusion of scientific names of herbs in some published papers; thus, discretion had to be exercised in such cases. Another limitation stems from the common prescription of Chinese herbs in formulas, which renders

this combinatory effect of multiple Chinese herbs on warfarin difficult to address due to the customisation of prescribed formulas, and thus, this has not been explored in our paper. Notably, there was a paucity of high-level evidence (such as meta-analyses and randomised controlled trials) in this area of research. The deliberate inclusion of *in vitro* studies, animal studies and case reports in this review article was made in an attempt to elucidate the possible interactions with warfarin *in vivo*. Finally, conflicting results of herb-warfarin interaction further complicated the review of data. For instance, in the case of danshen, while some case reports, animal studies and *in vitro* studies have suggested a possible potentiation effect, other clinical studies and animal studies have suggested a possible antagonistic effect between the two instead. As such, we recommend that more high-quality studies (i.e. randomised controlled trials) be conducted and that more case reports be documented regarding herb-warfarin interaction.

CONCLUSION AND RECOMMENDATIONS FOR PRACTICE

This review article has identified the possible effects of 44 commonly consumed TCM herbs and supplements on warfarin, and provided recommendations with regard to concomitant ingestion with warfarin. We strongly encourage

the cooperation of both Western doctors and Chinese physicians in ensuring safety in patients on warfarin. Western doctors are advised to regularly screen for TCM use, especially in patients with indications as listed in Table IV, and to advise against the use of herbs that interact with warfarin. Chinese physicians, likewise, are advised to screen for warfarin use in their patients and to adjust their choice of herbs accordingly.

Many of the interactions of herbs with warfarin are extrapolated from experimental studies; the *in vivo* effects on humans, however, remain to be found. We also acknowledge that many other herb-warfarin interactions likely go unrecognised by unsuspecting practitioners. As such, we advise that practitioners be cognisant of the entity of herb-warfarin interactions and maintain a high index of suspicion in patients with poor INR control. In view of the documented reports and studies highlighting the risk of over- or under-anticoagulation of the 11 herbs (i.e. danshen, ginkgo, dong quai, American ginseng, safflower, peach kernel, licorice, Asian ginseng, lycium, ginger and notoginseng) with warfarin, we opine that it would only be prudent to exercise caution in cases of concomitant use of these herbs with warfarin.

Despite their vast differences, both Western and Chinese medicines are employed with the similar goal of optimising patient outcomes. It is our belief that in the near future, with the aid of further studies dedicated to the advancement of knowledge in this area, close cooperation between Western and Chinese physicians will allow for Chinese herbs and Western medicines to be concomitantly prescribed for synergistic effects.

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Appendix

Mechanism of interaction: danshen on warfarin

Pharmacodynamic: Danshen contains coumarin derivatives,⁽³³⁾ and has been found to exhibit antiplatelet effects by inhibiting platelet aggregation using platelet cAMP.⁽³⁴⁾

Pharmacokinetic: *In vitro* studies have found that tanshinones in danshen inhibit CYP1A1, 2C6 and 2C11-mediated warfarin metabolism, and that sodium tanshinone IIA sulfonate replaces warfarin from the binding site on human serum albumin-warfarin complex, increasing free warfarin concentration in blood.^(35,36) However, *in vivo* and *ex vivo* studies have found that danshen components induce CYP3A4 in humans, and CYP1A, 2C and 3A in mice.^(37,38)

Mechanism of interaction: ginkgo on warfarin

Pharmacodynamic: In a crossover study (n = 6), BN52063 in ginkgo was found to inhibit platelet-activating factor-induced platelet aggregation.⁽³⁹⁾ However, another crossover trial (n = 50) found no effect of EGb761 on platelet aggregation or blood coagulation, and no relationship between EGb761 and haemorrhagic complications.⁽⁴⁰⁾

Pharmacokinetic: *In vitro* studies with human microsomes and animal studies found that *Ginkgo biloba* extract and active components (flavonoidic and terpenoidic fractions of EGb761) significantly inhibit CYP1A2, 2E1, 2C9, 3A4, 2C19, which may interfere with metabolism of warfarin.^(41,42) However, other studies have yielded conflicting results. An animal (mice) study concluded that warfarin anticoagulation effects were significantly attenuated by *Ginkgo biloba* extract and bilobalide, which decreased the concentration of R-warfarin by inducing CYP1A1, 1A2, 2B, 2C and 3A.⁽⁴³⁾ In elderly volunteers, ginkgo had no effect on CYP3A4, 2D6, 2E1 and 1A2 when midazolam, debrisoquine, chlorzoxazone and caffeine were used as probes.⁽⁴⁴⁾

Mechanism of interaction: dong quai on warfarin

Pharmacodynamic: Dong quai contains coumarin constituents (ferulic acid, osthole) which have been shown to inhibit platelet aggregation.⁽³³⁾ Animal steady state studies have found that Dong quai significantly increased PT⁽⁴⁵⁾ without any effect on warfarin concentration, suggesting the presence of pharmacodynamics, but not pharmacokinetic interactions.

Mechanism of interaction: safflower on warfarin

Pharmacodynamic: A clinical study of healthy volunteers (n = 30) found that 3 weeks of safflower oil and canola oil diets significantly reduced platelet aggregation.⁽⁴⁶⁾

Mechanism of interaction: peach kernel on warfarin

Pharmacodynamic: Animal studies have found that peach kernel has antiplatelet and anticoagulation effects. Ethanol extract inhibits platelet aggregation, and petroleum ether extract prolongs thrombin time.⁽⁴⁷⁾

Mechanism of interaction: licorice on warfarin

Pharmacokinetic: the supratherapeutic effects of licorice on warfarin can be explained by experimental studies, which showed pharmacokinetic inhibition of CYP3A4, 2B6, 2C9 of glabridin.⁽⁴⁸⁾

Pharmacodynamic: Licorice components, glycyrrhizin and GU-7, have been found to exhibit antiplatelet activity in rabbit and human *in vitro* studies.^(49,50) However, in experimental rat studies, licorice has been found to activate pregnane X receptor *in vitro* and increase warfarin metabolism *in vivo*. If these results are extrapolated, licorice may reduce the antithrombotic effect of warfarin.⁽⁵¹⁾

Mechanism of interaction: Asian ginseng on warfarin

Pharmacokinetic: *In vitro* studies (human) have found that ginseng extract, constituents (kaempferol) and metabolites (compound K, protopanaxadiol, protopanaxatriol) inhibit CYP450 enzymes (CYP3A4, 2C9, 2C19, 2D6), which are involved in the metabolism of warfarin.⁽⁵²⁻⁵⁴⁾ However, a randomised crossover study of healthy volunteers (n = 24) found that *Panax ginseng* had a nonclinically significant effect on the clearance of warfarin.⁽⁵⁵⁾ Also, 28 days of *Panax ginseng* (1,500 mg/day) use in both young (mean age 25 years) and elderly (mean age 67 years) healthy volunteers had no effect on CYP3A4, 2E1 and 1A2 activities. Although CYP2D6 was significantly inhibited by *Panax ginseng* in the elderly, the magnitude of the effect was not clinically significant.^(44,56)

Pharmacodynamic: Antiplatelet and anticoagulant effects have also been described. *In vitro* studies (rabbit, rat, human) found that ginseng and its components (panaxynol, ginsenosides Ro, Rg1, Rg2, lipophilic fraction) inhibit platelet aggregation, possibly by regulating the levels of cGMP and TXA2, as well as inhibit release reaction and thromboxane formation.⁽⁵⁷⁻⁵⁹⁾ A recently published *in vitro* study found that *Panax ginseng* water extract (0.05 mg/mL), Rg1 and Rg2 significantly extended blood clotting time in human plasma as compared to that of the control group.⁽¹⁸⁾ However, a crossover trial of healthy adults (n = 10) found no significant alteration of platelet function after two weeks of ginseng consumption in recommended doses.⁽⁶⁰⁾

Mechanism of interaction: lycium on warfarin

Pharmacokinetic: An *in vitro* study found that lycium weakly inhibits S-warfarin metabolism by CYP2C9, but the dissociation constant (Ki) value of 3.4 mg/mL suggests that other factors other than the CYP450 system may be responsible for the interaction.⁽⁶¹⁾

Mechanism of interaction: ginger on warfarin

Pharmacodynamic: Ginger (5 g dose) has been found in randomised placebo-controlled trials to inhibit platelet aggregation, possibly by inhibiting platelet COX products and thromboxane synthetase, and increase fibrinolytic activity.⁽⁶²⁻⁶⁴⁾ However, an open-label, three-way crossover, randomised study (n = 12) found no evidence of pharmacodynamics or pharmacokinetic interaction with warfarin.⁽¹⁵⁾

Mechanism of interaction: notoginseng on warfarin

Pharmacodynamic: *In vitro* studies (human, rat) found that both raw and steamed *Panax notoginseng* exhibits antiplatelet activity, and significantly inhibited platelet aggregation and plasma coagulation. This was positively translated to prolongation of *in vivo* rat bleeding time at a dosage of 500 mg/kg.^(65,66)