Received: 30 October 2021 | Revised: 21 January 2022 | Accepted: 26 January 2022

DOI: 10.1002/ptr.7408

REVIEW

WILEY

Potential clinical applications of phytopharmaceuticals for the in-patient management of coagulopathies in COVID-19

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Funding information
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Abstract

Thrombotic complications occur in many cardiovascular pathologies and have been demonstrated in COVID-19. The currently used antithrombotic drugs are not free of adverse reactions, and COVID-19 patients in particular, when treated with a therapeutic dose of an anticoagulant do not receive mortality benefits. The clinical management of COVID-19 is one of the most difficult tasks for clinicians, and the search for safe, potent, and effective antithrombotic drugs may benefit from exploring naturally bioactive molecules from plant sources. This review describes recent advances in understanding the antithrombotic potential of herbal drug prototypes and points to their future clinical use as potent antithrombotic drugs. Although natural products are perceived to be safe, their clinical and therapeutic applications are not always apparent or accepted. More in-depth studies are necessary to demonstrate the clinical usefulness of plant-derived, bioactive compounds. In addition, holistic approaches in systematic investigations and the identification of antithrombotic mechanisms of the herbal bioactive molecule(s) need to be conducted in pre-clinical studies. Moreover, rigorous studies are needed to compare the potency of herbal drugs to that of competitor chemical antithrombotic drugs, and to examine their interactions with Western antithrombotic medicines. We have also proposed a road map to improve the commercialization of phytopharmaceuticals.

KEYWORDS
anticoagulant, antiplatelet, antithrombotic, cardiovascular diseases, chemical marker-assisted quality control, herbal drug, medicinal plants, natural products, phytopharmaceuticals, thrombosis

1 | THE COVID-19 PANDEMIC: A COMMUNITY HEALTH DISASTER

Billions of people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was initially identified in December 2019. By the end of March 2020, the infections had been rapidly transmitted in several countries, and to date, more than 175 million cases have been confirmed worldwide, with at least 3.8 million deaths. The World Health Organization (WHO) declared that coronavirus disease 2019 (COVID-19) was a global pandemic and a great concern for community health. COVID-19 symptoms can be extremely variable (Table 1) and patients with COVID-19 usually display several physiological complications and distress. Seriously ill patients, however, show an alarming risk of thrombotic complications, including microvascular thrombosis, venous thromboembolic disorder, and stroke that can lead to multi-organ failure, which contributes to the high mortality rate in COVID-19 (Acharya, Alameer, Calpin, Alkhattab, & Sultan, 2021; McFadyen, Stevens, & Peter, 2020). Importantly, thrombosis-associated cardiovascular diseases (CVDs) are also the leading causes of death globally (Jackson, 2011; Montrief, Davis, Koyfman, & Long, 2019; Raskob et al., 2014). Consequently, approaches for curbing the thrombotic

TABLE 1 The most common clinical symptoms are shown by patients suffering from COVID-19

1. Complications of respiratory system	• Acute lower respiratory infection characterized by the following symptoms-congestion, running nose, mild fever, sore throat, and dry fever. • Acute respiratory distress syndrome (ARDS), where lungs are severely damaged, is characterized by severe breathing trouble, sometimes confusion, and fatigue. • Pneumonia is characterized by cough maybe with bloody mucus, rapid and shallow breathing, occasional chest pain, fever, and loss of appetite. • Pneumothorax, also known as a collapsed lung, shows the clinical symptoms of chest pain, shortness of breath, increased heart rate, dizziness, and the patient may undergo a coma in severe conditions. • Respiratory failure.
2. Circulatory and hematological disorders	• Acute myocarditis and myocardial injury • Cardiac arrest • Disseminated intravascular coagulation (DIC) results in stroke and sometimes death. Symptoms are bold clots, fall in blood pressure, bleeding, and confusion. • Lymphocytopenia due to low lymphocyte count in blood is characterized by joint pains, skin rash, weight loss, night sweat, enlarged lymph node, cough, fever, and running nose. • Pulmonary embolism is characterized by a rapid and irregular heartbeat, anxiety and sweating, dizziness, and swelling of legs due to deep vein thrombosis. • Thrombocytopenia due to low circulatory platelet count is characterized by bleeding of gums, blood in urine, stool, or vomit, and rectal bleeding. • Venous thromboembolism (VTE) is characterized by swelling(oedematous) of legs with intense pain, tenderness of the thigh or calf, and reddish discoloration.
3. Disorders of liver and kidney	• A liver function test can assess an acute liver injury. • Acute kidney injury may lead to kidney failure.
4. Some uncommon symptoms	• The appearance of rash and discoloration of fingers or toes • Aches and pains. • Complete or partial loss of taste and smell. • Diarrhea. • Headache.

complications in COVID-19 and CVDs, in general, have received much attention in clinical research.

The highly regulated physiological hemostatic coordination, which encompasses platelet aggregation, blood coagulation, and subsequent fibrinolysis maintains the closed circulatory system that operates under high pressure in mammals post vascular injury (Montrief et al., 2019; Raskob et al., 2014). As shown in Figure 1, the thrombus (blood clot) formation inside the blood vessels, which is temporary and spatial under normal physiological conditions, is under strict control of the regulatory system (Raskob et al., 2014). When runaway processes (like those observed in COVID-19) override the hemostasis or a swing in the hemostatic equilibrium occurs toward pro-coagulation, the result is the development of a thrombus (clot) in the vein and artery. In microvascular circulation, the ultimate result is a clinical condition known as thrombosis (Day et al., ; Lippi, Franchini, & Targher, 2011; McFadyen et al., 2020; Raskob et al., 2014). The anticipated mechanism of SARS-CoV-2-induced coagulopathies in COVID-19 is shown in Figure 2.

The clinical diagnosis is plasma D-dimer (indicating activation of the pro-coagulant pathways), interleukin-6 (IL-6), cardiac-specific troponins, and thrombocytopenia (low blood platelet count) emerge as prognostic markers in COVID-19 (McFadyen et al., 2020; Page & Ariëns, 2021). Individuals at high risk of CVDs and women taking oral contraceptives, for example, are more prone to developing thrombi in the blood vessels (Jackson, 2011; Previtali, Bucciarelli, Passamonti, & Martinelli, 2011). In COVID-19 patients, thrombosis is triggered via intrinsic and extrinsic coagulation pathways (Page & Ariëns, 2021). Microvascular thrombotic disorders that result from disseminated intravascular coagulation and microangiopathy hemolytic anemia, occurring in both CVDs and COVID-19 are usually also associated with thrombo-inflammation (Bray, Sartain, Gollamudi, & Rumbaut, 2020; McFadyen et al., 2020). A recent article applying the principles of the Virchow's triad showed irregularities in the vascular endothelium and platelet function, and modified blood flow that may also result in venous and arterial thromboses in COVID-19 (Ahmed, Zimba, & Gasparyan, 2020). Since treatment and the prevention of thrombosis-associated CVDs, and hypercoagulability in COVID-19 is a challenging task for clinicians, many researchers are searching for potent, safe, and affordable drugs to curb these life-threatening diseases (Ibrahim, Rondina, & Welt, 2018; Islam, Alam, Ibrahim Khalil, HaryoSasongko, & Hua, 2016; Li, Yuan, & Yuan, 2020; McFadyen et al., 2020).

2 | CLINICAL THERAPY AND PROPHYLAXIS OF THROMBOTIC COMPLICATIONS IN COVID-19: THE KEY ISSUES AND CHALLENGES

Currently, three major classes of antithrombotic drugs: blood thinners (anticoagulants), antiplatelet drugs (inhibitors of platelet aggregation), and clot-busting drugs (fibrinolytic drugs) are widely applied to treat

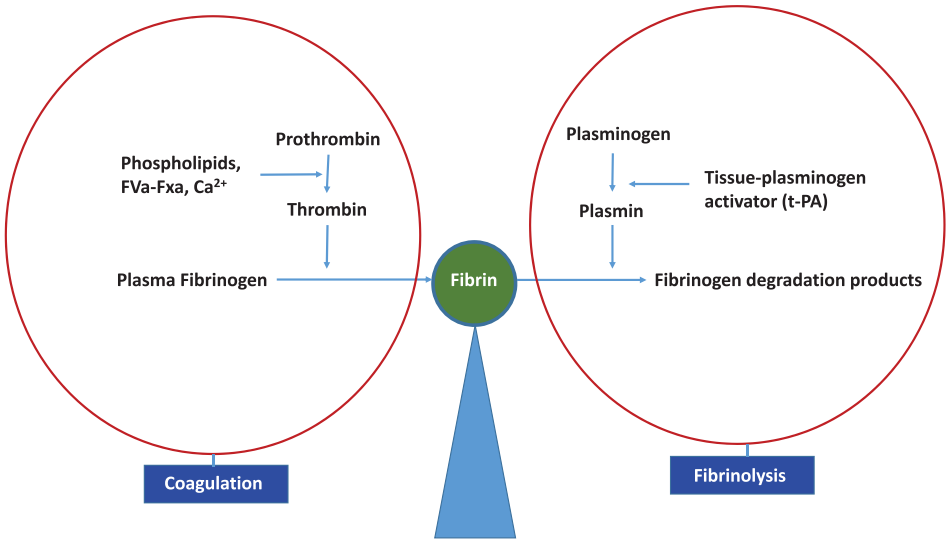


FIGURE 1 A schematic diagram shows a fine balance between fibrin clot formation (blood coagulation) and fibrinolysis (clot lysis) processes under normal physiological conditions. However, a deviation from this delicate balance due to physiological disorder causes a hemostatic disturbance, leading to thrombosis and other cardiovascular complications

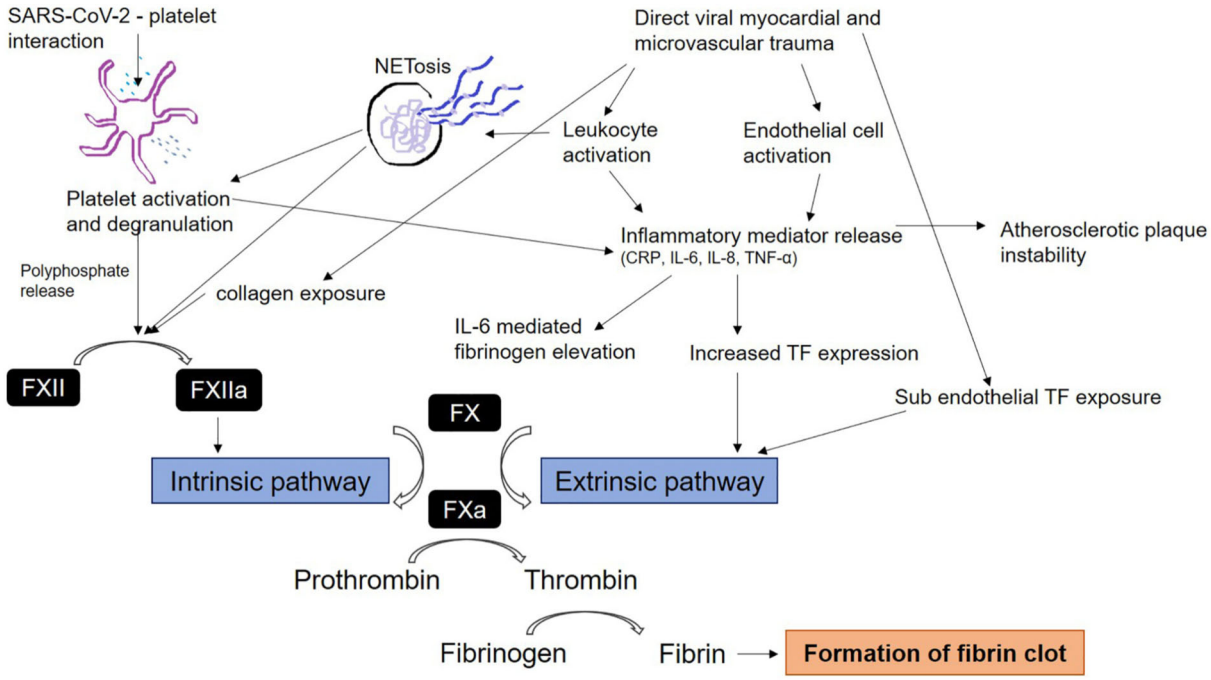


FIGURE 2 The proposed antithrombotic mechanism of SARS-CoV-2-induced coagulopathies in COVID-19. Direct SARS-CoV-2—platelet interaction results in high levels of platelet activation, promoting a pro-thrombotic state. Direct viral trauma and resultant inflammation lead to fibrinogen elevations through IL-6, leukocyte activation, NETosis, endothelial cell activation, and inflammatory mediator release. Subsequent activation of both the tissue factor and contact activation pathways of the coagulation cascade further potentiates a hyper-coagulable state, which leads to the development of thromboembolic complications in patients. CRP, C-reactive protein; FXII, coagulation factor XII; FXIIa, activated coagulation factor XII; FX, coagulation factor X; FXa, activated coagulation factor X; IL-6, interleukin 6; IL-8, interleukin 8; TNF-α, tumour necrosis factor α; TF, tissue factor. (Reprinted Figure 1 from Page & Ariëns, 2021 with permission from the publisher)

arterial and venous thrombosis in thrombotic complications (Li et al., 2020; McFadyen et al., 2020; Wijaya, Andhika, & Huang, 2020). Table 2 shows some of the modern Western drugs used to treat or prevent thrombosis in CVDs and COVID-19. The oral anticoagulants, which act at different levels in the blood coagulation cascade, have short-term and long-term goals for preventing venous thromboembolism (VTE), stroke, and systemic embolism and controlling arterial and venous thrombosis (Bielecki, Lee, & Hamad, 2018). These antithrombotic drugs are not free of adverse reactions, however, as indicated by the following issues:

1. Despite extensive research to develop potent antithrombotic cardiovascular drugs, a significant proportion of CVD-related mortality cannot be prevented (Ibrahim et al., 2018).

TABLE 2 A list of some commercial drugs used for the treatment and/or prevention of thrombosis-associated cardiovascular diseases

Category of drug	Commercial name	Mechanism of action	References
Anticoagulant (blood thinner)	Argatroban	Direct inhibitor of thrombin	Di Nisio, Middeldorp, & Büller, 2005
	Bivalirudin	-do-	Gladwell, 2002
	Dabigatran	-do-	Di Nisio et al., 2005; Sorbera, Bozzo, & Castaner, 2005
	Edoxaban	Factor Xa inhibitor without the requirement of antithrombin	Plitt & Giugliano, 2014; Stacy, Call, Hartmann, Peters, & Richter, 2016
	Fondaparinux	Selective inhibitor of FXa, does not inhibit thrombin	Dong et al., 2016
	Heparin, unfractionated (UFH)	Antithrombin and anti-Xa activity	Warkentin et al., 1995; Robertson & Strachan, 2017
	Heparin, low molecular weight (LMWH) (enoxaparin, dalteparin)	Mostly anti-Xa activity	Hirsh, 1993; Weitz, 1997
	Lepirirudin	Direct inhibitor of thrombin	Petros, 2008; Parissis, 2011
	Rivaroxaban	FXa inhibitor binds to both free and unbound FXa	Abdulsattar, Bhambri, & Nogid, 2009; Diener, Halperin, Fox, & Hankey, 2015
	Warfarin	Vitamin K antagonist	Ezekowitz et al., 1992; Rishavy et al., 2018
	Ximelagatran	Direct inhibitor of thrombin	Ho & Brighton, 2006
Antiplatelt drugs (inhibitors of platelet aggregation)	Abciximab	Inhibitor of platelet GPIIa/IIIb receptor	Mascelli & Nakada, 1999
	Aspirin	Irreversible inhibitor of ADP receptor of platelet	Vane & Botting, 2003; Parker et al., 2019
	Clopidogrel	-do-	Gurbel & Bliden, 2003
	Dypiridamole	Inhibitor of nucleoside transport and PDE3	FitzGerald, 1987
	Eptifibatide	Inhibitor of platelet GPIIa/IIIb receptor	Phillips & Scarborough, 1997
	Prasugrel (discontinued from few markets)	Platelet ADP P2Y12 receptor antagonist.	Angiolillo, Suryadevara, Capranzano, & Bass, 2008
	Ticagrelor	-do-	Capodanno, Dharmashankar, & Angiolillo, 2010
	Tirofiban	Inhibitor of platelet GPIIa/IIIb receptor	Kumar & Herrmann, 1997
Thrombolytic drugs (clot-busting)	Alteplase	Tissue plasminogen activator (tPA)	Hacke et al., 2008
	Lumbrokinase	Direct fibrinolytic enzyme	Wang, Tull, Cooper, Wang, & Liu, 2013
	Nattokinase	Fibrinolytic enzyme of bacterial origin	Sumi, Hamada, Tsushima, Mihara, & Muraki, 1987; Chen et al., 2018
	Reteplase	Recombinant non-glycosylated human tPA	Mohammadi, Seyedhosseini-Ghaheh, Mahnam, Jahanian-Najafabadi, & Mir Mohammad Sadeghi, 2019
	Streptokinase	Plasminogen activator	Young et al., 1998
	Tenecteplase	Recombinant tPA	Davydov and Cheng, 2001
	Urokinase	Directly cleaves plasminogen to produce plasmin	Blasi, Vassalli, & Danø, 1987

2. Some limiting factors (e.g., resistance or poor efficacy of the drugs in some patients, drug–food or drug–drug interactions, adverse effects including increased risk of bleeding, gastrointestinal dysfunctions, and low therapeutic index) are significant obstacles to the success of these life-saving drugs (Li et al., 2020; Schurgers, Aebert, Vermeer, Bültmann, & Janzen, 2004; Vranckx, Valgimigli, & Heidbuchel, 2018).

3. Recent clinical studies have unambiguously shown the adverse effects in patients with COVID-19 who are admitted to hospitals post-treatment with anticoagulants, and no mortality benefits of COVID-19 patients treated with therapeutic-dose anticoagulation (reviewed by Wijaya et al., 2020).
4. Interactions between antiplatelet and anticoagulant drugs can lead to serious complications in patients.
5. Thrombosis repeatedly occurs in critical conditions in COVID-19 patients irrespective of precautionary treatments with low molecular weight heparin (LMWH) (Miesbach & Makris, 2020).

Recent studies have shown that plant-derived active compounds and some natural compounds can find practical therapeutic applications in treating various complications of COVID-19 (Brendler et al., 2021; Ganguly & Bakhshi, 2020; Islam et al., 2020; Kalita, Saviola, Samuel, & Mukherjee, 2021). Consequently, as discussed below, a far-reaching drug discovery program is needed to develop superior and safe antithrombotic drugs by exploring natural resources for the hospital management of thrombotic complications in COVID-19 and other CVDs (Cordier, Cromarty, Botha, & Steenkamp, 2012; Li et al., 2020).

3 | PLANT-DERIVED NATURAL PRODUCTS AS POTENTIAL ANTITHROMBOTIC DRUGS: THE PROS AND CONS

The innovative advancements made in combinatorial chemistry and the drugs obtained from natural resources may have a tremendous impact on drug discovery, and as a result, nearly half of the commercial pharmaceuticals are from the exploration of natural resources (Cragg & Newman, 2013; Maiti, Nagori, & Singh, 2017; Newman & Cragg, 2020; Rastelli, Pellati, Pinzi, & Gamberini, 2020; Rijo & Mori, 2020). Natural resources display a significant chemical diversity in terms of the structure and function of their biomolecules, and they serve as an essential reservoir of bioactive compounds to improve medications by providing unique prototypes. Such compounds can also serve to create new configurations and structural modifications for more powerful and safer medicines (Cragg & Newman, 2013; Maiti et al., 2017; Mukherjee, Bahadur, Harwansh, Biswas, & Banerjee, 2017). Plants are currently envisaged to be the chief source of novel drugs, new compounds, and new chemical molecules (Atanasov et al., 2015; Mukherjee, 2012; Newman & Cragg, 2020). In a recent study, about 85% of the conventional herbal medicines were shown to cater to the drugs of approximately 65% and 80% of the world's populations and developing countries, respectively (Newman & Cragg, 2020).

Recent studies have focused on discovering natural products as active supplements or as replacements for ongoing synthetic antithrombotic drugs (Zhao et al., 2020). The active ingredients of natural products (e.g., extracts of traditional herbs and medicinal plants), the traditional system of medicine used in several countries (e.g., Chinese medicines), the Indian system of ancient medicine (Ayurveda), and functional foods have shown remarkable antithrombotic properties in vitro and in pre-clinical studies (Cordier et al., 2012; Gogoi, Ramani, Bhartari, Chattopadhyay, & Mukherjee, 2019; Li, Liang, & Sun, 2019; Memariani, Moeini, Hamedi, Gorji, & Mozaffarpur, 2018; O'Kennedy, Raederstorff, & Duttaroy, 2017; Sen & Chakraborty, 2017; Yamamoto et al., 2018). The significant advantages of using plant-derived natural products for therapeutic treatment have been realized because several of these compounds (as crude extracts or as partially purified plant extracts) are comprised of multiple components. Each component may target different factors in the coagulation cascade and their synergistic interactions may enhance their therapeutic efficacies (Gogoi et al., 2018,b, 2020). Moreover, numerous intriguing properties of natural products (e.g., rapid absorption when ingested by the oral route, marginal side-effect(s) in the gastrointestinal tract, and their non-immunogenicity) suggest their strong efficacy and safety (Fuentes & Palomo, 2014).

Before herbal antithrombotic drugs can be widely accepted and commercialized, a number of key issues must be addressed (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016; Sahoo & Manchikanti, 2013; Sen & Chakraborty, 2017; Zhang, Wider, Shang, Li, & Ernst, 2012; Zhao et al., 2020):

1. The manufacturing of authenticated herbal drugs to treat CVDs is minimal. Presently, the handful of traditional herbal medicines that are targeted toward CVDs are considered as health supplements, and few therapeutic agents are approved for use by mainstream clinicians since in-depth knowledge about their indications are lacking, and little is known about their molecular mechanisms of coagulation, thrombus formation, or clot-busting activity. Moreover, few pre-clinical studies have been conducted on herbal drugs or their purified components, to determine their fundamental properties, safety, therapeutic index, and possible therapeutic levels.
2. The effective doses of cardiovascular herbal medicines, including antithrombotic herbal drugs, still need to be evaluated according to the patient's body mass index, age, and other possible complications. The results of such studies would also need to be standardized.
3. Because the therapeutic efficacies of herbal medicines have not yet been compared to commercially prepared drugs, allopathic practitioners are reluctant and lack the confidence to prescribe such drugs. A gap in knowledge also exists with regards to the potential benefits and risks associated with herbal drugs (Izzo et al., 2016) and mainstream clinicians are often unaware of cardiovascular herbal medicines, which hinders their large-scale commercialization (Clement et al., 2005).
4. The use of chemical markers for quality control of cardiovascular herbal medicines and the authentication of raw materials has been neglected, resulting in batch-to-batch variations in their quality and production (Sahoo & Manchikanti, 2013), and both physicians and patients are less confident about the quality of herbal medicines.
5. The regulations for commercializing herbal drugs are country-specific. For example, the Ayurveda, Yoga, Unani, Siddha, and

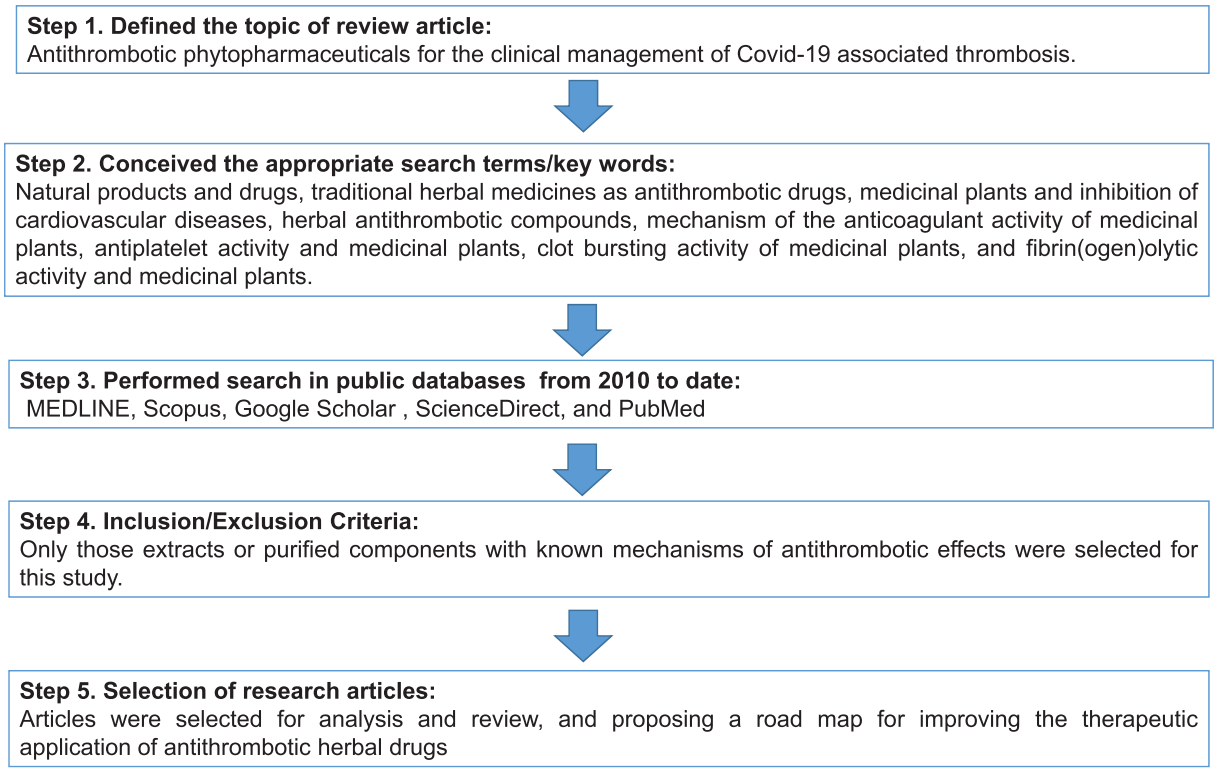


FIGURE 3 A schematic diagram showing the search process and the databases used for the systematic review of antithrombotic herbal drugs

Homeopathic (AYUSH) drugs are considered safe in India, and according to the Drugs and Cosmetics Act of 1940, herbal drugs that are manufactured according to AYUSH protocols do not require marketing approval in India. In the United States and Canada, however, AYUSH/herbal drugs are not considered mainstream medicines because they do not disclose the necessary information. Such drugs are only poorly marketed in European Union countries (Sahoo & Manchikanti, 2013; Sen & Chakraborty, 2017), often sold as dietary supplements or natural health/beauty products. Usually, herbal drugs can be purchased without a prescription from a registered medical practitioner, which limits their potential for commercialization (Sahoo & Manchikanti, 2013; Sen & Chakraborty, 2017).

6. Concerns have been raised about possible interactions between herbal antithrombotic and mainstream cardiovascular drugs, and bleeding complications may occur. Currently, little information is available on such drug–drug interactions, raising serious concerns among clinicians, which is adding to their reluctance to prescribe herbal medicines (Izzo et al., 2016; Tsai, Lin, Lu, Chen, & Mahady, 2013; Zuo et al., 2020).
7. Antithrombotic herbal compounds may modulate a patient's gut microbiota and influence a number of physiological functions. Some natural antithrombotic compounds may be harmful to the gut microbiota, or even more readily absorbed in the gut (Vamanu & Gatea, 2020), but again, little is known about such interactions.
8. The successful commercialization of green medicines is hindered by the lack of modern analytical approaches for their research and collaborations among researchers, governmental and non-governmental organizations (NGOs), and pharmaceutical companies that are needed.
9. The lack of planning and potential overexploitation of medicinal plants for drug manufacturing could result in habitat loss and habitat destruction, or even a rapid extinction of such medicinal plants and herbs.

These issues serve as a backdrop for the critical appraisal of antithrombotic, antiplatelet, and blood clot lysis herbal drugs or their active components and their potential use as potent cardiovascular drugs. The literature review explores various herbal drugs from searches on public databases (i.e., MEDLINE and Scopus) dealing with the antithrombotic effects of plant extracts or their components since 2010. In this review, only extracts or purified components with known mechanisms of antithrombotic effects were considered. Keywords used in the search included "natural products and drugs," "traditional herbal medicines as antithrombotic drugs," "medicinal plants and inhibition of CVDs," "herbal antithrombotic compounds," "mechanism of the anticoagulant activity of medicinal plants," "antiplatelet activity and medicinal plant," "clot busting activity of medicinal plants," and "fibrin(ogen)olytic activity and medicinal plants". Searches were also conducted on Google Scholar (https://scholar.google.com/), ScienceDirect (https://www.sciencedirect.com/), and PubMed (pubmed.ncbi.nlm.nih.gov) (see Figure 3). While considering the large

hindrances to the commercialization and globalization of herbal medicines, we also propose a roadmap for improving the applications of herbal drugs as alternatives to synthetic anticoagulant and antithrombotic drugs.

4 | EXPLORING ANTITHROMBOTIC MECHANISM(S) OF MEDICINAL PLANTS AND THEIR ACTIVE CONSTITUENTS FOR POSSIBLE PROPHYLACTIC AND THERAPEUTIC APPLICATIONS

The standard protocol for determining anticoagulant activity involves preparing aqueous or organic solvent extracts of various aerial or subaerial parts of a medicinal plant, which are chosen/selected according to their mention in folklore or in traditional medicine. Plant extracts are assessed in vitro or in vivo for their anticoagulant activity (inhibition of plasma clotting activity), inhibition of activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), antiplatelet activity, and clot-busting properties (Gogoi et al., 2018, b, 2019). The combination of multidimensional chromatographic techniques may further fractionate crude extracts to show the promising antithrombotic activity of isolated antithrombotic components or purified active substances. The antithrombotic effects of crude extracts or their bioactive constituents from 2010 to the present are shown in Table 3. The anticoagulant and antiplatelet mechanism(s) of crude/partially purified extracts and their bioactive constituents are described below (and shown in Figure 4a,b). In most instances, researchers have not compared the activities of plant extracts or the purified active components to the antithrombotic drugs that are widely prescribed by clinicians. Moreover, the dose-dependent efficacies of several plant extracts/active compounds have not been determined, so this pre-requisite data are still needed before further preclinical or clinical studies can be conducted. The lack of such studies is a significant impediment to the successful clinical application of antithrombotic phytopharmaceuticals. The following sections describe the antithrombotic mechanisms of these phytopharmaceuticals.

4.1 | Anticoagulant activity by inhibiting the key coagulation factors of blood

The antithrombotic activity of many plant extracts and purified active compounds has been shown by the inhibition of activated APTT, PT, and TT (Table 3). In vitro studies have also shown that several plant extracts or purified non-enzymatic bioactive compounds exert anticoagulant activity by inhibiting critical components in the blood coagulation cascade (i.e., thrombin, FXa, and/or TF/FVIIa). Among the isolated herbal compounds, an intense inhibitory effect has been shown against human thrombin by natural flavonoids, including myricetin (Liu et al., 2010) and quercetin (Bijak et al., 2014), kaempferol, isorhamnetin, kaempferol-3-o-(2″,4″-di-E-pcoumaroyl)-rhamnoside, and kaempferol-3-o-(2″-di-E-pcoumaroyl)-rhamnoside; baicalein, luteolin, apigenin, and acacetin (Liu et al., 2010); biflavones like hinokiflavone (Liu et al., 2010); lactones like senkyunolide I (Zhang et al., 2017); catechin-like epicatechin gallate and epigallocatechin gallate (Li et al., 2018; Li et al., 2018); tanshinones like 15, 16-dihydrotanshinone and tanshinone IIA (Lu et al., 2015); and plant-derived β-sitosterol (Gogoi, Pal, et al., 2018) (Figure 5i-xvi).

The analysis of structure–activity relationships (SARs) has revealed the crucial role played by the hydroxyl group at C-3 in these flavonoid compounds for their thrombin-inhibiting activity, which can be improved by increasing the number of OH groups in the B-ring of the flavonoids (Liu et al., 2010). Generally, the mechanism of thrombin inhibition by plant compounds is achieved by direct inhibition of the catalytic site of thrombin via hydrogen bonding or indirect inhibition by binding to exosite-I (binds to fibrinogen and fibrin) and/or anion-binding exosite-II (binds to heparin) of the thrombin, which leads to a competitive, uncompetitive, and mixed-mode of thrombin inhibition, respectively (Kolodziejczyk-Czepas et al., 2017; Yu et al., 2019). For clinical applications, these mechanisms of thrombin inhibition are effective in preventing pathological thrombus formation (Dahlbäck, 2000; Sivaraja et al., 2018), and therefore, the data suggest the possibility of developing antithrombotic herbal drugs based on their known composition and mechanisms of action.

Some of the crude extracts/active components also demonstrated dual inhibition of thrombin and/or FXa, in either in vitro or in vivo (pre-clinical) conditions, albeit the examples of such dual inhibitors of the major coagulation proteins are few (Al-Awwadi, 2010; Pawlaczyk et al., 2011). A lone example of a fibrinogenolytic serine protease (lunathrombase) showed anticoagulant activity via dual inhibition of thrombin and FXa (Gogoi, Arora, et al., 2018). Such dual inhibitors may be in great demand by the pharmaceutical industry for preparing herbal antithrombotic drugs (Gogoi, Arora, et al., 2018). Some of the herbal compounds tested under in vitro conditions demonstrated low anticoagulant potency compared to the commercial synthetic direct inhibitors of thrombin (i.e., dabigatran and bivalirudin); however, the preclinical studies suggest that these compounds are safe to administer (Gogoi, Arora et al., 2018,b, 2020). In some instances, the purified active compounds demonstrated less anticoagulant potency than the crude or partially purified plant extract, which suggests that the active components act synergistically to enhance their antithrombotic activity (Gogoi et al., 2019). Clinical studies are still needed to evaluate the therapeutic efficacies of these herbal compounds.

4.2 | Anticoagulant activity by plasma defibrinogenation

Under normal physiological conditions, the fibrinogen level in adult human plasma is within the range of 200–400 mg/dL. An elevated plasma concentration of fibrinogen, a pathological condition known as hyperfibrinogenemia, is associated with the enhanced risk of thrombosis and other CVDs and the condition has significant implications in thrombolytic therapy (Machlus, Cardenas, Church, & Wolberg, 2011).

TABLE 3 List of some medicinal plants and their components acting on coagulation factors and pathways of blood coagulation

Plants species	Type of crude extract/active compound	Type of study	Antithrombotic mechanism	References
Inhibition study with crude/partially purified plant extracts				
Abies webbiana	Aqueous-ethanol (80%) extract of plant	In vitro	Inhibited the ADP and epinephrine-induced aggregation of human platelets, thus showing antiplatelet activity.	Yasin, Hussain Janbaz, Imran, Gilani, & Bashir, 2014
Achillea santolina	Aqueous leave extract and organic solvent fractions	In vitro and in vivo	Dose-dependent in vitro inhibition of ADP and collagen-induced platelet aggregation; however, unclear in vivo effects in rats.	Al-Awwadi, 2010
Allium sativum	15–20% ethanol extract of aged garlic	In vitro	Inhibited binding of fibrinogen to GP IIb/IIIa and increased the level of cAMP.	Allison, Lowe, & Rahman, 2012
Artocarpusheterophyllus	Aqueous seed extract	In vitro	Prolonged APTT but not PT.	Gangaraju et al., 2015
Averrhoa bilimbi	Aqueous soluble fraction (AQSF) obtained from the methanol extract of plant	In vitro	Clot-busting activity.	Ramjan, Hossain, Runa, Md, & Mahmodul, 2014
Browneagrandiceps	Aqueous flower extract	In vitro	Prolonged PT, APTT, TT and inhibited FXa at high concentrations to show anticoagulant activity.	Pereira & Brazón, 2015
Bulnesia sarmienti	Aqueous extract	In vitro and in vivo	Antiplatelet activity via inhibiting granule secretion, aggregation, and thrombus formation without altering the bleeding time in mice. Inhibition of P38, JNK1, and ERK2 phosphorylation.	Kamruzzaman et al., 2010
Cassia petersiana Belle	Aqueous and methanolic extracts	In vitro	Prolonged PT.	Cordier et al., 2012
Clerodendrum viscosum	Carbon tetrachloride soluble fraction (CTSF), obtained from the methanol extract of plant	In vitro	Clot-busting activity.	Ramjan et al., 2014
Couropita Guianensis	Aqueous and chloroform extracts of leaves	In vitro	Anticoagulation of platelet-poor plasma (mechanism unknown).	Patro, Sarangi, & Mekap, 2020
Crassocephalum crepidioides	Methanol extraction of leaves and subsequent hexane fraction	In vitro	Increased the blood clotting time, prothrombin, and activated partial thromboplastin times.	Ayodele, Onajobi, & Osoniyi, 2019
Drynaria quercifolia	Pet-ether soluble fraction (PESF), obtained from the methanol extract of plant	In vitro	Clot-busting activity.	Ramjan et al., 2014
Glycyrrhiza glabra	Butanol, ethyl acetate, methylene chloride, and petroleum ether fractions of whole plant	In vitro	Anticoagulant activity by Fxa inhibition (IC_{50} value of 0.363 mg/mL).	Ibrahim, Mahrous, Fathy, Omar, & EL-Khair RMA., 2020
Hirudinaria manillensis	Saline extract	In vivo	Prolonged APTT, PT, and TT.	Guan et al., 2012
Humulus lupulus L.	Supercritical CO_2 extraction of plant	In vitro	Enhanced the anticoagulant activity of human endothelial cells and demonstrated potent antiplatelet activity.	Luzak et al., 2016
Licania rigida Benth	Crude aqueous extract and ethyl acetate fraction of leaves	In vitro	The crude extracts prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) at a dose of 50 μg/mL. The ethyl acetate fraction inhibits blood coagulation by antithrombin activity (extrinsic coagulation pathway).	Da Luz et al., 2021

(Continues)

TABLE 3 (Continued)

Plants species	Type of crude extract/active compound	Type of study	Antithrombotic mechanism	References
Marsypianthes chamaedrys	Aqueous extract of aerial parts	In vitro	Anticoagulant activity by increasing activated partial thromboplastin time.	Coelho et al., 2020
Momordica charantia	Active anticoagulant fraction	In vitro and in vivo	Fibrinogenolyic activity, inhibition of the collagen/ADP-induced aggregation of mammalian platelet, thrombolytic activity and inhibited the k-carrageen-induced thrombus formation in the tails of mice.	Gogoi et al., 2020
Olea europaea	Butanol, ethyl acetate, methylene chloride, and petroleum ether fractions of whole plant	In vitro	Anticoagulant activity by FXa inhibition (IC_{50} value of 0.866 mg/mL).	Ibrahim et al., 2020
Phellinus baummii	Methanol extract	In vitro	Exerts antiplatelet activity by inhibiting collagen-induced platelet aggregation, mediated by increasing the CAMP level and suppressing ERK2 and JNK1 phosphorylation.	Kamruzzaman et al., 2011
Punica granatum L.	Fresh juice	In vitro and in vivo	Exerts antithrombotic activity by decreasing platelet aggregation, calcium mobilization, thromboxane A2 synthesis, hydrogen peroxide synthesis.	Riaz & Khan, 2016
Spatholobus suberectus	95% ethanol extract	In vitro and in vivo	Blocks fibrinogen binding to the GP IIb/IIIa, suppression of TXA2formation.	Lee et al., 2011
Syzygium malaccense	Hydroalcoholic extract of leaves	In vitro	Thrombolytic (clot-busting) activity.	Patel, Desai, Desai, Dave, & Meshram, 2019
Trifolium alexandrinum	Butanol, ethyl acetate, methylene chloride, and petroleum ether fractions of whole plant	In vitro	Anticoagulant activity by FXa inhibition (IC_{50} value of 0.729 mg/mL).	Ibrahim et al., 2020
Inhibition study with purified active compounds				
Agrocybe aegerita (fruiting bodies)	ACase (a heterodimer fibrinolytic serine protease of molecular mass 31.4 and 21.2 kDa, of subunit I and subunit II, respectively)	In vitro	Exerts anticoagulant activity by possessing plasmin-like, plasminogen activating, and thrombin inhibiting activities.	Li, Liu, Cong, Deng, & Zheng, 2021
Artocarpus heterophyllus	AMP48 (48 kDa serine protease)	In vitro	Hydrolysis of Aα followed by partial hydrolysis of β and γ subunits of human fibrinogen.	Siritapetawee, Thumanu, Sojikul, & Thammasirirak, 2012
Aster yomena	Kitamase (50 kDa fibrinogenolytic enzyme)	In vitro and in vivo	Hydrolysis of Aαfollowed by γ subunits of fibrinogen, prolongation of APTT and PT.	Choi et al., 2014
Calamus quiqeusetinervius Burret	Quiquelignan B, C, D, F, and H	In vitro	Decreases collagen-induced platelet aggregation.	Chang et al., 2010
Canna edulis Ker Gawl	(Z,E)-[2-(3,4-dihydroxyphenyl) ethenyl] 3-(3,4-dihydroxyphenyl)-2-propenoat (nepetoidin B)	In vitro	Inhibition of ADP, and collagen-induced platelet aggregation.	Nguyen et al., 2020
	4,5-dihydroxy-6-methyl-2H-pyran-2-one (epimedokoreanone A)		Anticoagulant activity (unknown mechanism).	

TABLE 3 (Continued)

Plants species	Type of crude extract/active compound	Type of study	Antithrombotic mechanism	References
Carthamus tinctorius	Dilinoleic acid, safflower yellow, compatibility preparation	In vivo	Prolonged APTT, TT, CT, and BT.	Guo, Yang, & Wang, 2012
Cinnamomum cassia	Eugenol and coniferaldehyde	In vitro	Antiplatelet activity is exerted via inhibition of arachidonic acid, U46619, and epinephrine-induced platelet aggregation.	Kim et al., 2010
Clerodendrum colebrookianum	Clerofibrase (serine protease), 30 kDa	In vitro and in vivo	Anticoagulant activity, fibrinogenolytic activity, and inhibited platelet aggregation. In in vivo showed dose-dependent plasma defibrinogenating, anticoagulant, and inhibition of k-carrageen-induced thrombus formation in the tails of mice.	Gogoi et al., 2019
Codium fragile	Codiase (48.9 kDa bi-functional fibrinolytic serine protease)	In vitro and in vivo	Fibrinolytic activity (in vitro) and enhanced the activated partial thromboplastin time (APTT) and prothrombin time (PT). In in vivo conditions, it reduces thrombosis in a dose-dependent manner.	Choi, Sapkota, Park, Kim, & Kim, 2013
Codium vermilara	Sulphated (1 → 3)- -L- arabinan	In vitro	Prolonged APTT, PT, and TT to show antithrombotic activity.	Fernández et al., 2013
Cordyceps militaris	Cordycepin-enriched (CE)-WIB801C, a n-butanol extract of hypha	In vitro	Dose-dependent inhibition of collagen- and ADP-induced platelet aggregation and inhibition of binding of fibrinogen to glycoprotein IIb/IIIa of platelets required to induce platelet aggregation.	Lee, Kim, Lim, Kim, & Park, 2015; Lee et al., 2015
Crinum asiaticum	Crinumin (67 kDa serine protease)	In vitro	Plasmin-like fibrinolytic activity, and inhibits thrombin-induced platelet aggregation.	Singh, Nayak, Jagannadham, & Dash, 2011
Croton zambesicus	Diterpenes	In vitro	Decreases thrombin activity.	Robert, Baccelli, Devel, Dogné, & Quetin-Leclercq., 2010
Curcuma aromatic	CAP-II (12.4 kDa serine protease)	In vitro	Hydrolyses Aα followed by Bß and γ subunits of fibrinogen to exert anticoagulant activity.	Shivalingu, Vivek, Priya, Soujanya, & Swamy, 2016
Erigeron canadensis L	Polyphenolic-polysaccharides (polysaccharide part is represented by hexuronic acids and the polysaccharide part is rich inhydroxylic rests as well as in carboxylic groups)	In vitro	Demonstrates anticoagulant activity by inhibition of thrombin and FXa, and antiplatelet activity.	Pawlaczyk et al., 2011
Euphorbia hirta	Hirtin (serine protease), 34 kDa	In vitro	Hydrolyses Aα, followed by Bβ and γ−γ subunits of fibrinogen and fibrin clot.	Patel, Kawale, & Sharma, 2012
Euphorbia lacteal	Eup-82 (34.7 kDa serine protease),	In vitro	Hydrolyses all subunits of human fibrinogen to show anticoagulant activity.	Siritapetawee, Sojikul, & Klaynongsruang, 2015
Euphorbia milii	Eumiliin (30 kDa serine protease),	In vitro and in vivo	Hydrolyses Aα followed by Bβ subunits of the human fibrinogen to exert anticoagulant activity.	Fonseca et al., 2010

(Continues)

TABLE 3 (Continued)

Plants species	Type of crude extract/active compound	Type of study	Antithrombotic mechanism	References
Goniothalamus sp. (*Goniothalamus velutinus* Airy-Shaw, *Goniothalamus* woodii Merr., *Goniothalamus clemensii* Ban, *Goniothalamus tapis* Miq. and *Goniothalamus tapisoides* Mat Salleh)	Essential oils from bark and root containing a high amount of sesquiterpenes and sesquiterpenoids	In vitro	The bark oil of *G. velutinus* inhibited both arachidonic acid (AA), and ADP-induced platelet aggregation. The bark oils of *G. clemensii*, *G. woodii*, *G. velutinus*, and the root oil of *G. tapis* showed intense PAF antagonistic activity.	Moharam, Jantan, Ahmad, & Jalil, 2010
Leucas indica	Lunathrombase (35 kDa serine protease),	In vitro and in vivo	Hydrolyzes Aα, followed by Bβ and γ subunits of fibrinogen inhibit platelet aggregation.	Gogoi, Arora, et al., 2018
Leucas indica	β-sitosterol	In vitro and in vivo	Antithrombin activity inhibits thrombin-catalyzed platelet aggregation.	Gogoi, Pal, et al., 2018
Licania pittieri	Pomolic acid (triterpenoid)	In vitro	Decreases ADP and epinephrine-induced platelet aggregation to exert antithrombotic activity.	Alvarado-Castillo, Estrada, & Carvajal, 2012
Lindera obtusiloba L.	Secolincomolide A	In vitro and in vivo	Inhibits collagen and Cox-1 (AA pathway)-mediated platelet aggregation.	Jung et al., 2017; Kim et al., 2016; Lee, Kim, Lee, & Oak, 2010
Marsypianthes chamaedrys	Pectic polysaccharides and type II arabinogalactans (homogalacturonan, type I rhamnogalacturonan, type II arabinogalactan, and α-glucan)	In vitro	Anticoagulant activity by increasing activated partial thromboplastin time.	Coelho et al., 2020
Natural bicyclic terpene derivative found in many plants	Borneol	In vivo	Prolongs PT and TT for exerting anticoagulant activity and inhibits venous thrombosis.	Ku, Yoo, Zhou, Na, & Bae, 2014
Petasites japonicas	40 kDa Chymotrypsin like serine protease	In vitro and in vivo	Hydrolyzes Aα, Bβ, and γ−γ subunits of the human fibrinogen, and prolongs APTT but has little effect on PT to influence the anticoagulant activity.	Kim et al., 2015
Petroselinum crispum L.	Polyphenols	In vitro and in vivo	Decreases platelet aggregation, increased tail bleeding time.	Agyare, Appiah, Boakye, & Apenteng, 2017; Ed Nignpense, Chinkwo, Blanchard, & Santhakumar, 2019
Polygonum-multiflorum	2,3,5,4 -Tetrahydroxystilbene-2-O-D-glucoside(TGHS)	In vitro	Inhibitscollagen-induced platelet aggregation, and inhibition of platelet Fc RIIa, Akt (Ser473), and GSK3 (Ser9) phosphorylation.	Xiang et al., 2014
Rabdosia japonica (Burm. f.) var. glaucocalyx (Maxim.) Hara	Glaucocalyxin A (GLA)	In vitro and in vivo	Inhibits collagen-induced platelet aggregation, tyrosine phosphorylation of Syk, LAT, phospholipase C2, and P-selectin secretion.	Li et al., 2013
Rhus verniciflua Stokes	Fisetin, butein, and sulphuretin	In vitro and in vivo	Inhibits collagen, thrombin, and adenosine-5′-diphosphate-mediated platelet aggregation.	Lee et al., 2015
Rhododendron brachycarpam	Hyperoside	In vitro and in vivo	Prolongs APTT and PT of platelet-poor plasma Inhibits thrombin- and collagen-induced platelet aggregation in vitro, and adenosine diphosphate-induced platelet aggregation in vivo.	Ku et al., 2014

TABLE 3 (Continued)

Plants species	Type of crude extract/active compound	Type of study	Antithrombotic mechanism	References
Salvia miltiorrhiza	Salvianolic acid B	In vitro	Shows antiplatelet activity by binding to ADP (P2Y12) receptor.	Liu et al., 2014
	Tanshinone IIA	In vitro and in vivo	Inhibits ADP-induced platelet aggregation.	Maione et al., 2014
Sanguisorba officinalis L.	Polyphenol-polysaccharide conjugates	In vitro	Antithrombin activity.	Pawlaczyk-Graja et al., 2016
Scutellaria baicalensis Georgi	Wogonin (WGN) and wogonoside (WGNS) flavonoids	In vitro	Prolongs APTT and PT and inhibition of thrombin.	Ku & Bae, 2014
Solanum tuberosum	StSBTc-3 (Subtilisin type serine protease), 72 kDa	In vitro	Hydrolyzes Bβ followed by Aα and γ subunits of fibrinogen inhibits platelet aggregation.	Pepe et al., 2016
Taxus cuspidata Siebold & Zucc.	Taxenes (taxinine, taxanine A, B, 2-deacetoxytaxinine, taxacin, taxchinin B, and taxol)	In vitro	Inhibition of platelet activation induced by arachidonic acid.	Kim & Yun-Choi, 2010
Umbilicaria esculenta	UEP (polysaccharide compound)	In vitro and in vivo	Prolongs APTT, PT, and TT of platelet-poor plasma. Decreases ADP-activated platelet aggregation; however, it does not affect coagulation times and fibrinolytic activity.	Wang et al., 2014
Urtica dioica L.	Flavonoids	In vitro	Decreases platelet aggregation by inhibiting glycoprotein IIb/IIIa receptor.	El Haouari & Rosado, 2019
Zingiber officinale Roscoe	[6]-gingerol and [6]-shogaol	In vitro	Inhibition of arachidonic acid medicated activation of platelets.	Liao, Leu, Chan, Kuo, & Wu, 2012

Abbreviations: AA, Arachidonic acid; APTT, activated partial thromboplastin time; BT, bleeding time; CT, coagulative time; PT, prothrombin time; RT, re-calcification time; TT, thrombin time.

Hyperfibrinogenemia also induces the proliferation of lipids in the blood vessel wall, which can lead to atherosclerosis and ischemic pathologies (Singh, Mengi, Xu, Arneja, & Dhalla, 2002). Therefore, reducing the elevated fibrinogen level in plasma is essential for regulating the clinical progression to thrombus formation.

A class of enzymes (proteases) can degrade fibrin, fibrinogen, and/or fibrin and fibrinogen, and are designated as fibrinolytic, fibrinogenolytic, and fibrin(ogen)olytic enzymes, respectively. The plant-derived fibrin(ogeno)lytic enzymes also demonstrate defibrinogenation activity (lowering the fibrinogen content of blood plasma) (Table 3). The fibrin(ogen)olytic enzymes that have an affinity and can subsequently catalyze α- and β-chains of fibrin/fibrinogen are classified as α and/or β fibrinogenases. Some fibrinogenases, purified from medicinal plants, demonstrate preferential hydrolysis of the Aα-subunit of fibrinogen (Choi et al., 2013, 2014; Kim et al., 2013), and purified αβ-fibrinogenase from plants has also been reported (Gogoi et al., 2020; Gogoi, Arora, et al., 2018). Besides having fibrin(ogeno)lytic activity, some of these enzymes in vitro have shown the twin inhibition of thrombin and FXa, antiplatelet activity, and the inhibition of in vivo thrombus formation in the mouse tail. They did not show any adverse effects in mice, indicating their safety and therapeutic efficacy (Gogoi et al., 2020; Gogoi, Arora, et al., 2018). Further preclinical and clinical studies are necessary to demonstrate their therapeutic potency.

4.3 | Antiplatelet activity inhibiting blood coagulation

Platelet activation is one of the most critical events in initiating the coagulation cascade and maintaining cellular hemostasis (Tomaiuolo, Brass, & Stalker, 2017). Likewise, inhibiting platelet aggregation by crude extracts or active constituents of plants is a crucial mechanism to delay the onset of blood coagulation (Figure 4b). In vitro antiplatelet activity has been shown for several herbal extracts and purified herbal compounds (e.g., hydroxycinnamaldehyde, methoxycinnamaldehyde, coniferaldehyde, eugenol, amygdalactone, and cinnamic alcohol (Figure 6i-vii) by inhibiting a specific ligand (collagen, ADP, ATP, or arachidonic acid) in platelet aggregation (Table 3, Figure 4b). For example, oligoporin A (Figure 6vii) (molecular weight

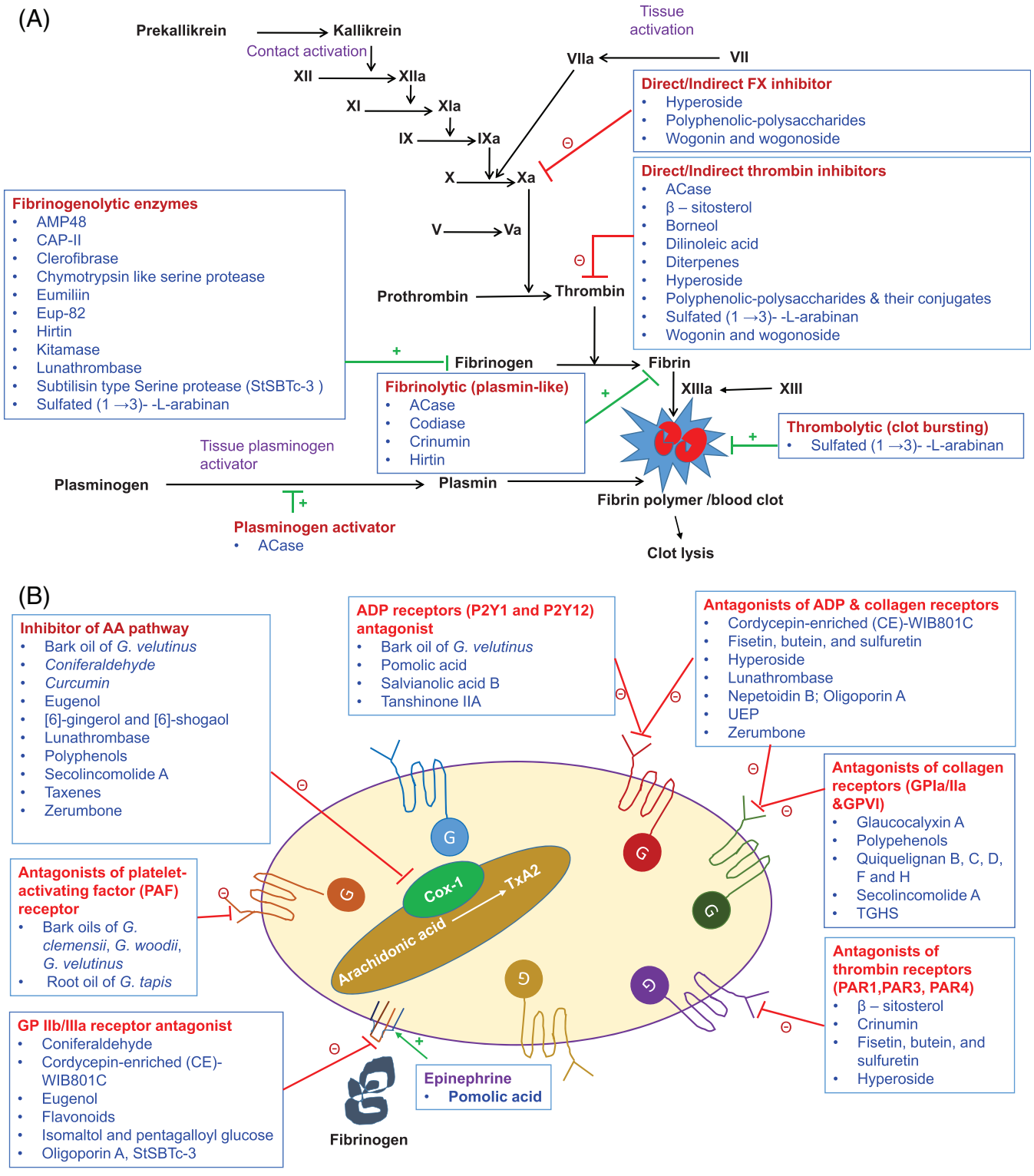


FIGURE 4 Mechanism of antithrombotic activity of purified bioactive components from medicinal plants. (a). Antithrombotic activity mechanism of phytopharmaceuticals by inhibiting key coagulation factors (factor Xa and thrombin), fibrin(ogen)olytic activity, and thrombolytic (plasmin-like) activity. (b). Mechanism of antiplatelet activity of some phytopharmaceuticals by inhibiting the different receptors requires inducing platelet aggregation to initiate blood coagulation

630.8 g/mol) extracted from an edible mushroom (*Oligoporus tephroleucus*) demonstrated preferential inhibition of collagen-induced aggregation of mammalian platelets in a dose-dependent manner, though it did not inhibit thrombin and the ADP-induced platelet aggregation (Park et al., 2012). A detailed investigation of the mechanism of antiplatelet activity showed that oligoporin A caused a

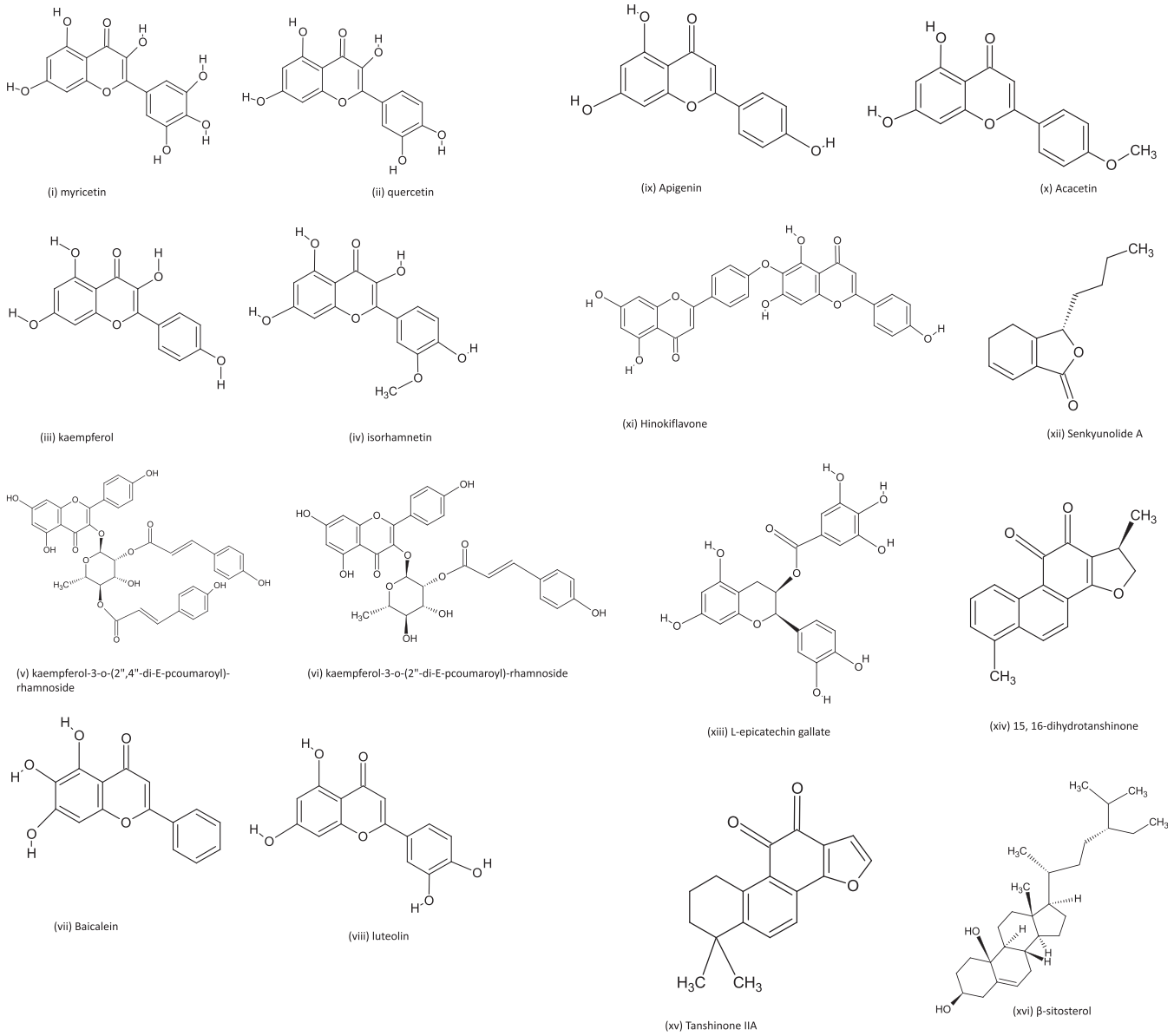
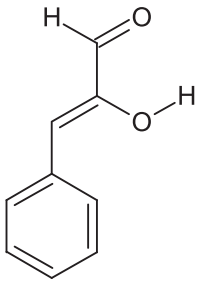


FIGURE 5 Chemical structure of the antithrombotic herbal compounds. The figures were drawn using ChemSketch software. (i) myricetin, (ii) quercetin, (iii) kaempferol, (iv) isorhamnetin, (v) kaempferol-3-o-(2″,4″-di-E-pcoumaroyl)-rhamnoside, (vi) kaempferol-3-o-(2″-di-E-pcoumaroyl)-rhamnoside, (vii) baicalein, (viii) luteolin, (ix) apigenin, (x) acacetin, (xi) hinokiflavone, (xii) senkyunolide A, (xiii) L-epicatechin gallate, (xiv) 15, 16-dihydrotanshinone, (xv) tanshinone IIA, and (xvi) β-sitosterol

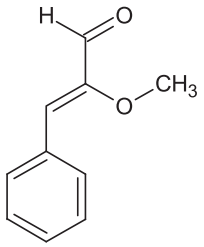
dynamic increase in intracellular levels of both cAMP and cGMP in platelets and significantly repressed the collagen-induced ERK2 phosphorylation while diminishing the binding of fibrinogen to its cognate receptor, integrin IIb/IIIa to exert its antiplatelet activity (Figure 7) (Park et al., 2012). Thus, various mechanisms are involved in oligoporin A's antiplatelet activity.

In another study, antiplatelet activity of a methanol extract of *Phellinus baummii* (an edible mushroom used as folk medicine to fight various diseases) dose-dependently inhibited collagen, thrombin, and ADP-induced platelet aggregation with an IC_{50} ranging from 51.0 to 54.0 μg/ml (Kamruzzaman et al., 2011). The authors suggested that the extract could be acting as an herbal antiplatelet agent by activating cyclic AMP and concomitantly inhibiting ERK2 and JNK1 phosphorylations. In any case, further research is necessary to identify and isolate the active compounds, and preclinical and clinical studies would be needed to determine the safety, efficacy, pharmacokinetics, and pharmacodynamical properties to move the compounds from the bench to the bedside.

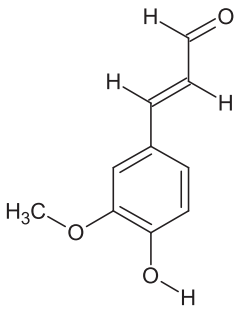
The inhibition of thromboxane A2 (TXA2)-mediated platelet activation and vasoconstriction via the arachidonic acid (AA) pathway is another important mechanism to exert antiplatelet activity (Wang et al., 2021). Drugs like aspirin and ozagrel can inhibit TXA2-producing enzymes like cyclooxygenase (COX-1) and thromboxane synthase (TXAS), respectively, and they have been used



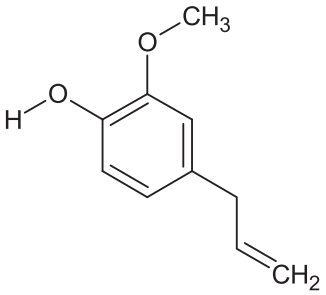
(i) Hydroxycinnamaldehyde



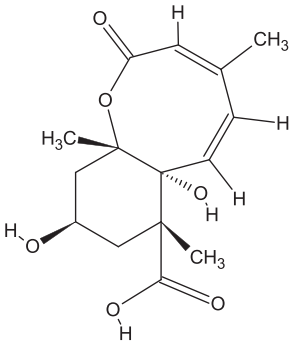
(ii) Methoxycinnamaldehyde



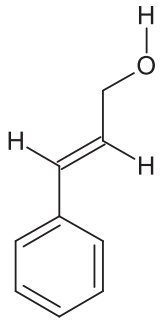
(iii) Coniferaldehyde



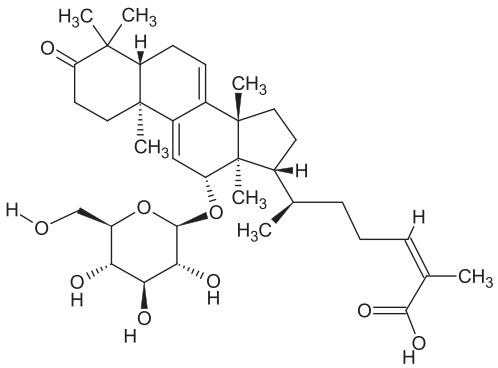
(iv) Eugenol



(v) Amygdalactone



(vi) Cinnamic alcohol



(vii) Oligoporin A

FIGURE 6 Chemical structure of antithrombotic herbal compounds showing antiplatelet activity. The figures were drawn using ChemSketch software. (i) hydroxycinnamaldehyde, (ii) methoxycinnamaldehyde, (iii) coniferaldehyde, (iv) eugenol, (v) amygdalactone, (vi) cinnamic alcohol, and (vii) oligoporin A

commercially as antiplatelet agents for decades, even with their limitations (Fitzpatrick et al., 1986). The ratio of TXB2 and 6-keto-PGF1 to the stable metabolites of TXA2 and prostaglandin I2 (PGI2), respectively, also regulates thrombus formation. The higher the ratio of TXA2/PGI2, the more thrombus formation, and the lower the ratio of TXA2/PGI2, the less platelet aggregation and thrombus formation, with a greater risk of bleeding (Rucker & Dhamoon, 2021).

In an in vitro study by Chang et al. (2013), an ethyl acetate extract of *Caesalpinia sappan* L. inhibited human platelet activation by maintaining a balance between TXA2 and PGI2 levels. Further, the inhibition of metabolic enzymes like COX-1, COX-2, TXAS, and LOX in the AA pathway by plant extracts leads to the suppression of TXB2, PGD2, and 12-HETE production and the eventual inhibition of platelet aggregation (Li, Yu, & Fan, 2014; Yu et al., 2012; Zuo, Wang, & Ai, 2012). Lunathrombase, a fibrin(ogen)olytic serine protease, also exhibited antiplatelet activity by inhibiting COX-1 and upregulating the level of cAMP in platelets (Gogoi, Arora, et al., 2018). These studies reveal that the inhibition of platelet activation by plant extracts and their purified compounds can reduce antithrombotic activity, with possible clinical significance. Nevertheless, further preclinical and clinical studies are needed to substantiate the claim.

4.4 | Clot-busting activity (thrombolysis)

The decisive coagulation and thrombotic cascade are controlled by the catalytic transformation of plasma fibrinogen to fibrin, with the resulting development in a steady fibrin mass (Standeven, Ariëns, & Grant, 2005). Clot-buster drugs (i.e., fibrinolytic drugs) such as the plasmin-like proteases (e.g., nattokinase and lumbrokinase) and

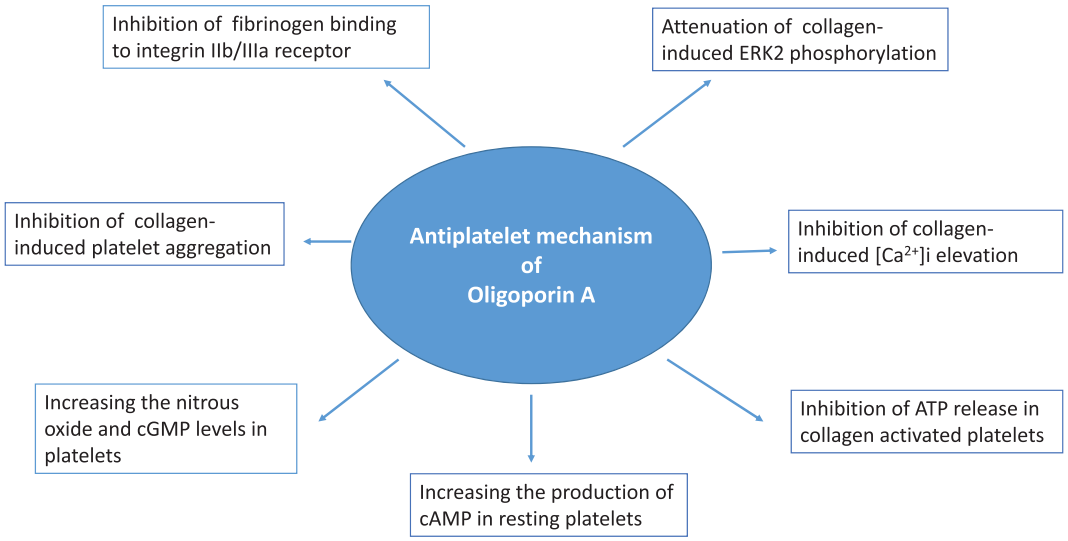


FIGURE 7 A schematic diagram is showing the antiplatelet mechanism of oligoproin A (Park et al., 2012)

plasminogen activators (e.g., tissue-type plasminogen activator tPA and streptokinase) dissolve the fibrin clot(s) inside the blood vessels via direct and indirect mechanisms, to restore blood flow in the affected area (Standeven et al., 2005). As shown in Table 3, only a few plant extracts or their active compounds (i.e., the flavonoids, sulphuric compounds, rutin, and fibrinolytic enzymes [serine proteases]) have been assessed under in vitro conditions to show clot-busting activity, and their potencies varied significantly (Al-Mamun, Amrin, Begum, & Mazid, 2012; Anwar et al., 2011; Ebenezer, Kenneth, Monday, & Hilda, 2014; Pepe et al., 2016; Rajput, Mathur, Agrawal, Chandrawanshi, & Pilaniya, 2011; Ramos et al., 2012; Safaeian, Zolfaghari, Aghaye-Ghazvini, & Behnampour, 2017; Singh et al., 2011; Zhang et al., 2013; Zolfaghari et al., 2012). The thrombolytic potencies, both in vitro and in vivo, of plant extracts and their purified compounds need to be evaluated more fully for their development as effective thrombolytic phytopharmaceuticals.

5 | KNOWLEDGE OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF THE ANTITHROMBOTIC HERBAL DRUG PROTOTYPES CAN ADVANCE THEIR THERAPEUTIC APPLICATIONS

Preclinical studies are needed to determine the pharmacokinetic properties (bioavailability, adsorption, distribution in tissues, metabolism, excretion route, and toxicity) and pharmacodynamic properties of the drug prototypes to understand the effective drug dose and the efficacy before conducting clinical trials. Preclinical data for the plant components that show antithrombotic activity can facilitate the rapid entry to clinical trials for possible therapeutic or prophylactic applications. Some of the pharmacokinetic parameters and pharmacodynamic properties of purified compounds with antithrombotic activity are shown in Table 3 and Figure 4a,b. Some of the bioactive phytocompounds are also candidates for alternative therapy against COVID-19 and thrombosis-associated CVDs, though clinical studies are still needed.

5.1 | β-Sitosterol

β-Sitosterol (BS) ($C_{29}H_{50}O$), with a melting point of 139–142°C, is a thermally unstable compound (PubChem CID: 222284) (Figure 5xvi). Its pharmacokinetic properties and bioavailability have been investigated in an experimental animal model (Ritschel, Kastner, Hussain, & Koch, 1990) and in humans (Duchateau et al., 2012). In a clinical study, the absolute oral bioavailability, plasma clearance, distribution volume, and BS turnover were determined to be 0.41%, 85 ml/h, 46 L, and 5.8 mg/day, respectively, in healthy human volunteers (Duchateau et al., 2012). Preclinical studies showed the tissue distribution of BS in the ovaries, adrenal glands, brain, testicles, and skin; however, it is metabolized to different compounds in the liver and other tissues, and the excretion of a significant proportion (80%) of the absorbed BS is reported to occur via feces (reviewed by Bin Sayeed, Karim, Sharmin, & Morshed, 2016). In vivo animal studies have also shown that the bioavailability of BS post oral intake is approximately 9%, and its distribution half-life and terminal distribution half-life is 3 and 129 hr, respectively (Ritschel et al., 1990). In a preclinical model, BS demonstrated an in vivo anticoagulant activity via inhibition of thrombin and inhibition of thrombin-catalyzed platelet aggregation (Gogoi, Pal, et al., 2018). According to the FAO/WHO Expert Committee on Food Additives, the No-Observed-Adverse-Effect-Level for BS is 4,200 mg/kg/HBW/day, though the in vivo oral anticoagulant dose of BS in mice was determined to be 50 mg/kg. BS did not show in vivo defibrinogenation in the plasma of mice (Gogoi, Pal, et al., 2018). This data suggests a high therapeutic index of BS

that would be suitable for its application in treating thrombosis-associated disorders.

5.2 | Borneol

Borneol ($C_{10}H_{18}O$), a terpene derivative with a molecular mass of 54.253 g/mol (PubChem CID: 1201518), is widely used to relieve pain, reduce inflammation, and treat CVDs (Figure 8i). Preclinical studies in mice have shown the absolute bioavailability of borneol after intranasal and oral administrations to be 90.68 and 42.99%, respectively though injection of borneol via the parental route was found to have a higher bioavailability, and fast distribution and metabolism compared to oral supplementation (Zhao et al., 2012). Natural borneol was detected in mice brain post 5 min of oral intake with a maximum concentration of 86.52 μg/g (Li et al., 2012). Studies have also shown that intravenous and intranasal administration of borneol in mice resulted in its distribution in blood-supply tissues, particularly in the heart, brain, and kidney, but less in the liver, spleen, and lung (Zhao, Du, Lu, Wu, & Li, 2013). The oral toxicity (LD_{50}) of borneol was found to be 5,800 mg/kg in rats, though no information is available about its effects on reproductive organs, mutagenicity, teratogenicity, and neurotoxicity. Such studies would be essential if borneol is to be developed as an oral natural antithrombotic agent.

5.3 | Butein

Butein ($C_{15}H_{12}O_5$), has a molecular mass of 272.25 g/mol, and is a chalcone of chalconoids, which is represented by an (E)-chalcone moiety that has four supplementary hydroxy substituents at positions 2′, 3, 4, and 4′ (PubChem CID: 5281222) (Figure 8 ii). A pharmacokinetic study in rats showed that 53 and 20% of the total administered dose of butein is excreted in urine and feces, respectively, within 24 hr following administration via the parental and oral routes (Brown & Griffiths, 1983). Butein at an oral dose of 2000 mg/kg was safe in rats and devoid of cytotoxicity against cultured mammalian cells under in vitro conditions (reviewed by Semwal, Semwal, Combrinck, & Viljoen, 2015). The pharmacokinetic parameters of butein (5 mg/kg) post i.v. administration in male Sprague–Dawley rats are shown in Table 4. These pharmacokinetic and antithrombotic properties, determined by preclinical studies are inspiring for developing a phytopharmaceutical-based oral antithrombotic agent following further in-depth clinical studies.

5.4 | Fisetin

Fisetin ($C_{15}H_{10}O_6$) is a plant flavonoid with a molecular weight of 1.688 g/ml (PubChem CID: 5281614) (Figure 8iii). The preclinical pharmacokinetics and metabolic studies show that i.p. injection of fisetin at a dose of 223 mg/kg body weight in mice resulted in the maximum plasma concentration of 2.5 μg/ml post 15 min administration. Its concentration in plasma declined biphasically with a rapid half-life of 0.09 hr and a terminal half-life of 3.1 hr (Touil et al., 2011). The liver rapidly biotransforms the fisetin to sulphates and glucuronides (Shia, Tsai, Kuo, Hou, & Chao, 2009). A nanoemulsion of fisetin was shown to have an improved pharmacokinetic and therapeutic efficiency (Ragelle et al., 2012).

A recent study in male Sprague–Dawley rats determined the pharmacokinetic parameters and biotransformation of fisetin with average area under the curve (AUC) ratios (k (%) = AUC conjugate/AUC free-form of fisetin, its glucuronides, and its sulphates being 1:6:21 in plasma and 1:4:75 in bile, respectively (Huang, Hsueh, Cheng, Lin, & Tsai, 2018). The P-glycoprotein facilitated biliary excretion rates of fisetin and its metabolites, glucuronide conjugates, and its sulphate conjugates post fisetin administration at 30 mg/kg via parental routes in rats which were determined to be around 144, 109, and 823%, respectively (Huang, Hsueh, et al., 2018). Although rat is considered an excellent animal model for biotransformation and pharmacokinetic studies, clinical trials are necessary to prove the therapeutic efficiency of fisetin as an antithrombotic herbal drug.

5.5 | Glaucocalyxin A

Glaucocalyxin A (GLA) ($C_{20}H_{28}O_4$), with a molecular weight of 332.4 g/mol, is an ent-kauranoid diterpene (PubChem CID: 10471963) possessing anticoagulant and antithrombotic activity (Figure 8 iv). As many as 58 natural ent-kaurane diterpenoids considered as derivatives of GLA have been identified from medicinal plants (reviewed by Xiang, Wu, Liu, & Jin, 2014). In a preclinical pharmacokinetic study by Cao, Sun, Shen Li, Chen, and Li (2009), intravenous injection of GLA in rats was shown to follow a two-compartment open model. The values of t1/2α and t1/2β were determined to be 4.327 and 28.56 min, respectively, whereas the area under the plasma concentration-time curve (AUC) was 222.744 μg min ml^{-1}, as determined by liquid–liquid extraction and high-pressure liquid chromatography (HPLC) (Cao et al., 2009). In another pharmacokinetic study, the GLA concentration in Sprague–Dawley rats post intravenous or oral administration was determined (Ren et al., 2013).

In addition, a preclinical study showed that the GLA concentration reached the maximum concentration in rat plasma at approximately 0.71–0.75 hr post-oral feeding of *Rabdosia japonica*, which was rapidly eliminated from the plasma (t1/2 = 1.1 hr). GLA could still be detected in rat plasma post 6 hr by liquid chromatography–mass spectrometry (LC–MS)/MS analysis (Huang, Guan, & Lv, 2018). Further, by the UHPLC–MS/MS method, GLA was shown to infiltrate the blood–brain barrier in rats, though the concentrations of GLA in rat brain and lung tissues were substantially lower compared to the plasma concentrations at the same dose. A comparison showed that the Cmax of GLA in plasma was 1.4-fold and 2.6-fold greater than the Cmax of GLA in lung and brain tissue, respectively, and the mean tissue:plasma ratio of GLA (AUC (0-t, tissue)/AUC (0-t, plasma) was 0.74 and 0.47, for lungs and brain, respectively (Deng, Liu, He, Zhang, &

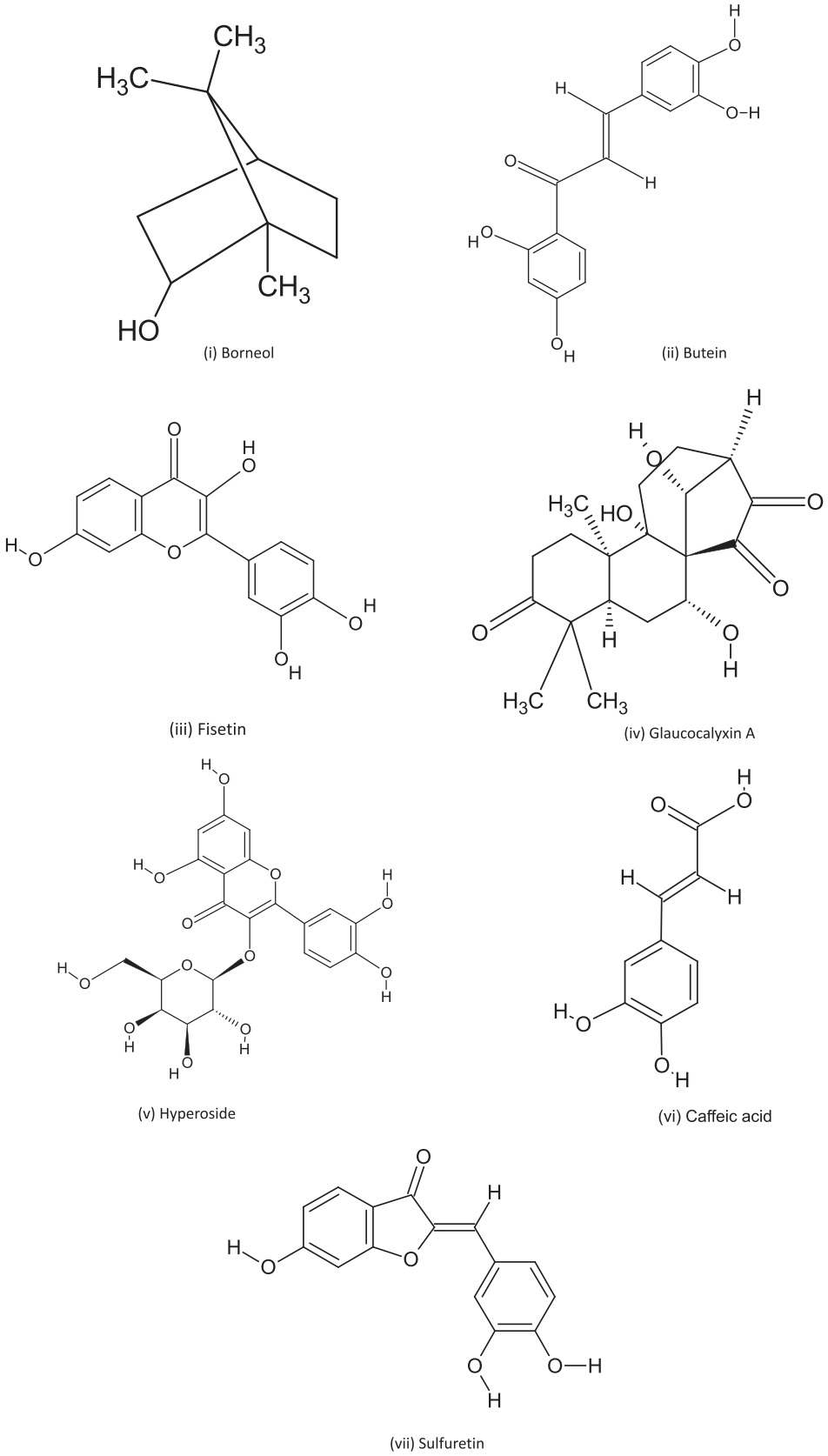


FIGURE 8 Structure of antithrombotic herbal drug prototypes whose pharmacokinetics and pharmacodynamics properties were determined. The figures were drawn using ChemSketch software. (i) borneol, (ii) butein, (iii) fisetin, (iv) glaucocalyxin A, (v) hyperoside, (vi) caffeic acid, and (vii) sulphuretin

Zhou, 2020). In vivo studies in rats showed that GLA was biotransformed to 32 phase I metabolites with different structures and 6 phase II metabolites comprising 25, 18, 17, and 7 structures, in rat urine, feces, and bile plasma, respectively (Sun et al., 2020). The preclinical study data support further clinical trials of GLA as a potential oral antithrombotic agent.

TABLE 4 Pharmacokinetic parameters of butein obtained after intravenous injection (5 mg/kg) in male Sprague–Dawley rats ($n = 4$, mean ± *SD*) (reproduced from Lee et al., 2004 with permission from the publisher)

Pharmacological parameters	Value
$t_{1/2\lambda z}$ (hr)	2.1 ± 0.8
AUC (μg min ml^{-1})	145.6 ± 24.3
AUMC (μg min^2 ml^{-1})	8,659.7 ± 6,036.7
V_z (l/kg)	5.57 ± 1.15
C_{max} (g/ml)	13.0 ± 6.2
Cl (ml kg min^{-1})	32.0 ± 6.8
Fe (%)	1.6 ± 1.4

5.6 | Hyperoside

Hyperoside ($C_{21}H_{20}O_{12}$) (HP), having a molecular mass of 464.38 g/mol, is the O-galactoside of quercetin (PubChem CID: 5281643) (Figure 8v). Preclinical pharmacokinetic parameters of hyperoside were determined by the LC–MS/MS method post-oral administration in beagle dog plasma. HP reached the maximum level (T_{max}) at 2.17 ± 0.41 r with an average maximum concentration (C_{max}) of 4,063.87 ± 360.91 ng/ml (Yin et al., 2013). The area under the plasma concentration-time curve from time zero to infinity (AUC0–1) and the mean residence time were determined at 29,215.12 ± 1,355.75 (h ng/ml) and 8.8 ± 1.3 hr, respectively (Yin et al., 2013). The tissue distribution of HP post-oral feeding in rats showed a rapid and extensive distribution throughout the whole body. The maximum distribution of HP occurred in the stomach, and it was followed by the kidney at 0.5 hr post-oral administration, which was correlated to the metabolism in the liver and clearance by the kidneys (Yin et al., 2014). A toxicity study of HP post-6-month oral administration was followed by a 1-month recovery period in Wistar rats, which showed kidney damage. The damage was reversible after withdrawal of HP treatment, which suggests the importance of regular monitoring of kidney function and hematological parameters of patients undergoing HP treatment (Ai, Huang, Wang, & Zhang, 2012).

5.7 | Polyphenols

Polyphenols (e.g., flavonoids, tannic acid, and ellagitannin) represent a large group of natural organic compounds possessing antioxidant properties. The structural diversity of polyphenols affects their bioavailability. For example, LMWH phenolic acids (i.e., caffeic acid [$C_9H_8O_4$]) (PubChem CID: 689043) (Figure 8 vi) are easily absorbed by the gut, though high molecular weight polyphenols, for example, the proanthocyanidins (a class of oligomeric flavonoids) are absorbed with more difficulty. The polyphenols are biotransformed to a wide variety of LMWH phenolic acids by the gut microbiota, and then conjugated with sulphate, glucuronide, and methyl groups in the gut mucosa and inner tissues, which leads to the virtual absence of free polyphenol in plasma (reviewed by Scalbert, Morand, Manach, & Rémésy, 2002). The plasma concentration, bioavailability, tissue distribution, and pharmacodynamic properties of polyphenol metabolites are influenced by their structure, nature, plant source, and interaction with transporter proteins (Hoda, Hemaiswarya, & Doble, 2019). Polyphenol metabolites are quickly removed from the plasma, and depending on the kind of metabolite, lesser conjugated metabolites are excreted in the urine, while extensively conjugated metabolites are eliminated via the biliary system (Hoda et al., 2019). Higher doses of dietary and plant sources of polyphenols are reported to cause hepatotoxicity (Martin & Appel, 2010), and therefore, further studies are warranted to optimize the in vivo dosage of the polyphenols before they are used as therapeutic anticoagulants or cardiovascular drugs.

5.8 | Sulphuretin

Sulphuretin ($C_{15}H_{10}O_5$), with a molecular weight of 270.2369 g/mol (Figure 8 vii), represents a flavonoid glycoside from plants (PubChem CID:5281295). The pharmacokinetic parameters of sulphuretin and its conjugates are shown in Table 5 (Jin et al., 2015). Little is known about the acute and sub-acute toxicity of sulphuretin; and accordingly, more preclinical and detailed clinical studies are required to develop sulphuretin as an herbal antithrombotic drug.

5.9 | Tanshinone IIA

Tanshinone IIA (C19H18O3) (TS), with a molecular weight of 294.3 g/mol (Figure 5 xv), is a derivative of a phenanthrene-quinone type that shows pharmacological activity (PubChem CID:164676). The pharmacokinetic analysis post i.v. administration of TS (2 mg/kg) in Sprague–Dawley rats showed a triexponential pattern of distribution, with (a) rapid distribution in liver, lung, and spleen with a t1/2 α value of 0.024 hr, (b) slow redistribution in other tissues with a t1/2 β value of 0.34, and (c) a terminal elimination phase (t1/2 gamma, 7.5 hr) (Hao et al., 2006). By LC–MS/MS analysis, the tissue distribution of TS was found in the following tissues, in descending order: stomach > small intestine > lung > liver > fat > muscle > kidneys > spleen > heart > -plasma > brain > testes; however, most of the rat tissues post 20 hr oral administration at a dose of 60 mg/kg showed the presence of TS (Bi et al., 2007). Approximately 99.2% of TS is bound to plasma proteins in plasma, including 77.5% lipoprotein (Hao et al., 2006). TS's low aqueous solubility and partial membrane permeability resulted in its poor absorption and low bioavailability (<3.5%). Nevertheless, at a concentration of 6 μM, TS demonstrated pericardial edema, spinal curvature, and missing tails in zebrafish embryos, indicating its potential cardiotoxicity at a higher dose (Wang et al., 2017). In vivo dose optimization and clinical studies of TS are warranted to understand its potential as an antithrombotic cardiovascular drug.

TABLE 5 Pharmacokinetic parameters of sulphuretin and its conjugated metabolites in rat plasma determined by LC–MS/MS analysis (Jin et al., 2015)

Pharmacological parameters	Sulphuretin	Sulphuretin conjugates
Cmax (nmol/ml)	0.05 ± 0.04	0.70 ± 0.16
AUC (nmol·hr ml^{-1})	0.03 ± 0.03	2.68 ± 0.36
Tmax (hr)	0.50 ± 0.00	1.00 ± 0.00
t1/2 (hr)	NA	3.46 ± 1.14
MRT0 − t (hr)	0.54 ± 0.03	3.84 ± 1.15

6 | A PROPOSED ROADMAP FOR THE DEVELOPMENT AND COMMERCIALIZATION OF ANTITHROMBOTIC HERBAL DRUGS

Natural compounds are often considered to be the primary sources of novel drug candidates, and the idea that "natural is safe" has prevailed in society; however, for the reasons discussed above, the commercialization and mainstream medical use of herbal products as potent, safe medicines for treating or managing thrombosis-associated CVDs requires proper strategic planning. The production and quality assessment of herbal drugs must follow stringent regulatory guidelines, such as the Traditional Medicine Strategy 2014–2023, put forward by the World Health Organization (https://www.who.int/medicines/publications/traditional/trm_strategy14_23/e). The following suggestions and strategies can be adopted by scientists, clinicians, herbal drug manufacturing pharmaceutical companies, and governmental and non-governmental regulatory agencies in different countries for the development and commercialization of new antithrombotic herbal drugs. With improvements to the efficacies of existing herbal drugs, they may be more broadly accepted on the global market (Zhang et al., 2012). Table 6 and Figure 9 provide a blueprint for the development and globalization of antithrombotic herbal medicines.

6.1 | Encourage basic research to explore the antithrombotic properties of medicinal plants

Regional evidence for ethnomedicine and herbal remedies as antithrombotic drugs gathered from different communities should be the first step to improve their commercialization. Detailed information about the parts of the plant being used, the specific season of collection, and the method of drug preparation, dose, and route of administration need to be documented with pertinent photographs or drawings. The documentation can also prevent the loss of indigenous knowledge about traditional herbal medicines used to treat CVDs, and prevent the exploitation of indigenous intellectual property. The collected information should be held by national regulatory agencies and before a patent is granted for commercializing a product, permission must be obtained from the relevant agencies.

A herb or its parts must be carefully selected for the production of an antithrombotic drug, preferably based on monographs of traditional medicinal plants prepared by the WHO or from a list of herbal plants from the country of interest. The choice of herb for preparing an antithrombotic drug must be done cautiously to avoid using restricted or endangered species from a particular region.

The practice of collecting a herb should include authenticating the starting material to avoid adulterations and identifying the geographical locale, specific harvesting time, and season(s) to obtain the optimal quality of the active antithrombotic compound(s). To accurately identify herbs and plant parts (roots, barks, and powders) that are sold commercially, modern molecular biology approaches (i.e., DNA barcoding of different genomes (Jiang et al., 2018) and high-resolution melting should be used (Yu et al., 2021)). Metabarcoding technology that uses next-generation sequencing is a highly proficient method that could be used to identify mixed samples.

The purification and molecular mass determination of bioactive components from herbal plants could help to elucidate their antithrombotic activity, mechanism of action, and chemical structure. Importantly, the efficacies of herbal drugs should be compared to those from drugs that are already available on the market, in preclinical studies. Ligand-based, computer-aided drug designing techniques (in silico analysis) and target-based drug discovery (i.e., reversed pharmacology) should be used to explore the active compounds from herbal plants as potential inhibitors of the coagulation cascade (e.g., antithrombin or -FXa or other coagulation factors) (Ibrahim et al., 2020). Network pharmacology that integrates pharmacology and information technologies (i.e., bioinformatics, system biology, and high-throughput histology) are new and promising research strategies that could be used for evaluating traditional herbal medicines (Hopkins, 2007; Zhou et al., 2020). Similar computer-based approaches that take advantage of high-throughput screening could be used with different herbs to discover next-generation antithrombotic drugs (Zhou et al., 2020).

The absorption, distribution, metabolism, excretion, and toxicity properties of bioactive components from plants with antithrombotic activities can also be predicted using the pkCSM online server (http://biosig.unimelb.edu.au/pkcsm) (Pires, Blundell, & Ascher, 2015) or similar software programs. The drug properties can be used to reveal possible therapeutic applications of a given antithrombotic herbal drug. In particular, Lipinski's "rule of five" is an ideal tool for assessing the connection between predicted structures and drug-like properties (Lipinski, Lombardo, Dominy, & Feeney, 1997) and any predicted structure of an antithrombotic herbal drug/compound should not violate this rule. Predicted inhibitors can be chemically synthesized or isolated from the medicinal plant (natural inhibitor), and their antithrombotic potencies determined in vitro before being evaluated under in vivo conditions (i.e., the classic or forward pharmacological approach).

Machine learning is another advanced tool that can predict the biochemical properties and antithrombotic effects of plant-derived natural products (Jeon, Kang, & Kim, 2021). Machine learning can also predict the toxicity and drug–drug interactions of novel antithrombotic molecules solely based on their molecular structures (Jeon et al., 2021).

TABLE 6 Blueprint proposed for the development and improved commercialization of antithrombotic herbal drugs

Strategies	Impact
1. Encouraging basic research: a region-wise survey to document the ethnomedicine against thrombosis and cardiovascular complications to augment the development of antithrombotic herbal drugs with known composition and property.	(i) Regional documentation on the use of ethnomedicines and herbal remedies as antithrombotic drugs will be available. This strategy will safeguard the interest and traditional knowledge of the indigenous people and communities from exploitation. (ii) A list of such plants in different geographical locales of the country will be made available to each country's national regulatory agency to ensure the exploitation and habitat destruction of these plants. (iii) A country-specific monograph of antithrombotic herbal medicinal plants, including the list of restricted or endangered species of herbs, should be made available to the World Health Organization. (iv) This action will encourage the proper selection of herb/plant or parts for antithrombotic drug production, preferably from the monograph of traditional medicinal plants available in each country. (v) This effort will lead to modern molecular biological approaches for good collection practice, including authenticating starting material (herb) to avoid adulteration. (vi) Purification of active constituents from plants. Characterization of chemical and biochemical properties of active constituents for discovering novel antithrombotic compounds from plants and assessment of their potency as compared to their competitors in the market. (vii) The ligand-based computer-aided drug designing (in silico analysis) or target-based drug discovery program will be encouraged. (viii) It will augment the research on network pharmacology that integrates pharmacology and information technology (bioinformatics, system biology, and high-throughput histology). (ix) Using online software, this strategy will help predict adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of antithrombotic phytomedicines. (x) This strategy will also help apply machine learning to predict biochemical properties, including antithrombotic effects, toxicity, drug–drug interaction, and plant-derived natural products, to shed light on their possible therapeutic application as a cardiovascular drug.
2. Augmentation of the pre-clinical and clinical research on antithrombotic herbal drug prototypes for translation to a therapeutic agent ready for commercialization.	(i) This effort will help explore in vivo efficacy, mechanism of antithrombotic action, safety, storage stability, and therapeutic index of plant-derived natural compounds, preferably in a GLP-compliance laboratory for their dose optimization. (ii) Synergistic interaction of two or more herbal compounds to significantly enhance their antithrombotic activity in vivo conditions to develop a more potent and effective drug will be explored. (ii) Determination of pharmacodynamics parameters of antithrombotic herbal drugs in rodent models to analyze their ADEMT properties and the potency of the herbal drugs with contender synthetic drugs will be known. (iv) Understanding the risk: benefit ratio will attract the pharmacological companies' interest to take forward the lead molecule(s) in the following stages of drug development. (v) Knowledge on the interaction of herbal drugs with Western medicines and food components, including their mechanism(s) of interaction, significances, and severity of such interactions, will be beneficial to determine their safety post-administration. (vi) Knowledge of the influence of human gut microbiota on the bioavailability and bioactivity of antithrombotic herbal compounds will help design effective ways(s) of oral delivery of antithrombotic herbal drugs.
3. Advancement of globalization and commercialization of antithrombotic herbal medicine.	(i) Good manufacturing practice (GMP) of cardiovascular herbal drugs will be boosted to maintain customers' and clinicians' quality and acceptance. (ii) Phytochemical markers-based quality control and quality assurance (QA and QC) of herbal antithrombotic drugs will ascertain the quality and prevent batch-to-batch variation which will augment their acceptability and enhance the commercialization of antithrombotic herbal medicines in Western countries.

TABLE 6 (Continued)

Strategies	Impact
	(iii) Setting QA and QC laboratories by government, private industries, or public-private partnership (PPP) programs will enhance drugs' trust and acceptability and provide employability to technicians and scientists.
	(iv) The tremendous increase in physicians' choice to prescribe the phytochemical marker-assisted quality assured, formulated herbal drug composition.
	(iv) The above steps would help toward international cooperation on the use and proposition of antithrombotic herbal drugs fulfilling all the regulatory compliances of each nation.
4. Conservation and cultivation strategies of medicinal plants demonstrating antithrombotic activity.	(i) A well-planned national policy on the conservation of medicinal plants will emerge to prevent the extinction of plants.
	(ii) Prevent the commercialization of antithrombotic herbal drugs prepared from wildly grown plants/herbs.
	(iii) Establishment of new research centers. Launching of the new programs on in situ and ex situ conservation of medicinal plants.
	(iv) Training of local farmers on scientific ways of cultivation and organic farming and sustainable use of medicinal plants will tremendously increase the production of antithrombotic herbs and plants and will be a source of income to farmers.
	(v) Enhanced production and cultivation of antithrombotic medicinal plants will also boost the establishment of herbal-drug-based bio-industrial sectors for that region's income generation and economic development.

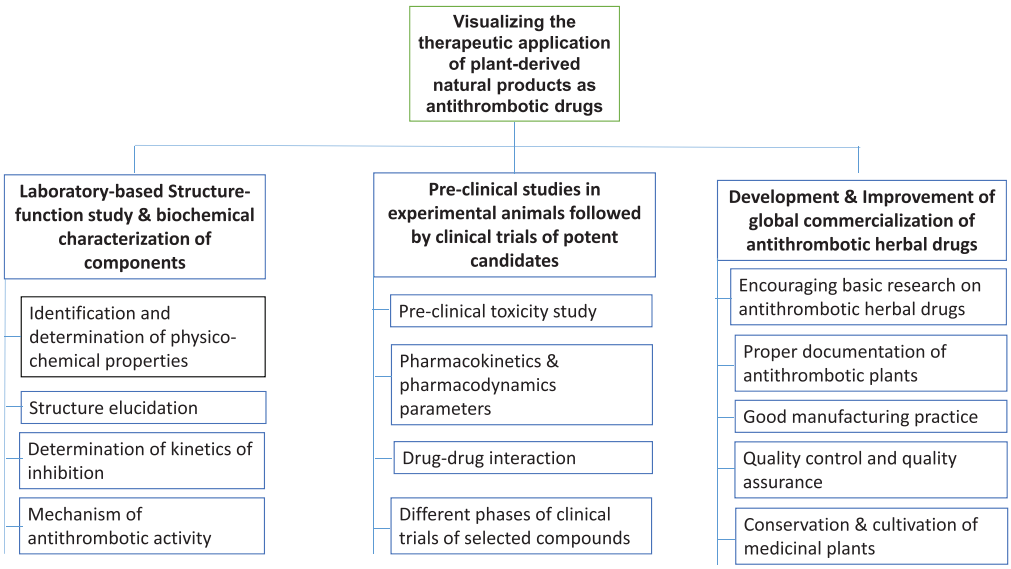


FIGURE 9 A roadmap is proposed to show the developing and improved globalization of antithrombotic herbal medicine

6.2 | The need for more pre-clinical and clinical research on antithrombotic herbal drugs

The identification and mechanism of action of herbal constituents and their efficacies need to be compared to modern antithrombotic drugs. Herbal drug safety profiles also need to be established through preclinical studies in GLP-certified laboratories before such compounds can be registered with the regulatory authority of a country and before clinical trials can begin. Each country's Health Authority would have to grant ethical clearance for a new drug (i.e., cardiovascular herbal drug) before clinical trials can be conducted.

With the goal for clinical development of antithrombotic herbal drugs, more studies are needed to determine a natural compound's in vivo efficacy, storage stability, and toxicity (Butler et al., 2014). Further biochemical, pharmacological, and clinical research is needed to evaluate antithrombotic herbal medicines. Besides phytochemical and biochemical analyses, in vitro and in vivo pharmacological and preclinical analyses should be conducted with pharmacokinetic and pharmacodynamic analyses to determine the efficacy, safety, metabolism, tissue distribution, and elimination of herbal compounds. The potency of herbal drugs must also be compared to the potency of contender synthetic drugs. In clinical studies of promising antithrombotic herbal drugs, previously unreported or new bioactive molecules may be

discovered from indigenous herbs or plants. From the safety assessments of herbal drug prototypes, pharmacological companies may be encouraged to further explore the commercialization of herbal compounds and move them along the drug development process.

The interactions between herbal antithrombotic drugs and Western medicines could lead to unwanted side-effects (e.g., bleeding complications), and consequently, rigorous evaluation of the literature and pharmacological or clinical reports is needed to understand the mechanism(s) of interaction, and the significance and severity of any interactions between allopathic (Western) anticoagulant/antiplatelet drugs and herbal antithrombotic drugs (Tsai et al., 2013; Zuo et al., 2020). Because the antithrombotic efficiency of any formulation from two or more purified natural products could surpass the treatment efficacy of the individual components, potential herb-–drug interactions need to be carefully scrutinized (Zuo et al., 2020).

The bioavailability and bioactivity of some natural compounds can be influenced by the patient's gut microbiota, and some probiotic strains can enhance intestinal and colon absorption and bioavailability (Vamanu & Gatea, 2020). This area of research is particularly active to understand how herbal compounds can have enhanced oral bioavailability and avoid being degraded in the colon, leading to improved clinical efficacy.

6.3 | Good manufacturing practices, quality assurance, and international cooperation can enhance the commercialization and globalization of antithrombotic herbal drugs

Good manufacturing practices (GMP) for cardiovascular herbal drugs must be used to maintain their quality and gain the acceptance of consumers and clinicians. GMP can be monitored by analyzing the quality of herbal drugs, to further support their broad acceptance and commercialization. The active constituent(s) of herbal antithrombotic drugs can be monitored and accurately quantified with phytochemical markers that use biochemical and biophysical techniques (i.e., biochemical assays, molecular mass determinations by gas-chromatography–MS (GC–MS) and high-resolution MS, and purity determinations by RP-HPLC and MS). Such combination analyses are known as analytical fingerprinting techniques, which can involve both targeted and untargeted approaches. The result is better quality control (quality assurance) and less chance of batch-to-batch variations in the product quality (Kharbach, Marmouzi, El Jemli, Bouklouze, & Vander, 2020).

Large-scale herbal drug manufacturers should also establish in-house quality control laboratories for quality assurance and quality control (QA and QC) of their herbal antithrombotic drugs. Nevertheless, setting up a modern QA and QC laboratory can be overly expensive for a small-scale herbal manufacturer. To compensate for the high cost, government or private agencies could use a public–private partnership (PPP) model to set up a number of regional laboratories for QA and QC and the routine analysis of antithrombotic cardiovascular drugs. Certificates of analysis provided by a national laboratory could help to standardize herbal drugs for the purpose of marketing.

International cooperation for the regulation and compliance of antithrombotic herbal drugs should be encouraged. International Regulatory Cooperation for Herbal Medicines, established in 2006 by the WHO could serve as the basis for improving the regulation of herbal medicine. While only a handful of countries are current members of this organization, more are expected to join and strengthen the international acceptance of herbal drugs, including antithrombotic cardiovascular drugs.

A Physician's choice to use a cardiovascular herbal drug is a crucial aspect for the international market and could boost the production and commercialization of cardiovascular herbal drugs. To encourage the use of herbal remedies for treating thrombosis-associated CVDs, drug regulatory agencies need to develop guidelines and policies that will stimulate interest among healthcare professionals and contribute to the knowledge base for the therapeutic use of quality-controlled antithrombotic herbal drugs.

6.4 | Conservation approach for medicinal plants

The national conservation strategy for medicinal plants should be given the highest priority. The identification and conservation of medicinal plants used traditionally to treat CVDs can have a tremendous impact on the conservation of biodiversity and cultural heritage in a given region. By developing the market for antithrombotic herbal drugs, especially those from the wild, the demand for products could exceed the legal supply. Well-planned conservation and cultivation initiatives for such plants and herbs should be framed, with consideration for indigenous knowledge and practices.

Strategies need to be developed to balance overgrazing and urbanization to prevent habitat destruction of traditional medicinal herbs. For example, the taxonomic identification of medicinal plants and herbs used for treating CVDs, research and training for their cultivation, the in situ and ex-situ conservation of such plants, and sustainable use initiatives may help to avoid the overexploitation of such plants for commercial purposes, and prevent their habitat loss and degradation (Chen et al., 2016).

Finally, the optimal production of natural components can be facilitated by enhancing the growth of herbal plants and encouraging organic farming practices to produce medicinal plants with higher biomass yields (Chen et al., 2016).

7 | CONCLUSION AND FUTURE PROSPECTS

Recent evidence on the therapeutic value of antithrombotic herbal drugs has led to envisaging their great promise as an effective natural therapy for treating thrombosis complications in cardiovascular and COVID-19 diseases, though several drawbacks associated with the

production and quality assurance of antithrombotic herbal drugs need to be adequately addressed. One of the most critical issues is applying the scientific parameters for assessing pharmaceuticals to herbal products. Consumers often use herbal products based on the herbalism approach (using only herbal components) rather than using the phytotherapy approach (using standardized herbal products). Accordingly, the pharmacological efforts to produce herbal products must first be evidence-based before the products are accepted by clinicians.

The challenging tasks can be achieved by herbal drug manufacturers by following standard guidelines for production and quality assurance, but without QA and QC certification, these drugs should not be sold on the market. Rigorous studies are needed to establish the clinical efficacy of plant-derived compounds, and in-depth studies must be carried out to elucidate the antithrombotic mechanism of herbal drugs, and their safety and potency, compared to the properties of Western medicines. International cooperation for the standardized use and quality assurance of therapeutic herbal drugs must also be supported by research scientists, governments, and NGOs. Modern research methods, involving network pharmacology and machine learning will likely lead to the discovery and formulation of new antithrombotic herbal drugs, and specific herbal components with potent antithrombotic activity. Great care must also be taken to prevent the overexploitation or habitat destruction of possibly rare plants and their sustainable use and cultivation must be facilitated by specific farming practices.

By encouraging academic-industry partnerships, fundamental research on antithrombotic drug discovery may be translated into improved clinical products. The PPP model can link academicians, clinicians, research scientists, and governmental organizations with pharmacological companies to procure additional resources and escalate the discovery and development of next-generation natural antithrombotic herbal drugs. By improving the production quality of herbal medicines, products can be sustainable, clinically efficacious, and less costly, ultimately reducing the global burden of CVDs and mortality associated with COVID-19.

ACKNOWLEDGMENTS

The authors thank Ms. U. Puzari for drawing the chemical structure of antithrombotic molecules, Ms. Bhabna Das for technical help in preparing the manuscript, and Glen Wheeler, Canda for editing the manuscript. AKM received financial assistance from the core fund of the IASST, Guwahati.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Ashis K. Mukherjee concenived the idea, wrote and revised the manuscript, and Dhruba J. Chattopadhyay reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources

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How to cite this article: Mukherjee, A. K., & Chattopadhyay, D. J. (2022). Potential clinical applications of phytopharmaceuticals for the in-patient management of coagulopathies in COVID-19. *Phytotherapy Research*, *36*(5), 1884–1913. https://doi.org/10.1002/ptr.7408