Herbal remedies affecting coagulation – A review

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Abstract

Context: Herbal remedies are used to treat a large variety of diseases, including blood-related disorders. However, a number of herbal preparations have been reported to cause variations in clotting time, this is mainly by disruption of the coagulation cascade.

Objective: The compiling of plants investigated for effects on the coagulation cascade.

Methods: Information was withdrawn from Google Scholar and the journal databases Scopus and PubMed.

Results: Sixty-five herbal remedies were identified with antiplatelet, anticoagulant or coagulating ability. Bioactive compounds included polyphenols, taxanes, coumarins, saponins, fucoidans, and polysaccharides.

Conclusion: Although research has been conducted on the effect of herbal remedies on coagulation, most information relies on *in vitro* assays. Contradictory evidence is present on bleeding risks with herbal uses, though herb-drug interactions pose a threat. As the safety of many herbals has not been proven, nor their effect on blood parameters determined, the use of herbal preparations before undergoing any surgical procedure should rather be ceased.

KEYWORDS

Antiplatelet; antithrombotic; anticoagulant; extract; perioperative bleeding

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Introduction

Cardiovascular diseases remain a prominent killer in this time of age, including myocardial infarctions, strokes and thromboses that can arise from pathologies associated with coagulation (Chistokhodova et al, 2002; Rang et al., 2007; Buch et al., 2010; Eisenreich & Rauch, 2011). Over activity of the coagulation cascade (hypercoagulation) increases the risk of thromboses formation (Mekhfi et al., 2004). This can easily lead to thromboembolisms which block blood flow and lead to ischaemia with subsequent damage to the afflicted organs (Bruno et al., 2001). Hereditary defects and habits such as smoking increase blood coagulability (Rang et al., 2007). On the other hand, anticoagulants (such as heparin and warfarin), antiplatelet drugs (aspirin) as well as fibrinolytics (streptokinase) decrease blood coagulation and the risk of thrombus formation (Vane & Botting, 2003; Rang et al., 2007).

The use of plants as remedies for various ailments has formed the basis of our modern medicinal sciences (Hutchings et al., 1996). According the World Health Organization (2008) approximately 80% of Asia and Africa's population use traditional medicine as a form of health care for treatment of diseases that includes amongst others blood disorders. Plant extracts can be an alternative to currently used antiplatelet agents, as they constitute a rich source of bioactive chemicals. Compounds such as alkaloids, xanthones, coumarins, anthraquinones, flavonoids, stilbenes, and naphthalenes have been reported to have an effect on platelet aggregation (Aburjai, 2000; Elliott Middleton et al., 2000; Chen et al., 2001; Chung et al., 2002). Furthermore, polyphenol-rich diets have been shown to be beneficial in vascular functioning including platelet aggregation in humans (Murphy et al., 2003). In this article the effect of herbal remedies on blood parameters are reviewed. Literature was obtained through use of Scopus and PubMed databases, as well as Google Scholar using the following search parameters, or combinations thereof: 'anticoagulant', 'antiplatelet', 'coagulation', 'plant', 'extract', 'herbal' and 'remedy'; articles published prior to and including 2011.

Herbals and their effect on blood parameters

Various plants are used ethnomedicinally for use in blood-related treatments; as blood tonics, to prevent excessive bleeding, to treat haemorrhoids and as wound

dressing to staunch blood flow. The efficacy and safety of herbal preparations are not always clearly defined though, and the use of these may cause increased perioperative bleeding risk due to disrupted coagulation (Beckert et al., 2007). Whether or not these preparations have direct effects on the coagulation system or cause disruption due to drug interactions is not always known (Beckert et al., 2007). Plants studied for effects on coagulation *in vitro* and/or *in vivo*, as well as possible bioactive constituents, are listed in Table 1.

Various models exist to screen for activity, though popular experiments include effects on prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) both *in vitro* and *ex vivo*, while bleeding time and protection against thromboembolism-induced death are monitored *in vivo*. Since *in vitro* activity does not always translate to *in vivo* activity, continued research in this area is of essence.

Although the majority of plants decrease platelet activation and aggregation it should be kept in mind that many factors are at play. Microtubule stabilization from taxanes (Kim & Yun-Choi, 2010) and increased membrane fluidity from garlic-saponins (Su et al., 1996; Liao & Li, 1997) maintains a disaggregated platelet form. Harmane- and harmine-induced reduction of tyrosine phosphorylation limits calcium mobilization and arachidonic acid liberation, which decreases platelet aggregation (Im et al, 2009). The coagulation cascade is attenuated by various phytochemicals such as polyphenols, sulfated polysaccharides, lapachol, allicin and thiosulphates through inhibition or decreased activity of tissue factor (Lee et al., 2003, 2004), thrombin (Medeiros et al., 2008; Zhang et al., 2008), vitamin K-epoxide reductase (Preusch & Smalley, 1990), plasminogen activator, phospholipase, thromboxane A_2, lipoxygenase (Srivastava, 1986; Beckert et al., 2007), thiol enzymes (coenzyme A and 3-hydroxy-3-methylglutaryl coenzyme A reductase) (Liao & Li, 1997) and other clotting factors, as well as potentiation of heparin co-factor II (Medeiros et al., 2008; Mao et al., 2009) and increased fibrinolysis. Coumarin compounds have the ability to affect coagulation through scavenging of reactive oxygen species, inhibiting cyclic nucleotide phosphodiesterases, inhibiting the activity of vitamin K-dependent γ-carboxylase (activation of coagulation factors) and prostaglandin synthesis (Hoult & Paya, 1996; Coppinger et al., 2004). Increased coagulation could be explained through synthesis of protein networks and increased erythrocyte aggregation, such

as with Ankaferd Blood Stopper® (Goker et al., 2008), or activation of several clotting factors or platelets due to glycoconjugates (Pawlaczyk et al., 2010).

Adverse effects after herbal usage

Four plants have mainly been implicated in spontaneous or perioperative bleeding, which has been attributed to a drug-herb interaction (Table 2). Such interactions are especially of importance when used together with warfarin which has a narrow therapeutic window (Lee et al., 2004; Beckert et al., 2007; Jurgens & Whelan, 2009). St. John's Wort has been found to increase the metabolism of warfarin in humans and animals thereby decreasing its efficacy (Roby et al., 2000). Catechins (found to have antiplatelet activity) as well as vitamin K present in green tea would appear to antagonize the anticoagulant effects of warfarin (Taylor & Wilt, 1999). Intraoperative bleeding has been reported after the consumption of Aloe tablets – due to a possible herb-drug interaction with sevoflurane (Steenkamp & Stewart, 2007).

Ginkgo biloba L. (Ginkgoaceae) has been found to increase bleeding risks, especially during concomitant use of anticoagulants or antiplatelet drugs (Kim et al., 2010). However, an open-label, randomized, crossover study reported that there was no difference in bleeding times or platelet aggregation between ticlopidine (250 mg) and ticlopidine/*Ginkgo biloba* (250/80 mg) treatment groups (Kim et al., 2010).

A clinical study in which *Gingko biloba*, garlic, Asian ginseng (*Panax ginseng* C.A.Meyer (Araliaceae)), St. John's Wort and saw palmetto were given to adult volunteers (5 cycles of 4 weeks, 2 week treatment and 2 week wash-out) indicated that these plants were unable to induce any changes to *in vivo* platelet function (Beckert et al., 2007).

Increased blood coagulation time has been noted when using warfarin with *Peumus boldus* Molina (Monimiaceae), Dong quai and garlic. Whether or not this is due to additive anticoagulant activity or increased plasma concentration of warfarin has as yet not been established (Lambert & Cormier, 2001; Basila & Yuan, 2005).

Discussion

As with all research it is imperative to use a variety of methods to elucidate the mechanism of action of a compound or extract. Single assays are more likely to lead to false positives or inaccurate data, and the advantages or disadvantages must be weighed to magnify the value of a test. Furthermore, *in vivo* assays are of great

importance, as *in vitro* studies do not always predict the effect of an herbal or compound once pharmacodynamic and pharmacokinetic profiles come into play.

A review of the literature indicated that many herbals reduce clotting via inhibition of coagulation factors or platelet activity. Furthermore the majority of experiments to determine activity were carried out *in vitro*, with limited *in vivo* analyses. It is of great importance to validate *in vitro* results in animal studies, as there is always the chance that absorption, metabolism or excretion may lead to significant changes in the herbals effect on coagulation. Many phytochemicals, such as coumarins, polyphenolis, saponins and salicylates were elucidated as potent inhibitors, but the concentrations of these may be of such insignificant levels that they pose no threat. Also, depending on manufacturing and processing procedure concentrations and activity of extracts might differ (Chukwumah et al., 2007). Herbals have been found to alter the metabolism of anticoagulants as well as other medication through induction or suppression of certain genes. Induction of CYP2C9 (which is responsible for warfarin metabolism) remains a possible mechanism by which herbals cause a decrease in anticoagulant plasma concentration (Henderson et al., 2002).

Saw et al. (2006) reported that 21% of medical ward patients co-ingested herbs with antiplatelet or anticoagulant therapy. Of the latter 10.5% were at risk of potential herb-drug interaction. Uncontrolled anticoagulation therapy may result in altered international normalized ratio (INR), spontaneous bleeding and can prove fatal. Whether or not purported herbals have the ability to cause an increased risk of perioperative bleeding is not yet certain, as conflicting reports are available (Beckert et al., 2007).

Conclusion

Cardiovascular thrombotic disease results in widespread mortality and hospitalization, which can be successfully reduced through the use of anticoagulant medicines. The growing use of herbal remedies represents a serious risk of bleeding and thrombosis for patients taking anticoagulants. A relatively small number of studies have been carried out to determine the effect of herbal remedies on coagulation. There is however reports describing the effect of herbals on coagulation and platelet function indicating that herbal preparations show significant disruption of the coagulation cascade. As the safety of many herbals has not been

proven, nor their effect on blood parameters determined, the use of herbal preparations before undergoing any surgical procedure should rather be ceased. Patients on anticoagulant therapy should be warned against the concurrent use of herbals, and have their INR checked within a week of starting herbal remedy use.

Declaration of interest

The authors report no declarations of interest

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Table 1: Herbal remedies affecting coagulation

Family	Plant	Vernacular name (uses if stated)	Effect (phytochemical if stated)	References
i. Antithrombin activity				
Apiaceae	*Angelica sinensis* (Oliv.) Diels	Dong quai (menstrual symptoms)	Antithrombin activity[a] (coumarins suggested)	Page & Lawrence, 1999; Campos-Toimil et al., 2002; Basila & Yuan, 2005
Araliaceae	*Hedera helix* L.	Common ivy	Antithrombin activity[a]	de Medeiros et al., 2000
	Tetrapanax papyriferus C. Koch	Rice paper plant	Antithrombin activity[a]	Chistokhodova et al., 2002
Asteraceae	*Bidens tripartita* L.	Three-lobe beggarticks	Antithrombin activity[a]	Goun et al., 2002
Monostromataceae	*Monostroma latissimum* (Keutzing) Wittrock	Kelp	Increased aPTT and TT[a] (sulfated polysaccharides)	Mao et al., 2009
Euphorbiaceae	*Croton zambesicus* Müell.Arg	Tondibonhamey (menstrual pain)	Decreased thrombin activity[a] (diterpenes suggested)	Robert et al., 2010
	Jatropha curcas Linn.	Physic nut (abortifacient, haemostatic)	Procoagulant when concentrated, anticoagulant when diluted[a]	Osoniyi & Onajobi, 2003
Fabaceae	*Cassia petersiana* Belle.	Dwarf cassia	Increased PT[a]	Cordier et al., 2011
Fagaceae	*Querces robur* L.	English oak	Antithrombin activity[a]	Goun et al., 2002
Gramineae	*Festuca jubata* Lowe	Fescue	Antithrombin activity[a]	de Medeiros et al., 2000
Haloragaceae	*Gunnera tinctoria* (Molina) Mirb	Chilean rhubarb	Antithrombin activity[a]	de Medeiros et al., 2000
Laminariaceae	*Laminaria japonica* Areschoug	Kombu	Increased coagulation times[a] (low molecular weight fucoidans)	Wang et al., 2010

Lauraceae	*Laurus azorica* (Senb.) Franco	Azores laurel	Antithrombin activity[a]	de Medeiros et al., 2000
Lythraceae	*Lagerstroemia indica* Linn.	Crape myrtle	Antithrombin activity[a]	Chistokhodova et al., 2002
	Lythrum salicaria L.	Purple loosestrife (astringent, styptic)	Increased coagulation times[a,b], though thrombus formation[b] (glycoconjugates)	Pawlaczyk et al., 2010
Myricaceae	*Myrica cerifera* Bigelow	Bayberry (analgesic)	Antithrombin activity[a]	Chistokhodova et al., 2002
Myrsinaceae	*Ardisia crenata* Roxb.	Coral berry	Antithrombin activity[a]	Chistokhodova et al., 2002
Myrtaceae	*Callistemon lanceolatus* (Sm.) Sweet	Bottlebrush	Antithrombin activity[a]	Chistokhodova et al., 2002
	Magnolia virginiana Linn.	Sweetbay magnolia (internal pains, fever)	Antithrombin activity[a]	Chistokhodova et al., 2002
Phaeophyceae	*Lessonia vadosa* Searles	Brown seaweed	Increased coagulation times[a] (fucoidans)	Chandía & Matsuhiro, 2008
Pinaceae	*Larix sibirica* Ledeb.	Siberian larch	Increased aPTT[a] (arabinogalactan)	Drozd et al., 2008
Polygoneceae	*Antigonon leptopus* Hook. & Arn.	Mexican creeper	Antithrombin activity[a]	Chistokhodova et al., 2002
Rosaceae	*Sanguisorba officinalis* L.	Great burnet	Antithrombin activity[a]	Goun et al., 2002
Tropaeolaceae	*Tropaeolum majus* L.	Indian cress	Antithrombin activity[a]	de Medeiros et al., 2000
Vacciniaceae	*Vaccinium vitis-idaea* L.	Lingonberry	Antithrombin activity[a]	Goun et al., 2002
Violaceae	*Viola tricolor* L.	Heartsease	Antithrombin activity[a]	Goun et al., 2002
	Viola yedoensis Makino	Herba Violae (antifebrile, detoxifant)	Increased coagulation times[a] (dicoumarins: dimeresculetin, euphorbetin, esculetin)	Zhou et al., 2009
Zingiberaceae	*Hedychium gardnerianum* Rosc.	Kahili ginger	Antithrombin activity[a]	de Medeiros et al., 2000

ii. Antiplatelet activity				
Agavaceae	*Yucca schidigera* Roezl.	Mohave yucca	Decreased platelet aggregation and lipid peroxidation[a] (polyphenols and resveratrol)	Olas et al., 2002
Anacardiaceae	*Rhus verniciflua* Stokes	Lacquer tree (promoting blood flow, removing blood stasis)	Decreased platelet aggregation, calcium mobilization, PAC-1 and P-selectin membrane-receptor expression[a] and thrombotic-induced death/paralysis[b] (isomaltol and pentagalloyl glucose)	Jeon et al., 2006
Apiaceae	*Petroselinum crispum* L.	Parsley (arterial hypertension, cardiac diseases)	Decreased platelet aggregation[a,b], increased tail bleeding time[b] (polyphenols suggested)	Mekhfi et al., 2004; Gadi et al., 2009
Arecaceae	*Calamus quiqeusetinervius* Burret.	Rattan palm (hypertension)	Decreased collagen-induced platelet aggregation[a] (quiquelignan B, C, D, F and H)	Chang et al., 2010
Asteraceae	*Achillea falcata* L.	Yarrow (haemorrhagia)	Antiplatelet activity[a] (1,8-cineole, *p*-cymene or β-thujone suggested)	Aburjai & Hudaib, 2006
	Artemisia dracunculus L.	Tarragon (anticoagulant)	Decreased platelet adhesion, protein secretion[a] (polyphenols suggested)	Shahriyary & Yazdanparast, 2007

	Solidago chilensis Meyen	Goldenrod (anti-inflammatory)	Decreased platelet aggregation[a]	Rafael et al., 2009
Cistaceae	*Cistus ladaniferus* L.	Gum rockrose (antioxidant)	Decreased platelet aggregation[a] (polyphenols suggested)	Mekhfi et al., 2004
Clavicipitaceae	*Beauveria bassiana* (Bals.-Criv) Vuill.	White muscardine	Decreased platelet aggregation[a] (bassiatin)	Kagamizono et al., 1995
Equisetaceae	*Equisetum arvense* L.	Field horsetail (haemostatic)	Decreased platelet aggregation[a] (polyphenols suggested)	Mekhfi et al., 2004
Ericaceae	*Arbutus unedo* L.	Strawberry tree (astringent)	Decreased platelet aggregation[a] (polyphenols suggested)	Mekhfi et al., 2004
Formulation consisting of Rosaceae, Zingiberaceae, Santalaceae and Zingiberaceae, respectively	Honeyless herbal formula (*Prunus mume* Siebold & Zucc., *Amomum semen* Roxb., *Santali album* L. and *Amomum tsao-ko* Roxb., respectively)	Je-Ho-Tang (Japanese apricot, sain, sandlewood and black cardamom, respectively)	Decreased platelet aggregation, calcium mobilization[a]	Jeon et al., 2008
Hymenochaetaceae	*Inonotus obliquus* L.	Chaga mushroom	Decreased platelet aggregation[a] (novel tripeptide)	Hyun et al., 2006
Labiatae	*Anisomeles indica* (L.) Kuntze	Indian catmint (hypertension)	Decreased platelet aggregation[a] (cembrane-type diterpenoids: 2 novel, ovatodiolide and 4,5-epoxovatodiolide)	Chen et al., 2008

Lythraceae	*Punica granatum* L.	Pomegranate (health tonic)	Decreased platelet aggregation, calcium mobilization, thromboxane A2 synthesis, hydrogen peroxide synthesis[a] (polyphenols suggested)	Mattiello et al., 2009
Moraceae	*Ficus carica* L.	Common fig	Decreased platelet aggregation[a]	Gilani et al., 2008
Rutaceae	*Murraya omphalocarpa* Hayata	Orange jasmine	Decreased platelet aggregation[a] (coumarins: omphalocarpinol, 5,7-dimethoxy-8-(3'-methyl-2'-oxobutyl)-coumarin, murragleinin, minumicroline, acetonide, epimurpaniculol seneioate)	Chen et al., 2003; Chia et al., 2008
Taxaceae	*Taxus cuspidata* Siebold & Zucc.	Japenese yew	Antiplatelet activity[a] (taxinine, taxanine A, B, 2-deacetoxytaxinine, taxacin, taxchinin B, taxol)	Kim & Yun-Choi, 2010
Urticaceae	*Urtica dioïca* L.	Stinging nettle (prostatic hyperplasia)	Decreased platelet aggregation[a]	Mekhfi et al., 2004
Zingiberaceae	*Alpinia mutica* Roxb.	Small shell ginger	Decreased arachidonic acid-induced platelet aggregation[a] (cardamonin, pinocembrine, 5,6-dehydrokawain)	Jantan et al., 2008

	Curcuma aromatica Valeton	Curcuma	Decreased ADP-, collagen- and arachidonic acid-induced platelet aggregation[a] (curcumin)	Jantan et al., 2008
	Curcuma longa L.	Turmeric (menstrual disorders)	Decreased platelet aggregation[a] (*ar*-turmerone, curcumin, turemorone)	Lee, 2006
	Curcuma xanthorrhiza Roxb.	Java turmeric	Decreased ADP-, collagen- and arachidonic acid-induced platelet aggregation[a] (xanthorrhizol)	Jantan et al., 2008
	Kaempferia rotunda Linn.	Peacock ginger	Decreased arachidonic acid-induced platelet aggregation[a] (3-deacetylcrotepoxide)	Jantan et al., 2008
	Zingiber officinale Roscoe	Ginger (anti-emetic)	Antiplatelet activity[a] (8-paradol)	Nurtjahja-Tjendraputra et al., 2003; Kruth et al., 2004; Basila & Yuan, 2005
	Zingiber zerumbet Smith	Shampoo ginger	Decreased ADP-, collagen- and arachidonic acid-induced platelet aggregation[a] (zerumbone)	Jantan et al., 2008

Zygophyllaceae	*Perganum harmala* L.	Harmal (anti-emetic)	Decreased collagen-induced platelet aggregation, calcium mobilization, arachidonic acid liberation, PLCγ2 and protein tyrosine phosphorylation[a] (harmane and harmine)	Im et al., 2009
iii. Antithrombotic and antiplatelet activity				
Alliaceae	*Allium sativum* L.	Garlic (cardiovascular conditions)	Anticoagulant activity, decreased platelet aggregation[a] (allicin, thiosulfinates, adenosine, paraffinic polysulfides and ajoene)	Srivastava, 1986; Rose et al., 1990; Basila & Yuan, 2005; Beckert et al., 2007
Araliaceae	*Panax ginseng* C.A. Meyer	Korean ginseng	Decreased platelet aggregation, increased TT[a] (saponins and ginsenosides suggested)	Basila & Yuan, 2005; Beckert et al., 2007; Lau et al., 2009
	Panax notoginseng (Burk) F.H.Chen	Sangi (haemostatic, cardiovascular diseases)	Decreased platelet aggregation[a,b], increased coagulation times[a], bleeding[b] (saponins and ginsenosides suggested)	Su et al., 1996; Liao & Li, 1997; Yao et al., 2008; Lau et al., 2009
	Panax quinquefolium Linn	American ginseng	Decreased platelet aggregation, adhesion, increased TT, platelet fluidity[a]	Basila & Yuan, 2005; Lau et al., 2009

Fabaceae	*Glycyrrhiza glabra* L.	Licorice	Direct antithrombin activity on exosite 1[a], increased bleeding effect, decreased thrombus size, platelet aggregation[b] (glycyrrhizin suggested)	Francishetti et al., 1997; Goun et al., 2002; Mendes-Silva et al., 2003
	Maackia amyrensis L.	Amur maackia	Decreased coagulation, thrombus size, potentiation of endothelium-dependent vasodilatation[b] (isoflavonols suggested)	Plotnikova et al., 2009
Formulation consisting of Paeoniaceae, Apiaceae, Asteraceae, Cyperaceae, Asteraceae and Lamiaceae, respectively	*Peony* genus, C*nidium* genus, *Carthamus tinctorius* L., *Cyperus* genus, *saussurea* genus and *Salvia miltiorrhiza* Bunge	Peony, cnidium, safflower, cyperus, saussurea and Danshen (haemostasis)	Decreased platelet aggregation[a], increased tail bleeding time[b] (rosmarinic acid suggested)	Makino et al., 2002
Ginkgoaceae	*Ginkgo biloba* L.	Ginkgo biloba (cognitive function)	Decreased platelet aggregation[a], decreased thrombosis formation and death/paralysis, no effect on bleeding or coagulation times[b], increased bleeding risk with warfarin and cilostazol (ginkoglides)	Rosenblatt & Mindel, 1997; Matthews, 1998; Basila & Yuan, 2005; Ryu et al., 2009

Lauraceae	*Lindera obtusiloba* L.	Japenese spicebush (bruises, inflammation)	Decreased platelet aggregation[a], decreased death/paralysis[b]	Lee et al., 2010
Umbilicariaceae	*Umbilicaria esculenta* (Miyoshi) Minks	Seogi (bleeding treatment)	Decreased platelet aggregation, no effect on coagulation times and fibrinolytic activity[a], decreased death/paralysis, increase tail bleeding time[b] (phenolics suggested)	Kim & Lee, 2006
iv. Staunching activity				
Formulation containing Araliaceae	*Panax notoginseng* (Burk) F.H.Chen	Yunnan Baiyao (wound healing)	-	Pan et al., 2006
Formulation consisting of Lamiaceae, Fabaceae, Vitaceae, Zingiberaceae and Urticaceae	*Thymus vulgaris* L., *Glycyrrhiza glabra*, *Vitis vinifera* L., *Alpinia officinarum* Hance, *Urtica dioïca*	Ankaferd Blood Stopper® (wound healing)	Reduced bleeding time and volume[b]	Goker et al., 2008

N.S – not stated; aPTT – activated partial thromboplastin time; PT – prothrombin time; TT – thrombin time; a – *in vitro* assay; b – *in/ex vivo* assay

Table 2: Herbal remedies which have been reported to adversely affect clotting

Plant vernacular	Patient	Herbal usage		Procedure/medication	Incidence	Comments
		Dosage	Duration			
Ginkgo biloba	65 (M)	N.S	N.S	Hip arthroplasty	Post-operative wound haemorrhage	-
	61 (M)	40 mg (3-4x daily)	6 months	Spontaneous	Sub-arachnoid haemorrhage	No other causes found
	72 (F)	50 mg (3x daily)	N.S	Spontaneous	Subdural haematoma	No other causes found
	33 (F)	120 mg (daily)	2 years	Spontaneous	Bilateral haematomas	Prolonged bleeding time, normalized after cessation of herbal
	56 (M)	40 mg (3x daily)	18 months	Spontaneous	Intracerebral haemorrhage	No other causes found
	34 (M)	2 tablets (daily)	N.S	Laparoscopic cholecystectomy	Persistant haemorrhage from gall bladder	Transfusion required
	70 (M)	40 mg (2x daily)	N.S	Spontaneous, 325 mg aspirin daily	Hyphema	Appeared within 1 week of starting herbal
	78 (F)	N.S	N.S	Stable warfarin usage	Intracerebral haemorrhage	Appeared within 2 months of concomittant herbal usage
	77 (F)	120 mg (daily)	N.S	Hip arthroplasty, aspirin usage (ceased 10th day postoperation)	Persistant bloody drainage from wound (over 3 weeks)	Only reported aspirin usage initially, bleeding ceased after cessation of herbal
	73 (M)	N.S	6 months	Minor trauma and bleeding tendencies	Haemorrhoidal bleeding, ecchymosis	Bleeding gradually stopped after cessation of herbal

Garlic	87 (M)	2 g (daily)	N.S	Spontaneous	Epidural haematoma	Elevated bleeding time, normalized 3 days after herbal cessation
	72 (M)	N.S	N.S	Transfusion after transurethral prostate reaction	Bleeding	Impaired platelet function 3 months after starting herbal again
	32 (F)	Heavy usage	N.S	Breast augmentation	Haematoma	Prolonged bleeding time, normalized 1 week after herbal cessation
Ginseng	72 (F)	200 mg (daily)	1 month	Spontaneous	Vaginal bleeding	-
	44 (F)	Face cream	N.S	Spontaneous	Vaginal bleeding	-
	39 (F)	Oral and topical	N.S	Spontaneous	Menometrorrhagia	Stopped 10 days after herbal cessation
Danshen	62 (M)	N.S	2 weeks	Mitral valve replacement, stable warfarin usage (5 mg)	Chest pain, dyspnea, fatigue, pericardial and right pleural fluid collections	INR > 8.4, aPTT > 120 s

N.S – not stated; M – male; F – female; table comprised of Izzat et al., 1998, Bent et al., 2005 and Beckert et al., 2007