Current update on herbal sources of antithrombotic activity—a comprehensive review

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Abstract

Background: Herbs are commonly used to treat cardiovascular diseases in various traditional medicine. On the other hand, herb-drug interactions are most commonly encountered with conventional antiplatelet and anticoagulant drug prescriptions. This review presents a compilation of plants investigated for antiplatelet and anticoagulation recently and enumerates their possible lead compounds responsible for its action for paving further drug discovery and knowledge update.

Main body of the abstract: Information about the herbs was withdrawn from the PubMed database of the previous 5 years. We also hand-searched the bibliography of relevant articles for the acquisition of additional information. About 72 herbal sources were identified with the effect of antiplatelet activity, antithrombotic activity, and anticoagulant activity. Bioactive compounds and various secondary metabolites responsible for it, such as alkaloids, saponins, flavonoids, coumarins, polyphenols, furan derivatives, iridoid glycosides, sesquiterpenes, aporphine compounds, were reported.

Conclusion: Newer pharmacological moieties are needed to prevent or reduce the adverse effects of current antithrombotic agents and to improve the safety of patients and cost-effectiveness.

Keywords: Antiplatelet, Antithrombotic, Anticoagulant, Herbal medicine, Phytochemicals, Secondary metabolites, Alkaloids, Saponins, Flavonoids, Coumarins

Background

Cardiovascular disease (CVD) due to thrombosis comprises coronary artery disease (CAD), stroke, hypertension, peripheral arterial disease (PAD), venous-thrombo-embolic disease (VTE) [1]. As per the National Health and Nutrition Examination Survey (NHANES) 2013–2016, the prevalence of Coronary heart disease (CHD) in the USA was estimated as 18.2 million in > 20 years of age with more risk among males than females, whereas the prevalence of ischaemic stroke was 67.6 million and that of hemorrhagic stroke was 15.3 million [2]. CVD and stroke accounted for 14% of the total expenditure in 2014–2015, more than any diagnostic group results in immense health and economic burden in the USA globally. The AHA’s 2020 Impact Goals are to improve the cardiovascular health of all Americans by 20% while reducing deaths attributable to CVD and stroke by 20% [1].

Currently, witnessing an unprecedented pandemic, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS Co-V-2), associated with a significant risk of thromboembolic complications due to hypercoagulability state of blood which is called as Covid-19 associated coagulopathy (CAC) [3]. Though prophylaxis anti-coagulants were administered, the incidence of VTE complications was reported in two-thirds of ICU cases [4] and developed life-threatening thrombotic complications followed by Acute respiratory distress syndrome (ARDS) [5]. Venous thromboembolism
coagulants and anti-thrombotic medications remains the mainstay of treatment in cardiovascular and cerebrovascular disorders. Aspirin and clopidogrel were the commonly administered antiplatelet drugs to reduce recurrent ischaemic events in CAD and ischaemic stroke. Oral anticoagulants are prescribed for primary prevention and secondary prevention of venous thromboembolic disease [11] and as the best option in the prevention of stroke due to cardio-embolism in atrial fibrillation [12].

**Adverse drug reaction due to conventional antithrombotic drug regimen**

Aspirin is prone to cause gastrointestinal side effects, hypersensitivity, hypo-responsiveness in some, and bleeding episodes [13]. Low-dose aspirin is commonly used as primary and secondary prevention of cardiovascular disease, which is associated with the risk of upper and lower gastro-intestinal tract lesions, particularly in the upper gastro-intestinal tract which may cause asymptomatic lesions to peptic ulcer bleeding and/or even death Li et al. [14].

Until recently, the vitamin K antagonists were the only oral anticoagulant agents available and warfarin remains the most commonly prescribed oral anticoagulation worldwide [15]. Warfarin has significant variability in dose-response across individuals and a narrow therapeutic window and intensive therapeutic monitoring are essential. When combined with low-dose aspirin, NSAIDs, or clopidogrel, warfarin acts cumulatively and the risk of bleeding is significantly increased [16] The risk of major bleeding associated with oral anti-coagulants ranges from 3.26 to 7.2% annually [11]. Both oral anticoagulation and antiplatelet therapies are essential in 20–30% of patients with co-existing atrial fibrillation (AF) and CAD, together posing a major risk of thrombotic complications [17]. Currently, in the management of patients with IHD and AF, include triple therapy TT (an anticoagulant plus 2 antiplatelet drugs) and two types of dual therapy, DAPT (2 antiplatelet drugs) or DT (an anticoagulant plus a single antiplatelet drug) [18].

**Herbal resources and secondary metabolites**

Herbs play an indispensable role in natural product discovery to meet the growing healthcare needs. Researchers screen herbal sources through reverse pharmacology and observational therapeutics to find novel compounds and harness the potential for future drug discovery. According to WHO (World Health Organization), about 80% of the World's population depends on medicinal plants or herbs to fulfill their medicinal needs. Herbal medicines are a maximum part of complementary and alternative medicine and preferred treatment of people for various reasons such as ethnicity of use, family traditions, and past good experiences [19]. In this review, we have covered 72 herbs, their extracts, their secondary metabolites, and their pharmacological activities studied in both in vivo, ex vivo, and in vitro investigations. Acknowledging the growing significance of traditional medicine and usage, the WHO global report on traditional and complementary medicine 2019 states about the steps taken to promote the safety, quality, and effectiveness of traditional medicine by developing the WHO Traditional Medicine Strategy 2014–2023, in line with WHO Traditional Medicine Strategy (2002–2005). Healthcare professionals need to be aware of and monitor possible risks of concomitant medications of herbs with conventional medicine prescriptions if any [20].

**Methods**

We conducted a PubMed search for the in-vitro and in vivo studies published between 2016 and 2020 till December using multiple combinations of keywords, including the following: “anti-thrombotic activity”, “antiplatelet activity”, “anti-coagulant”, “antiplatelet aggregation”, “anti-hyper-viscosemia”, “anti-aggregant”, “platelet aggregation inhibitor”, “platelet aggregation inhibitor”, “platelet targeted pharmacologic agents”, “antiplatelet adhesion”, “medicinal plants”, and “herbal sources”. We found 296 publications that were reviewed by two authors. The retrieved articles were examined...
Table 1 List of herbal sources of antithrombotic and its phytoconstituents

| Family          | Botanical name                      | Parts used | Effect/activity                           | Phytochemicals                                      | References |
|-----------------|-------------------------------------|------------|-------------------------------------------|-----------------------------------------------------|------------|
| Apiaceae        | Angelica keiskei (Miq.) Koidz       | Stem       | Antithrombotic-anti-coagulant             | Xanthoangelol B                                     | [21]       |
| Apiaceae        | Angelica sinensis (Oliv.) Diels     | Aerial parts| Anti-coagulant, antiplatelet              | Z-Ligustilide                                       | [22]       |
| Malvaceae       | Abelmoschus manihot (J. Med.) Med.  | Plant      | Antiplatelet                              | Total flavone                                       | [23]       |
| Acanthaceae     | Andrographis paniculata (Burm.f.)   | Plant      | Antiplatelet                              | Diterpenoids                                        | [24]       |
| Liliaceae       | Anemarrhena asphodeloides Bunge     | Rhizomes   | Antiplatelet, antithrombotic              | Timosaponin A-II, timosaponin B-II, anemarsaponin B, steroidal glycosides | [25]       |
| Apiaceae        | Apium graveolens Linn               | Seeds      | Antithrombotic, antiplatelet              | 3-N-Butylphthalide (NBPI)-3-n-Butylphthalide (NBP)  | [26]       |
| Acanthaceae     | Achyranthes bidentata Blume         | Plant      | Anti-coagulant                            | Polysaccharides                                     | [27]       |
| Liliaceae       | Allium sativum L.                   | Cloves     | Antiplatelet                              | Aescin, adenosine,paraffinic polysulfides            | [28]       |
| Sapindaceae     | Aesculus hippocastanum L.           | Bark       | Anti-coagulant                            | Aescin (coumarin)                                   | [29]       |
| Berberidaceae   | Berberis vulgaris L.                | Plant      | Antiplatelet                              | Berberine                                           | [30]       |
| Myrtaceae       | Campononsea xanthocarpa (Mart.) Díberg| Leaf     | Antithrombotic,antiplatelet              | Flavonoids                                          | [31]       |
| Apiaceae        | Cyperus rotundus L.                 | Tuber      | Antiplatelet                              | (+)-nootkatone(isoquertoperoxid)                    | [32]       |
| Compositae      | Corasus mar. L.                     | Dried fruits| Anti-coagulant                            | Anthocyanins, polyphenols                           | [33]       |
| Berberidaceae   | Cassia filiformis L.                | Fresh herb | Antiplatelet                              | Aporphinoid alkaloids                               | [34]       |
| Zingiberaceae   | Curcuma aromatica Salis.           | Rhizome    | Antiplatelet                              | Curcumin                                            | [35]       |
| Asteraceae      | Chrysanthemum indicum L.            | Flowers    | Antiplatelet                              | CHNorogenic acid                                     | [36]       |
| Lauraceae       | Cinnamomum cassia Nees.             | Bark and twigs| Antiplatelet                              | Eugenol, amygdalactone, cinnamic alcohol, 2-hydroxycinnamaldehyde, 2-methoxyxincinaldehyde, coniferaldehyde | [37]       |
| Rutaceae        | Citrus hassaku Yu.Tanaka            | Fruits     | Antiplatelet                              | Rutin                                               | [38]       |
| Ranunculaceae   | Capsis chinensis Franch.            | Rhizome    | Antiplatelet                              | Berberine                                           | [39]       |
| Compositae      | Centaurea cyanus L.                 | Plant      | Antithrombotic                            | Hydroxyisoflavon yellow A                           | [40]       |
| Leguminosae     | Caesalpinia sappan L.               | Heartwood  | Antiplatelet                              | Brevin                                              | [41]       |
| Zingiberaceae   | Cimicifuga racemosa L.              | Rhizome    | Antiplatelet, anticoagulant, antithrombotic| Ar-turmerone, curcumin                              | [41, 42]  |
| Monocotae       | Cudrania tricuspisdata Bureau       | Roots      | Antiplatelet                              | Cudraticusxanthone A (CTXA)                         | [43]       |
| Compositae      | Cirsium oleraceum Hook. & Arn.      | Leaves     | Antiplatelet                              | Triterpenoids                                        | [44]       |
| Apiaceae        | Centella asiatica L. (Lith.)        | Herb       | Antiplatelet                              | Caffeoyl quinic acid compounds                       | [45]       |
| Fabaceae (Leguminosae) | Dalbergia odorifera T. Chen       | Heartwood  | Antiplatelet                              | Sesquiterpenes                                      | [46]       |
| Dioscoraceae    | Dioscorea zingiberensis C.H. Wright | Rhizome    | Antithrombotic, antiplatelet              | Dioscin-steroidal saponins                          | [47, 48]  |
| Ebenaceae       | Diospyros kaki Thunb.               | Leaves, fruits| Antiplatelet, antithrombotic             | Diosmin (diosimin 7-O-rutinoside), a disaccharide derivative | [49]       |
| Euphorbiaceae   | Euphorbia neriifolia L.             | Leaves     | Antithrombotic                            | Polyphenols, polyphenols                            | [50]       |
| Rutaceae        | Evodia rutacarpus A.Juss.           | Dried unripe fruit| Antiplatelet                              | Rutacearpine                                        | [51]       |
| Acanthaceae     | Evonon canadensis L.                | Whole plant| Antiplatelet                              | Polyphenolic polysaccharide                         | [52]       |
| Ginkgoacae      | Ginkgo biloba L.                    | Leaf       | Antiplatelet, anticoagulant activity      | Ginkgolides A, B, and C                              | [53]       |
| Leguminosae     | Glycyrrhiza uralensis               | Rhizome    | Antithrombotic                            | Isotrofolol                                         | [54]       |
| Himantandraceae | Galbulimima baccata F.M.Bailey      | Bark       | Antithrombotic                            | Gallulimima alkaloids-himbacine                     | [55]       |
| Saururaceae     | Houttuynia cordata                  | Plant      | Antiplatelet                              | Alkaldoids                                          | [56]       |
| Euphorbiaceae   | Polygonum multiflorum              | Roots, leaves| Antithrombotic                            | Protocatechic acid                                  | [57]       |
| Rutaceae        | Evodia rutaacarpus A.Juss.          | Dried unripe fruit| Antiplatelet                              | Rutacearpine                                        | [58]       |
| Asteraeae       | Euphorbia neriifolia L.             | Whole plant| Antiplatelet                              | Polyphenolic polysaccharide                         | [59]       |
| Ginkgoacae      | Ginkgo biloba L.                    | Leaf       | Antiplatelet, anticoagulant activity      | Ginkgolides A, B, and C                              | [60]       |
| Leguminosae     | Glycyrrhiza uralensis               | Rhizome    | Antithrombotic                            | Isotrofolol                                         | [61]       |
| Himantandraceae | Galbulimima baccata F.M.Bailey      | Bark       | Antithrombotic                            | Gallulimima alkaloids-himbacine                     | [62]       |
| Saururaceae     | Houttuynia cordata                  | Plant      | Antiplatelet                              | Aporphine compounds                                 | [63]       |
| Euphorbiaceae   | Polygonum multiflorum              | Roots      | Antiplatelet                              | Aporphine alkaldoids                                | [64]       |
| Rutaceae        | Evodia rutaacarpus A.Juss.          | Dried unripe fruit| Antiplatelet                              | -                                                   | [65]       |
| Aquifoliaceous  | Ilex paraguariensis A.St.           | Fruits     | Antithrombotic                            | Chikusetsusaponin IVA                               | [66]       |
| Lamiaceae       | Leonurus sibiricus                 | aerial parts| Antiplatelet                              | Leonurine                                           | [67]       |
| Caprifoliaceae  | Lonicera japonica Thunb.            | Plant      | Antiplatelet                              | Protocatechic acid                                  | [68]       |
| Lamiaceae       | Lycopus lucidus Turcz.              | plant      | Antiplatelet                              | -                                                   | [69]       |
| Asparagaceae    | Linope mucron L.H. Bailey.          | plant      | Anti-thrombotic                           | D39, a natural saponin                              | [70]       |
| Lauraceae       | Lindera obtusiloba Blume            | Leaf       | Antiplatelet, antithrombotic             | quecitrin and alfelin                               | [71]       |
| Rutaceae        | Melochia semecarpifolia Merr.       | root bark  | Antiplatelet                              | quinoline alkaldoids                                 | [72]       |
| Magnoliaceae    | Magnolia officinalis               | Bark       | Antiplatelet                              | Magnololhonokiol                                    | [73]       |
to eliminate potential duplicates or overlapping data. We also hand-searched the references of relevant articles for the acquisition of additional information. We included only those studies published in peer-reviewed journals in the English language only. Finally, 26 manuscripts were considered for this review. The botanical names of all the plants enumerated below (Table 1) were verified referring to www.theplantlist.org.

| Family                  | Botanical name                  | Parts used          | Effect/activity                                      | Phytochemicals                                                                 | References |
|-------------------------|---------------------------------|---------------------|------------------------------------------------------|-------------------------------------------------------------------------------|------------|
| Nelumbonaceae           | Nelumbo nucifera Gaertn.        | fruits, whole plant | anti-coagulant, antithrombotic                        | neferine, alkaloid, flavonoids in hydroalcoholic extract respectively          | [68]       |
| Lamiaceae               | Driganum majonana L.            | plant               | antiplatelet                                         | hydroquinone-D-glucopyranoside (Coomarin)                                     | [69]       |
| Oleaceae                | Osmanthus fragrans Loure.       | seeds               | antiplatelet                                         | secoiridoid glucoside                                                         | [70]       |
| Araliaceae              | Panax ginseng Meyer             | root                | antiplatelet                                         | Ginsenoside Rg1, Ginsenoside Rg3, Ginsenoside Rp4, Ginsenoside Rf (oleanane-type saponin) |            |
| Piperaeae               | Piper longum L.                 | Dried fruits        | antiplatelet                                         | piperlongumine, a pyridone alkaloid                                           | [71]       |
| Paeoniaceae             | Peonia suffruticosia            | dried root bark     | antiplatelet                                         | Paeoniflorin, Benzoyl-paeoniflorin, Benzoyl-xylopaeoniflorin, Methyl gallate, Catechin, Paeoniflorigenone, Galloylpaeoniflorin, Daucosterol | [72]       |
| Araliaceae              | Panax bipinnatifidus Seem.      | Roots               | antithrombotic, antiplatelet                         | saponins                                                                       | [73]       |
| Annonaceae              | Rollinia mucosa Jacq.           | stems               | antiplatelet                                         | N-methoxycarbonyl aporphine alkaloid, romucosine A (1), romucosine B (2), romucosine C (3), andromucosine D (4) | [74]       |
| Apocynaceae             | Rauwolfia serpentina Benth.     | roots               | antiplatelet                                         | Ajmaline                                                                       | [75]       |
| Rutaceae                | Ruta graveolens L.              | root and aerial parts | antiplatelet                                         | The quinoline alkaloid graveoline                                              | [76]       |
| Anacardiaceae           | Rhus verniciflua (Syn. Taxocoden-drax verniciflorum) | herb                | antiplatelet                                         | Isomaltol, Pentagalloyl glucose                                                | [77]       |
| Polygonaceae            | Rheum palmatum L.               | aerial parts        | antiplatelet                                         | Two stilbenes-trans-resveratrol-3-O-β-D-glucopyranosyl (I) and rhaponticin (II) | [78]       |
| Scrophulariaceae        | Rehmannia glutinosa (Gaertn.)   | dried roots         | antiplatelet                                         | furan derivatives                                                             | [79]       |
| Rosaceae                | Spiraea japonica L.             | roots               | antiplatelet                                         | atisine-type diterpenoid alkaloids                                            | [80]       |
| Lamiaeae                | Scutellaria baicalensis Georgi. | root                | anti-platelet, anticoagulant                         | Bicalin                                                                        | [81]       |
| Leguminosae             | Spatholobus subreectus Dunn.    | stem                | antiplatelet                                         | daidzein and genistein                                                        | [82]       |
| Fabaceae                | Sophora japonica L.             | plant               | antiplatelet                                         | flavonoids                                                                    | [83]       |
| Selaginellaceae         | Selaginella tamariscina (P. Beauv.) Spring | herb                | anti-coagulant                                       | dihydrocaffeic acid & amentoflavone                                            | [84]       |
| Typhaceae               | Sparganium stoloniferum Buch.   | plant               | antiplatelet, antithrombotic                         | flavonoids                                                                    | [85]       |
| Labiateae               | Salvia miltiorrhiza             | Root                | antiplatelet                                         | 15,16-dihydrotanshinone, Tanshinone IA, Cryptotanshinone, Danshensu, Salviannic acid B | [86]       |
| Sapindaceae             | Sapindus mukorossi Gaertn.      | Galls               | antiplatelet                                         | Sapinmusaponins F-I, Sapinmusaponins Q and R (1–50 µM) respectively           | [86]       |
| Asteraceae              | Silybum marianum (L.) Gaertn.   | Seeds/fruits        | antiplatelet activity                                | Silymarin, flavonoids                                                         | [87]       |
| Rosaceae                | Spiraea japonica L.             | roots               | antiplatelet                                         | spiramine C1                                                                  | [88]       |
| Violaceae               | Viol a yedoensis Makino         | whole plants        | anticoagulant                                         | dicoumarin: dimeresuclein, euphorbitin, esculetin                              | [88]       |
| Melanthaceae            | Veratrum dahuricum (Turcz.) O.Loes. | rhizomes          | antiplatelet                                         | Veratrofagmin-steroidal alkaloid                                              | [89]       |
| Zingiberaceae           | Zingiber officinale Roscoe      | rhizome             | antiplatelet                                         | Gingerol, paradol                                                             | [90]       |
Mechanism of antiplatelet and anticoagulant activity of herbs

Plant-derived compounds such as alkaloids, anthraquinones, coumarins, flavonoids, xanthones, lignans, saponins, stilbenes, etc. were found to affect platelet aggregation activity Werner Cordier et al. [91]. Inhibition of platelet adhesion or chemical mediators for activation of platelet function is the common potential of herbs for its antiplatelet activity. Various mechanisms had been postulated such as inhibition of ADP-induced platelet aggregation, inhibition of the arachidonic acid pathway, thereby inhibiting biosynthesis of thromboxane A2; plants containing lignans, xanthones, sesquiterpenes, flavonoids affect coagulation by inhibiting platelet-activating factor (PAF), or PAF receptor antagonists, inhibiting the factor X on the coagulation cascade. Plants containing the coumarin class of compounds antagonise vitamin K and
| Botanical name                      | Mechanism of action                                                                 |
|------------------------------------|--------------------------------------------------------------------------------------|
| Angelica keiskei (Miq.) Koidz.     | Inhibit platelet aggregation                                                         |
| Angelica sinensis (Oliv.) Diels    | Inhibit platelet aggregation                                                         |
| Abelm tesus manihot (L.) Medik      | Inhibit platelet aggregation                                                         |
| Andrographis paniculata (Burm.f) Nees | Inhibit platelet aggregation                                                        |
| Anemarhena asphodeloides Bunge      | Inhibit ADP-induced platelet aggregation                                             |
| Apium graveolens Linn               | Inhibit platelet aggregation                                                         |
| Achyranthes bidentatata Blume       | Prolonged coagulation time                                                           |
| Allium sativum L.                   | Inhibit platelet aggregation                                                         |
| Aesculus hippocastanum L.           | Preventing oxidative damage of fibrinogen & moderate antiplatelet aggregation activity |
| Berberis vulgaris L.                | Inhibit platelet aggregation                                                         |
| Campomanesia xanthocarpa (Mart) O. Berg | Inhibit platelet aggregation, fibrinolytic activity                                 |
| Cyperus rotundus L.                 | Inhibit collagen-, thrombin-, and AA-induced platelet aggregation                    |
| Cornus mas L.                       | Inhibit platelet aggregation                                                         |
| Cassytha filiformis L.              | Inhibit platelet aggregation                                                         |
| Curcuma aromatica Salisb.           | Inhibit AA-, collagen-, & ADP-induced platelet aggregation                            |
| Chrysanthemum indicum L.            | Inhibit platelet aggregation                                                         |
| Cinnamomum cassia Nees.             | Inhibit platelet aggregation                                                         |
| Citrus hassaku Yu. Tanaka           | Inhibit platelet aggregation                                                         |
| Coptis chinensis Franch.            | Inhibited thromboxane synthesis                                                     |
| Carthamus tinctorius L.             | Inhibited thromboxane synthesis                                                     |
| Caesalpinia sappan L.               | Inhibited collagen-induced platelet aggregation                                      |
| Curcuma longa L.                    | Inhibit platelet aggregation                                                         |
| Cudrania tricuspida Bureu           | Inhibit platelet aggregation, inhibited thrombin production                           |
| Callicarpa nudiflora Hook. & Am.    | Antiplatelet aggregation                                                             |
| Centella asiatica L. (Urb).         | Inhibition of platelet activation and coagulation                                     |
| Dalber gia odorifera T. Chen         | Inhibit platelet aggregation                                                         |
| Dioscorea zingiberensis C.H. Wright | Antithrombotic                                                                       |
| Diospyros kaki Thunb.               | Inhibited thrombin-catalysed fibrin formation                                         |
| Euphorbia neriifolia L.             | Prolonged bleeding time & clotting time                                              |
| Evodia rutaecarpa A. Juss.          | Prolonged bleeding time, antiplatelet aggregation                                    |
| Erigeron canadensis L.              | Inhibited thrombin                                                                   |
| Ginkgo biloba L.                    | Inhibit platelet aggregation                                                         |
| Glycyrrhiza uralensis                | Antithrombotic                                                                       |
| Galbulimima baccata F.M. Bailey      | Inhibit platelet aggregation                                                         |
| Houttuynia cordata                  | Antiplatelet aggregation                                                              |
| Hernandia nymphaefolia J. Presl.    | Antiplatelet aggregation                                                              |
| Illigera luzonensis Merr.           | Antiplatelet aggregation                                                              |
| Illex paraguariensis A. St.         | Inhibits fibrinogen & platelet aggregation                                            |
| Leonurus sibiricus                  | Antiplatelet aggregation                                                              |
| Lonicera japonica Thunb.            | Antiplatelet aggregation                                                              |
| Lycopus lucidus Turcz.              | Inhibit aggregation of red blood cells                                               |
| Linhaope muscari L.H. Bailey         | Inhibit thrombosis                                                                   |
| Lindera obtusiloba Blume            | Inhibit platelet aggregation & collagen-induced thromboxane production               |
| Melicope semecarpifolia Merr.       | Antiplatelet aggregation                                                              |
| Magnolia officinalis                | Antiplatelet aggregation                                                              |
| Nelumbo nucifera Gaertn.            | Inhibitory effect on platelet activation, adhesion & aggregation, and thromboxane A2 formation |
| Origanum majorana L.                | Inhibition of platelet adhesion & aggregation                                         |
| Osmnthus fragrans Loure             | Inhibit platelet aggregation                                                         |
| Panax ginseng Meyer                 | Antiplatelet aggregation                                                              |
prevent coagulation. Few naturally occurring compounds contain fibrinolytics which may activate plasminogen and affect coagulation. Phytochemicals that inhibit the CYP3A4, CYP2C9, and CYP1A2 metabolism were potent to affect coagulation Leite et al. [92]. Herbs identified in this review were listed with possible mechanisms of action responsible for their pharmacological activity in Table 2.

**Table 2** (continued)

| Botanical name                          | Mechanism of action                                                                 |
|----------------------------------------|--------------------------------------------------------------------------------------|
| *Piper longum* L.                      | Inhibit AA-, collagen-, & PAF-induced platelet aggregation                           |
| *Paeonia suffruticosa*                 | Inhibit platelet aggregation & blood coagulation                                      |
| *Paeonia lactiflora* Paill.            | Inhibit platelet aggregation & blood coagulation                                      |
| *Panax bipinnatifidus* Seem.           | Inhibit platelet aggregation & prolonged aPTT                                        |
| *Rollinia mucosa* Jacq.                | Inhibit platelet aggregation                                                        |
| *Rauwolfia serpentina* Benth.          | Inhibition of platelet-activating factor                                              |
| *Ruta graveolens* L.                   | Antiplatelet aggregation                                                            |
| *Rhus verniciflua* (Syn. *Taxodium vernicifluum*) | Antiplatelet aggregation                                                             |
| *Rheum palmatum* L.                    | Antiplatelet aggregation                                                            |
| *Rehmannia glutinosa* (Gaertn.)        | Antiplatelet aggregation                                                            |
| *Spirea japonica* L.                   | Antiplatelet aggregation                                                            |
| *Scutellaria baicalensis* Georgi.      | Inhibited fibrin polymerization and platelet function, prolonged aPTT, PT, and production of thrombin |
| *Spatholobus suberectus* Dunn.         | Inhibition of fibrinogen binding                                                     |
| *Sophora japonica* L.                  | Antiplatelet aggregation                                                            |
| *Selaginella tamariscina* (P. Beaux.) *Spring* | Antiplatelet aggregation & increased fibrinogen content                             |
| *Sparganium stoloniferum* Buch.        | Antiplatelet aggregation                                                            |
| *Salvia miltiorrhiza*                   | Inhibit platelet aggregation                                                        |
| *Sapindus mukorossi* Gaertn.           | Antiplatelet aggregation                                                            |
| *Silybum marianum* (L.) Gaertn.        | Antiplatelet aggregation                                                            |
| *Viola yedoensis* Makino               | Antiplatelet aggregation                                                            |
| *Veratrum dahuricum* (Turcz.) O. Loes. | Antiplatelet aggregation                                                            |

ADP adenosine di-phosphate, AA arachidonic acid, PAF platelet-activating factor, aPTT activated partial thromboplastin time, PT prothrombin time

**Table 3** Common therapeutic indication of herbs

| Herbs                        | Main uses of herb                                      | Reference                      |
|------------------------------|--------------------------------------------------------|--------------------------------|
| *Angelica sinensis* (Oliv.) Diels | Promoting circulation                                | Lu et al. [97] |
| *Andrographis paniculata* (Burm.f.) Nees | Myocardial ischaemia, fever, respiratory infections | Zhang et al. [6] |
| *Apium graveolens* Linn       | Hepatic and spleen disorders, brain disorders, sleep disturbances | Al-Asmari et al. [98] |
| *Allium sativum* L.           | Hypercholesterolaemia                                  | Izzo et al. [96] |
| *Aesculus hippocastanum* L.   | Anti-inflammatory, venotonic                           | Sparg et al. [29] |
| *Carthamus tinctorius* L.     | Chest pain, traumatic injuries                        | Lim et al. [99] |
| *Curcuma longa* L.            | Chest pain, amenorrhoea                                | Lim et al. [99] |
| *Centella asiatica* (L. (Urb). | Improving memory                                      | Satake et al. [46] |
| *Ginkgo biloba* L.            | CVD, angina, cerebral vasospasm, hypertension         | Lim et al. [99] |
| *Panax ginseng* Meyer         | Enhancing immunity, cognitive impairment              | Kim et al. [100]; Lim et al. [99] |
| *Salvia miltiorrhiza*         | Cardiovascular and cerebrovascular symptoms           | Kim et al. [100] |
| *Silybum marianum* (L.) Gaertn. | Liver and gallbladder disorders                      | Gurley et al. [101] |
| *Zingiber officinale* Roscoe  | Anti-bacterial, anti-ulcer                             | Mohd Nor et al. [102] |

Herb-drug interaction types and mechanism

Among older adults, concomitant herbal medicine use along with prescription drugs had been reported as 5.3
to 88.3% in a systematic review as potential cause of herbal-drug interaction Agbabiaka et al. [93]. Herb-drug interactions (HDI) may be either due to pharmacokinetic or pharmacodynamic interactions which affects the safety and efficacy of the treatment. Pharmacokinetic interactions affect the absorption, distribution, metabolism, and excretion of drugs which in turn results in a change in drug concentration in body fluids Lee et al. [94]. Various mechanism has been postulated for the altered drug concentration such as induction or inhibition of hepatic and intestinal drug-metabolizing enzymes such as cytochrome P450, UDP-glucorynyl transferase, and carrier proteins such as P-glycoprotein was suggested Kahrman et al. [95]. While pharmacodynamic interactions are related to the pharmacological activity of the interacting agents which may be synergistic or additive resulting in toxicities or antagonistic causing treatment failure Izzo [96].

**Herbal drug interaction with aspirin, clopidogrel, and warfarin**

Few frequently reported herbs, with its commonly used therapeutic indications (Table 3), and drug interactions with conventional anti-thrombotic medicines were enumerated with increased risk of bleeding as per current evidence (Tables 4, 5, and 6) and types of herb-drug interaction of few herbs are summarised (Table 7).

**Safety profile**

Salvia miltiorrhiza, Angelica sinensis (Oliv.) Diels and Zingiber officinale Roscoe were identified to cause major interactions with anticoagulant or antiplatelet drugs may lead to life-threatening complications or serious adverse events (Tsai et al. [110]).

**Conclusions**

In this review, extensive search has been done on herbal sources investigated for anti-thrombotic activity recently were highlighted. Adverse haemorrhagic complications

### Table 4 List of herb-aspirin interaction causing increased risk of bleeding

| Botanical name               | Herb-aspirin interaction (references)       |
|-----------------------------|---------------------------------------------|
| Angelica sinensis (Oliv.) Diels | Xiao et al. [103]                           |
| Carthamus tinctorius L.      | Lim et al. [99]                             |
| Curcuma longa L.             | Hu and Wang [104]                           |
| Ginkgo biloba L.             | Hu and Wang [104]                           |
| Panax ginseng Meyer          | Hu and Wang [104]                           |
| Salvia miltiorrhiza          | Hu and Wang [104]; Xiao et al. [103]        |

### Table 5 List of herb-clopidogrel interaction causing increased risk of bleeding

| Botanical name               | Herb-clopidogrel interaction (references)       |
|-----------------------------|------------------------------------------------|
| Angelica sinensis (Oliv.) Diels | Xiao et al. [103]                             |
| Carthamus tinctorius L.      | Lim et al. [99]                               |
| Curcuma longa L.             | Lim et al. [99]                               |
| Ginkgo biloba L.             | Lim et al. [99]                               |
| Panax ginseng Meyer          | Lim et al. [99]                               |
| Salvia miltiorrhiza          | Lim et al. [99]; Xiao et al. [103]             |

### Table 6 List of herb-warfarin interaction causing increased risk of bleeding

| Botanical name               | Herb-warfarin interaction (references)         |
|-----------------------------|------------------------------------------------|
| Angelica sinensis (Oliv.) Diels | Leite et al. [92]; Ge et al. [105]; Akram and Rashid [106]; Leite et al. [107] |
| Andrographis paniculata (Burm.f) Nees | Leite et al. [107]                             |
| Apium graveolens Linn        | Akram and Rashid [106]                         |
| Allium sativum L.            | Leite et al. [92]; Leite et al. [107]          |
| Aesculus hippocastanum L.    | Leite et al. [107]                             |
| Carthamus tinctorius L.      | Leite et al. [107]                             |
| Curcuma longa L.             | Leite et al. [92]; Ge et al. [105]; Akram and Rashid [106]; Shaikh et al. [108]; Leite et al. [107] |
| Centella asiatica L. (Urb.)  | Leite et al. [107]                             |
| Ginkgo biloba L.             | Leite et al. [92]; Ge et al. [105]; Akram and Rashid [106]; Shaikh et al. [108]; Leite et al. [107] |
| Panax ginseng Meyer          | Akram and Rashid [106]; Shaikh et al. [108]     |
| Salvia miltiorrhiza          | Akram and Rashid [106]; Shaikh et al. [108]     |
| Silybum marianum (L.) Gaertn.| Leite et al. [107]                             |
| Zingiber officinale Roscoe   | Leite et al. [92]; Ge et al. [105]; Leite et al. [107] |
due to current conventional medicines, patient safety, huge economic burden on healthcare, cognisance of herbal drug interaction, and complications due to recently emerged pandemic due to SARS Co-V2 virus, etc. all pose a need to search for newer pharmacological moieties for drug discovery.

Table 7 Types of herb-drug interaction in herbs

| Herb                        | Warfarin | Aspirin | Clopidogrel |
|-----------------------------|----------|---------|-------------|
| *Angelica sinensis* (Oliv.) Diels | (A) COX-inhibitor [Hu et al. 2005]; Inhibits CYP1A2 & CYP3A4 Leite et al. [92] | (A) Inhibition of rCyp2c11 & carboxylesterase activities Xiao et al. [103] | (A) Inhibition of rCyp2c11 & carboxylesterase activities Xiao et al. [103] |
| *Allium sativum* L.        | (A) Interferes with metabolizing enzymes Ge et al. [105]; (B) additive effect [Hu et al. 2005]; (B) PAF inhibitor Ge et al. [105]; (A) inhibits CYP3A4 Leite et al. [92] | – | – |
| *Aesculus hippocastanum* L. | (A) Increased bleeding [Hu et al. 2005] | – | (B) Potentiates its activity Lim et al. [99] |
| *Carthamus tinctorius* L.  | (B) PAF inhibitor Leite et al. [92] | – | (B) Potentiates its activity Lim et al. [99] |
| *Curcuma longa* L.         | (A) Inhibiting CYP2C9/C19, CYP3A4, CYP1A2 Costache et al. [109]; (B) Additive effect [Hu et al. 2005]; (B) PAF receptor antagonist Leite et al. [92] | (A) COX-inhibitor Lim et al. [99] | – |
| *Ginkgo biloba* L.         | (B) Additive effect [Hu et al. 2005] | (B) Inhibited platelet aggregation Lim et al. [99] | – |
| *Panax ginseng* Meyer      | (A) Increased bleeding; (B) additive effect [Hu et al. 2005] | (B) Additive or synergistic effect Lim et al. [99] | – |
| *Salvia miltiorrhiza*      | (A) Increased bleeding; (B) additive effect [Hu et al. 2005] | – | – |
| *Zingiber officinale* Roscoe | (B) PAF inhibitor Leite et al. [92] | – | – |

(A) pharmacokinetic interaction, (B) pharmacodynamic interaction

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