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Current antithrombotic therapies and prospects of natural compounds in the management of the thrombotic disorder

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ABSTRACT: Thrombosis-associated cardiovascular and cerebrovascular disorders are the leading causes of global mortality and morbidity; this rate is alarmingly rising. A diverse class of antithrombotic drugs like antiplatelet and anticoagulant agents are frequently used to manage thrombus-induced physiological consequences, including cardiovascular and cerebrovascular diseases. But these agents have reported producing a series of adverse effects on the body, including potential bleeding episodes, which makes it urgent to discover antithrombotic therapy with higher efficacy, novel mechanisms of action, and fewer side effects. Research is still going on to isolate antithrombotic agents from various natural sources, and researchers are making remarkable progress in this field. In different experimental models, medicinal plant extracts and plant-derived bioactive compounds have been documented to produce antithrombotic activity through mechanisms like conventional drugs, with minimal or no side effects. Plant extracts and their bioactive compounds (phenolics, polysaccharides, peptides, terpenes, flavonoids) have proven their efficacy as potential candidates for developing safe antithrombotic therapy in numerous *in vivo* and *in vitro* models. Our review aims to introduce the readers to the relationship between thrombus formation and cardiovascular diseases (CVDs), problems with traditional therapies, and the role of natural resources in managing thrombus-induced cardiovascular and cerebrovascular diseases with possible mechanisms.

1. INTRODUCTION

In mammals, the body's hemostatic system provides host protection by creating a closed circulating system of high-pressure and smooth blood flow without any interaction of blood cells with the blood vessels. The blood vessel is tiled with endothelial cells and is responsible for maintaining an inert and passive surface for the whole circulating system. Together with blood vessels and their cellular architecture, various cellular components of blood, along with leukocytes and platelets, derive microparticles that circulate through this closed system in an inert and inactive state and participate directly in maintaining the hemostasis. In response to cellular injury or tissue disruption, the hemostatic system and endothelial cells are activated, which initiates the expression of intracellular intercellular adhesion molecule-1 (ICAM-1), ICAM-2 and ICAM-3, vascular and platelet adhesion molecules, and Weibel–Palade bodies on the endothelial cell membrane. In response to pathological events in arteries and veins, the exposure of the endothelial surface to negatively charged blood phospholipids can interfere with tissue and coagulation factors, therefore promoting the prothrombotic signaling pathways to repair the changes within the plasma membrane architecture. The release of tissue and coagulation factors from the plasma membrane bilayer of injured endothelial cells activated a calcium-dependent enzymatic reaction to convert the inactive blood clotting protein (zymogens) to corresponding active enzymes, resulting in rapid generation of thrombin which further initiates thrombus formation (Furie & Furie, 2007; Lippi et al., 2011).

Thrombus formation on the disrupted atherosclerotic plaque is one of the critical factors for developing ischemic cardiovascular disorders (Asada et al., 2018). On the other hand, loss of integrity in the endothelium of brain-supplying arteries triggers platelet aggregation pathways, stimulation of the coagulation cascade, and changes in the erythrocyte or leukocyte constituents of the blood, resulting in thrombotic occlusion and cerebral ischemic tissue injury (Hacke et al., 1987). Antithrombotic drugs in routine use include antiplatelet drugs (aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists) and anticoagulants (unfractionated and low molec-

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ular weight heparin, warfarin, and direct thrombin inhibitors). Antithrombotic drugs, which include antiplatelet and anticoagulant therapies, prevent, and treat many cardiovascular disorders and, as such, are some of the most commonly prescribed drugs worldwide. The first drugs designed to inhibit platelets or coagulation factors, such as the antiplatelet clopidogrel and the anticoagulant warfarin, significantly reduced the risk of thrombotic events at the cost of increased bleeding in patients. However, both clopidogrel and warfarin have some pharmacological limitations, including interpatient variability in antithrombotic effects in part due to the metabolism, interactions (e.g., drug, environment, and genetic), or targets of the drugs (Mega & Simon, 2015; Watson et al., 2002). Therefore, it becomes essential to search for new antithrombotic agents having minimum adverse reactions. Medicinal plants and plant-derived natural bio-active compounds may serve crucial roles in this regard (C. Chen et al., 2015).

People are primarily inclined to natural traditional healing agents to maintain their health and as a source to diagnose, prevent, improve, or treat physical and mental ailments based on their beliefs, theories, and perceptions indigenous to different cultures (Che et al., 2017). Multiple lines of research are going on to find natural remedies against various chronic diseases based on the traditional use of indigenous people. Isolation of bioactive compounds and bioactive compound-based analysis are effective ways to prove the conventional efficacy of medicinal plants. *Dendropanax morbifera* Leveille is a Korean endemic tree species that people of the Republic of Korea have consumed for a long time as healthy food and traditional medicine; it is historically used to improve blood circulation, which is mentioned in Donguibogam (a precious book of Korean medicine written in the 17th century) and for the treatment of various other diseases (Choi et al., 2015). Celastrus orbiculatus Thunb (C. orbiculatus) is a traditional Chinese phytomedicine applied to relieve pain, improve blood supply, tranquilize, and mitigate excitement for centuries. This plant is auspicious with various bioactive compounds and proves its traditional effectiveness in different experimental set-ups (J. Zhou et al., 2019). A combination of four-herbal formulas from Radix astragali, *Radix scrophulariaceae*, *Panax notoginseng*, and *Salvia miltiorrhizae* develop a capsule formulation named Fufang Xueshuantong (FXST), which is well appreciated in Chinese medicine because of its effectiveness in the management of clinical cardiovascular disorders (Sheng et al., 2014). Another commonly used Chinese traditional medicinal herb named Danggui (*Radix Angelicae* Sinensis) and Honghua (*Flos Carthami* Tinctorii) are well recognized for stimulating blood supply and eliminating blood stasis. It has been reported that these two medicinal herbs potentiate the activity of clopidogrel (an antiplatelet medication) by prolonging bleeding times (Y. Li & Wang, 2010). Plant-derived natural bioactive compounds, including polyphenols, flavonoids, alkaloids, glycosides, polysaccharides, etc., possess the potential to maintain mitochondrial protein expression, oxidative phosphorylation, and regulate the production of ROS (reactive oxygen species). These properties make them potential candidates as cardioprotective agents (Arauna et al., 2019). Hovertrichoside C, hyperin, luteolin-7-O–D-glucuronide, pentacyclic flavonol, quercitrin and avicularin, hexacyclic flavonol (M.H. Lee et al., 2002), sesquiterpenes (Raskob et al., 2014) isolated from various plants and plant parts have been reported to produce antithrombotic and antiplatelet aggression activities through the inhibition of TFs activities. Hyaluronan (HA) polysaccharide, plasma free hemoglobin (PFH), hyperoside, withaferin A, wogonin (WGN), etc., induce anticoagulant activity by suppressing the intrinsic or extrinsic coagulation pathways (C. Chen et al., 2015).

This review will introduce the readers to the current therapies and their drawbacks and how the novel plants themselves or their bioactive compounds can manage the thrombosis complication in different cardiovascular disorders more efficiently with their probable mechanisms in light.

2. EPIDEMIOLOGICAL STATUS OF CARDIOVASCULAR DISORDER

Worldwide, cardiovascular, and cerebrovascular diseases are the leading causes of mortality, morbidity, and disability. It has been reported that the formation of thrombus into the vessels is considered the principal cause of the development of the acute brain and coronary artery occlusion and plays a cardinal role in the pathology of stroke, ischemic heart disease (IHD), and venous thromboembolism occurrence (Pifarre, 1998; Raskob et al., 2014). In the developed world, arterial and venous thromboembolic events, including deep vein thrombosis (DVT), acute coronary syndrome, strokes, pulmonary embolism (PE), and peripheral arterial thrombosis, is the most prominent causes of death than any other pathological complications. Various angiographic and pathologic data demonstrated that acute MI (myocardial infarction) and unstable angina are present with intraluminal thrombi, where the prevalence of thrombi in acute myocardial infarction is high (Pifarre, 1998). So, minimization of thrombus formation is one of the main prerequisites for the treatment of MI. Every year, an approximate count of 17 million people die from various cardiovascular and cerebrovascular complications. Among them, myocardial infractions and strokes contribute enormously to global morbidity and mortality and are recognized as significant barriers to sustainable human development (Richling et al., 2007). Globally, one in four deaths has been reported as a collective consequence of IHD and strokes (Lozano et al., 2012). Thrombus formation contributes to nearly half of all ischemic stroke deaths, and this death rate is alarmingly increasing. Globally, individuals over 75 years old experience 60% of new stroke, and 45% of death occurs from strokes in this age range (Feigin et al., 2014). A study of GBD (Global Burden of Diseases, Injuries, and Risk Factors) presented unambiguous evidence regarding the negative impact of arterial thrombosis on global health since arterial thrombosis covertly controls the pathologic mechanisms responsible for IHD and ischemic stroke development (Raskob et al., 2014). So, to avoid severe complications from intraluminal thrombus

and embolus, it is medically recommended to treat the patients with anticoagulant therapies as quickly as possible with an adequately adjusted dose and dose frequency. The primary function of currently available antithrombotic agents is to prevent the formation of blood clots. Most of the current antithrombotic agents are functioning by inhibiting platelet function directly (for example, aspirin, clopidogrel, and dipyridamole) or, via thrombin inhibition, by inhibiting platelet activation and fibrin formation (for example, heparins, warfarin and direct inhibitors of thrombin or factor Xa) (Mega & Simon, 2015).

3. CARDIOVASCULAR DISORDER AND THROMBUS FORMATION

Blood coagulation is crucial in reducing blood loss from vascular wall injury in the body. Hemostasis is of Greek origin that is characterized as the stop of hemorrhage. The hemostasis mechanism reflects a complex and responsive balance between blood clotting and the breakdown of fibrin polymers (Thornton & Douglas, 2010). Thrombus formation happens with the aid of blood vessels, platelets, and coagulation factors. When the damage to endothelial cells occurs, the platelets bind to the collagen located on the sub-endothelial sites and develop a short plug. This plug forming also induces coagulation cascades, which form a stable platelet plug by activating fibrin (Norris, 2003). The process of hemostasis occurs in four stages: vascular spasm, platelet aggregation, platelet plug formation, coagulation cascades activation, and stimulation of the breakdown of fibrin threads Gale (2011).

A vascular injury immediately triggers vasoconstriction governed by responsive neurologic pathways and discharges of specific chemicals such as endothelin and thromboxane A2 (TXA2) to reduce blood flow through the affected area (Cines et al., 1998). Collagens and von Willebrand factors (vWF) present in the sub-endothelial sites are revealed due to the breakdown of endothelial cells. Then platelets bind with collagens through glycoprotein-1b (GP1b) complex receptors with the help of vWF, causing structural changes in platelets, leading to multiple pseudopods, and significantly maximizing their outer region. This change indicates the activation of platelets (Berndt et al., 2001). Activated platelets secret various chemicals from two types of granules. α granules are present with fibronectin, fibrinogen, platelet factor IV, factor V, factor VIII, and platelet-derived growth factor. In contrast, dense granules are present with a massive number of Ca^{2+} and adenosine diphosphate (ADP). ADP and TXA2 promote the addition of more platelet, which induces the development of a platelet plug that transiently restricts vascular damage (Figure 1) (Heemskerk et al., 2002).

Vascular damage triggers coagulation by activating coagulation cascades to create a more stable platelet clot. This process occurs in three ways, e.g., extrinsic, intrinsic, and common pathways (Figure 2). The extrinsic or tissue factor pathway is first activated by the tissue factor (TF), which is liberated from the sites of the sub-endothelium (Bugge et al., 1996). In the case of sub-endothelial cell exposure, TF reveals in plasma, binds with factor VII, and converts into TF-VIIa complex, which also helps transform both factors IX into IXa and X into Xa (Morrissey, 2001). Initiation of intrinsic pathways activates factor XII that is converted into XIIa with the help of high molecular weight kininogen (HMWK), and plasma kallikrein, prekallikrein (PK) act as a precursor of plasma kallikrein (Colman & Schmaier, 1997). Factor XIIa also instigate the transformation of factor XI to XIa and prekallikrein to kallikrein. In this activation reaction of factor XIa, Ca^{2+} ions are required (Bouma & Griffin, 1977; Rasche, 2001). Activated factor XIa stimulates the conversion of factor IX to the activated form of IXa, mediated by Ca^{2+} ions and the TF-VIIa complex (Bouma & Griffin, 1977; Grover & Mackman, 2019). It also helps activate the factor X by converting it into Xa with the help of phospholipids (PL), Ca^{2+} ions, and the activated form of co-factor VIIIa (Borne et al., 1995). An activated form of VIIIa and IXa is known as "the tenase complex." (Norris, 2003) This activation form of factor Xa can be acquired from the extrinsic pathway. The activation process of factor X is also known as the initial step of the common pathway. In this pathway, Xa activates thrombin from prothrombin with the help of PL, Ca^{2+} ions, and the activated form of co-factor Va. Thrombin which is also recognized as an influential enzyme that catalyzes the conversion of fibrinogen into fibrin monomer by the cleavage process. This fibrin then links with one another to form a fibrin polymer. Thrombin also helps to convert factor XIII into the activated form of XIIIa (Brummel et al., 2002), which further facilitates the formation of a stable cross-linked fibrin polymer by providing additional bonding between fibrin polymers. Thrombin produces positive feedback in enhancing the conversion of factor XI to factor XIa (Gailani & Broze, 1991) and stimulates the activation of co-factor V to Va and VIII to VIIIa (Brummel et al., 2002). Thrombosis is considered one of the major risk factors for developing three leading CVDs: venous thromboembolism, (Gregson et al., 2019) IHD, and stroke (Raskob et al., 2014). Atherothrombosis develops when the atherosclerotic plug is disrupted, a recurrent condition that decreases blood flow passage into the artery (Figure 3). As a result, MI or ischemic stroke are seen for this atherothrombosis reason (Cate & Hemker, 2016). Patients with a high level of cholesterol and other fatty substances accumulate these into the damaged endothelial cells of the artery wall. Oxidation of cholesterol causes an inflammatory response that triggers white blood cells to enter the artery wall and transform into macrophages. This formation of white blood cells (WBC) digests sub-endothelium deposited cholesterol and turns into foam cells (Tedgui & Mallat, 2006). Within the artery wall, foam cells degenerate and release their contents, forming the atheroma. Calcium salts, smooth muscle cells, and collagen matrix accumulate within the atheroma and generate a hard plaque that reduces the elasticity of the artery wall and artery lumen (Hansson, 2005). When this plug ruptures, exposing collagens and TF that facilitate platelet aggregation and activation of coagulation cascades to generate a cross-linked fibrin platelet plug. This cross-linkage traps red

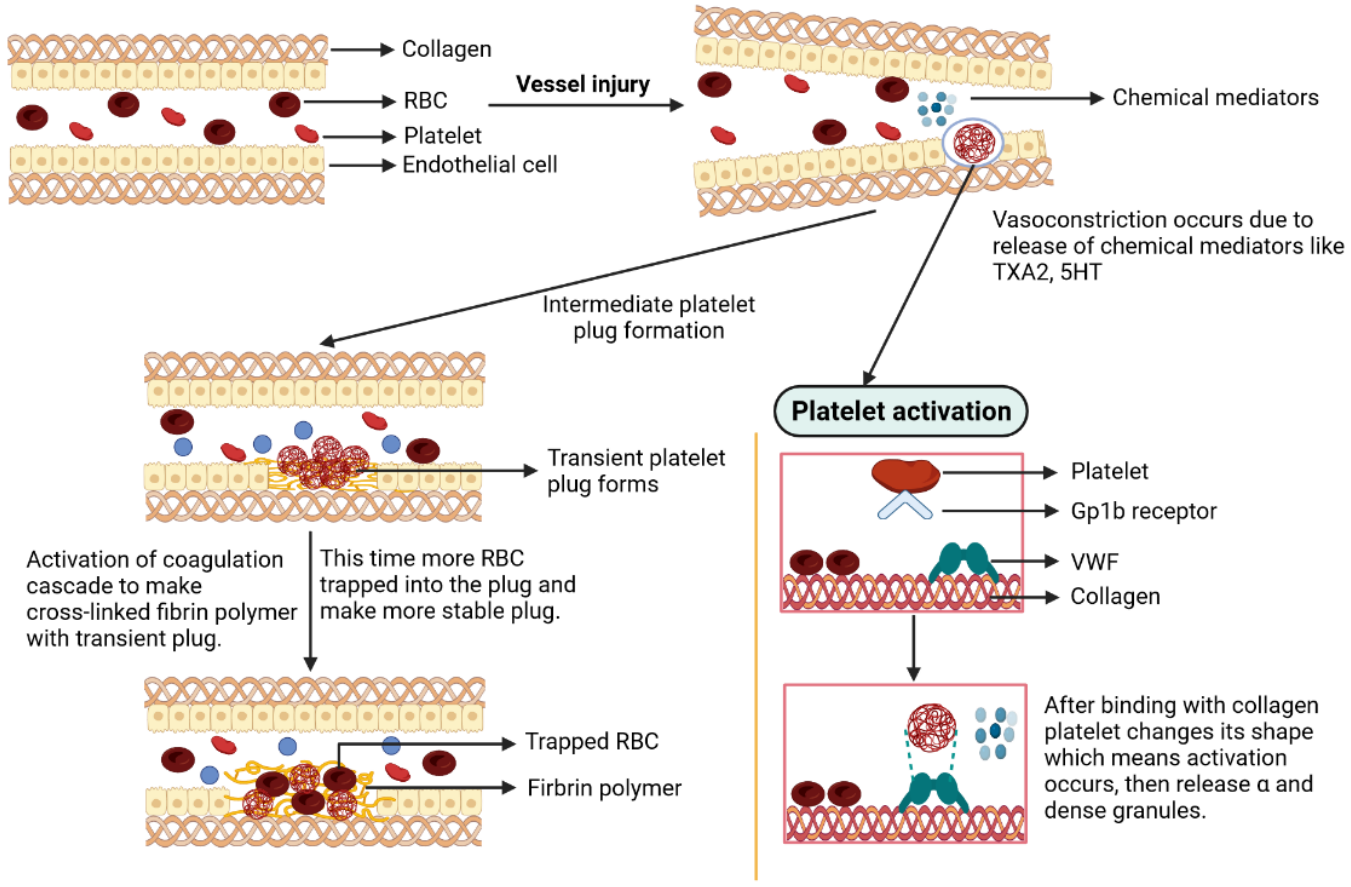

Figure 1. Mechanism of thrombus formation. RBC= red blood cell; TXA2= thromboxane A2; 5HT= 5-hydroxytryptamine receptors; VWF= von Willebrand factor.

blood cells, restricting the blood flow in the artery or breaking off and traveling elsewhere in the body, forming blockages where arteries narrow (Davì & Patrono, 2007). However, several studies asserted that natural products from both plant and animal sources could significantly contribute to treating cardiovascular diseases. For instance, orientin, resveratrol, tea polyphenols, curcumin, and allicin, are well-known bioactive compounds isolated from various natural extracts. These promising natural compounds defend against various cardiovascular diseases through their lipid-lowering potentials via the minimization of oxidative stress (C. Li et al., 2019; Lu et al., 2012; Yang et al., 2014; Yokozawa et al., 2002) . It has been reported that a combinational treatment of Coelatura aegyptiaca extract and lipid-lowering drug atorvastatin increased hypolipidemic efficacy and minimized the undesirable adverse effects of the drug (Mohamed et al., 2019) . On the other hand, various bioactive compounds of animal origin also play a significant role in reducing cholesterol levels. For instance, in common dietary products, L-carnitine, including fish, meat, and milk, reduces oxidized low-density lipoprotein (LDL) cholesterol levels (Malaguarnera et al., 2009). Choline is another important nutrient widely distributed in various food items, including fruits, vegetables, fish, meat, eggs, and dairy products. Studies reported that this auspicious natural compound plays a remarkable role in lipid regulation and cholesterol metabolism (Rajabi et al., 2014; Sivanesan et al., 2018). Teprotide is a simple nonapeptide that was isolated from the venom of Bothrops jararaca viper and was the lead compound to develop anti-hypertensive medications named captopril and cilazapril (Herzig et al., 2020).

4. CURRENT THERAPIES FOR THE TREATMENT OF THROMBOSIS IN CARDIOVASCULAR DISORDER

Thrombosis, described as localized blood clotting in the arterial or venous circulation, has had a severe medical effect on global public health. MI or heart attack is the most major consequence of arterial thrombosis, and approximately 80% of strokes result from arterial thrombosis; these two collectively become a vital threat for the developed world population. On the other hand, venous thromboembolism occurs as the third major cause of death due to CVDs (Mackman, 2008). Various treatment strategies are available against thrombus-

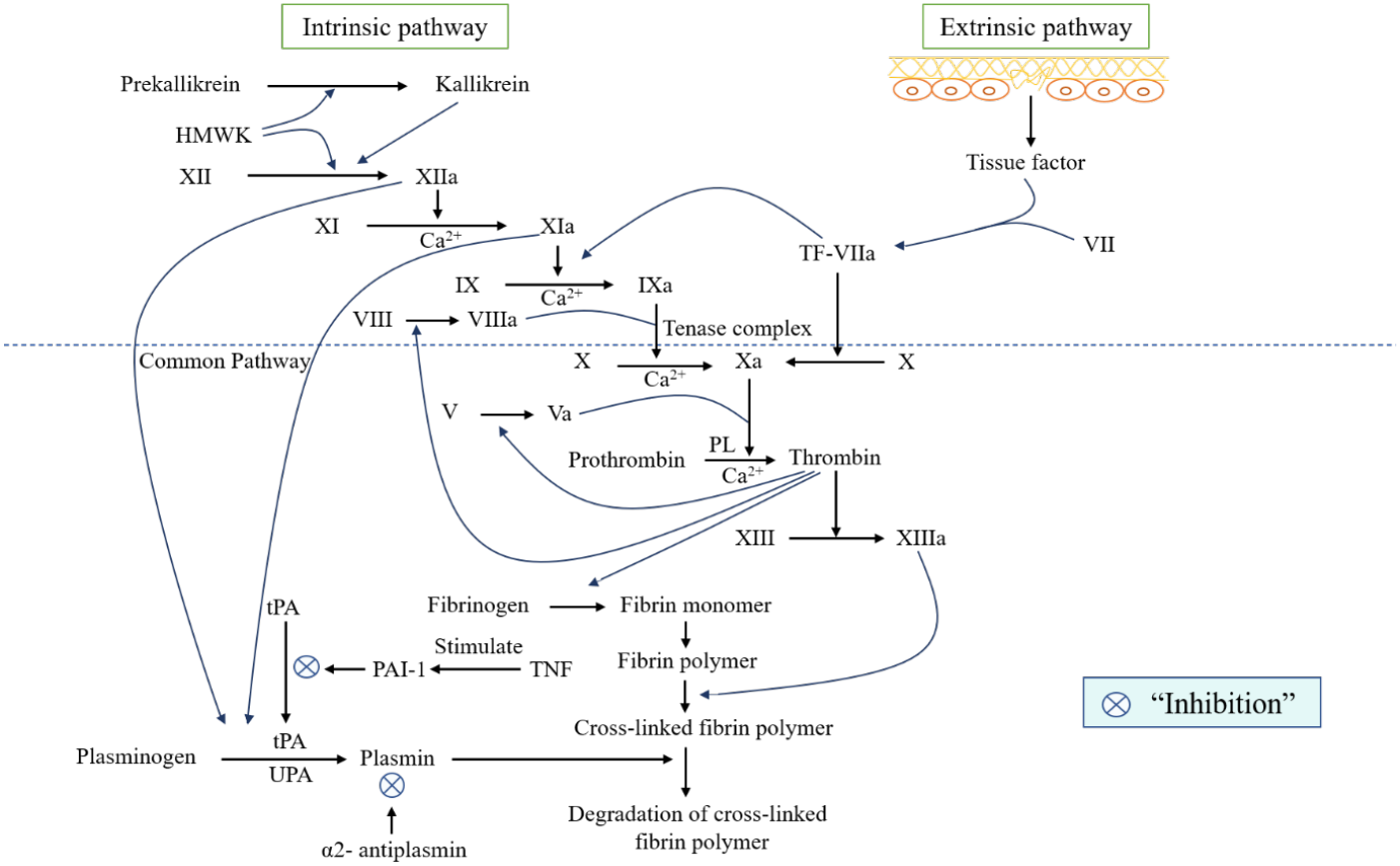

Figure 2. Schematic representation of intrinsic and extrinsic pathway of the coagulation cascade and the fibrinolytic system. HMWK= high molecular weight kininogen; tPA= tissue plasminogen activator; TNF= tumor necrosis factor; PAI-1= plasminogen activator inhibitor-1;uPA: Urokinase plasminogen activator.

induced CVDs with various mechanisms of action. Antiplatelet drug therapies are administered to reduce thrombus formation in patients present with acute thrombotic events, demonstrating their action by disrupting the platelet function in normal blood clotting and interfering with platelet aggregation and activation, further increasing the risk of bleeding episodes Meadows and Bhatt (2007). Administration of glycoprotein IIB (GPIIB)–GPIIIA, specifically αIIbβ3-integrin, which is a platelet integrin complex, as a short-term treatment strategy for patients with acute coronary syndromes who are experiencing percutaneous coronary intervention, has been believed to suppress platelet aggregation through encumbering the binding of activated platelets to fibrinogen as well as other ligands (Kong et al., 1998). ADP receptor P2Y12 is another important target of antiplatelet drugs to reduce platelet aggregation and activation. Ticlopidine, clopidogrel, and prasugrel are the most commonly used antiplatelet drugs that antagonize the P2Y12 receptor to inhibit platelet aggregation (Gachet, 2005; Mackman, 2008). Platelet cyclooxygenase 1 (COX1) inhibitors suppress the synthesis of TXA2, which is recognized as a potent activator of platelet, and through this kind of inhibition, aspirin produces antiplatelet action (Hennekens et al., 2006). Patients with atrial fibrillation generally administer anticoagulant therapy to protect against venous thromboembolism and long-term ischemic stroke. These drugs generally target a coagulation cascade to exert anticoagulant action. Warfarin, and rivaroxaban, are used as an anticoagulant to prevent venous thromboembolism (Mackman, 2008; Weitz & Linkins, 2007). Apart from all these established therapies, several new antithrombotic drugs are in the developmental stage, and research is ongoing to evaluate their safety and efficacy. For instance, terutroban and picotamide are two new antiplatelet drugs that inhibit platelet aggregation by antagonizing the TXA2 receptor. Vorapaxar and atopaxar induce antiplatelet action by inhibiting protease-activated receptor-1 (PAR-1). Various new anticoagulants, including tifacogin, pegnivacogin, idraparinux, idrabiotaparinux, semuloparin, recomodulin, solulin, pegmusirudin, and odiparcil are also in developmental stage to facilitate the treatment strategy of thrombotic disorders more promptly (Bivard et al., 2013).

5. CURRENTLY USED ANTITHROMBOTIC DRUGS AND THEIR POTENTIAL SIDE EFFECTS

Several classes of drugs are currently prescribed to manage thrombosis-induced cardiovascular diseases. But, most of them are associated with various side effects, including abnormal

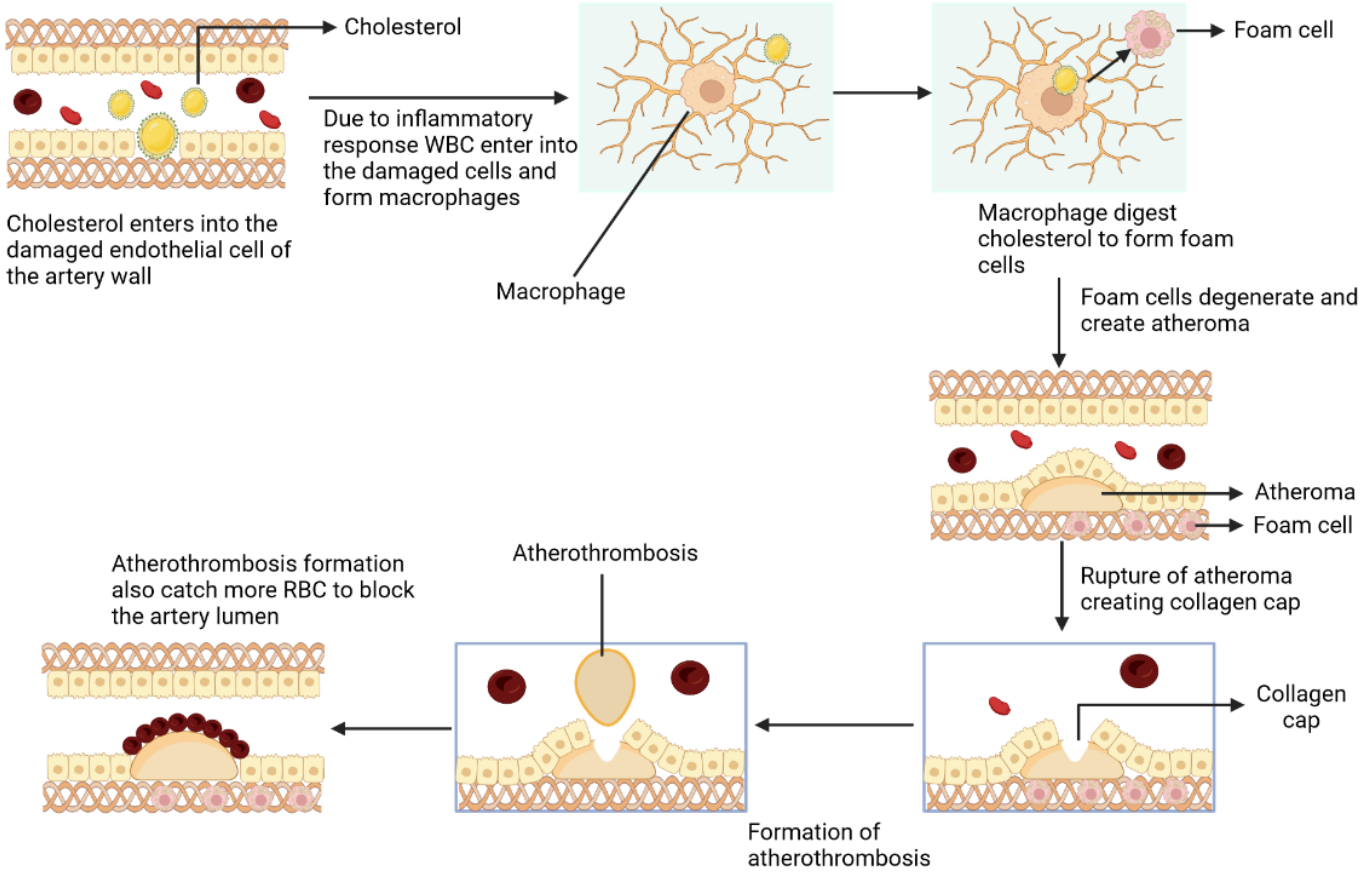

Figure 3. The mechanism of the formation of atherothrombosis.

bleeding events, gastrointestinal problems, low blood platelet count, kidney problems, and so on (Figure 4). Antiplatelet medications hold back the formation central to arterial thrombus formation and therefore be an important therapy to manage cardiovascular diseases. Among the drugs of this class, clopidogrel is in the first market race. This drug irreversibly put a stop to binding ADP to its platelet receptors. ADP is responsible for activating the GP IIb/IIIa complex, the central fibrinogen receptor for platelet aggregation. Thereby, blockade of ADP receptors stands in the way of platelet activation, which further inhibits platelet activation. ADP receptor blockers demonstrated a wide range of variability in clinical outcomes due to their unstable binding characteristics. As a result, prasugrel takes the place of clopidogrel utilizing its more predictable binding characteristics. The higher binding affinity of this drug increases the bleeding episode and is consequently enforced to treat individuals with a higher risk of acute coronary syndrome who are going through percutaneous coronary intervention (Stern & Lebowitz, 2010). To solve this acute problem, ticagrelor is being studied as the first reversible oral ADP antagonist, a specific inhibitor of the P2Y12 receptor on platelets, a crucial target receptor for ADP. A study reported that ticagrelor's safety and tolerability status corresponded to clopidogrel. These two drugs demonstrated the same significant bleeding profile, but a higher dose escalated the minor bleeding episode. As a reversible inhibitor of the P2Y12 receptor, ticagrelor facilitates several surgical procedures, including coronary bypass, after winding up the drug (Moons et al., 2003) . Vorapaxar or SCH 530348 is an antagonist of the protease-activated receptor (PAR)-1, the primary thrombin receptor on human platelet. Blockade of (PAR)-1 receptor inhibits thrombin-induced platelet aggregation without altering the functional activity of fibrinogen and thrombin. This drug is currently in phase III Thrombin Receptor Antagonist for Clinical Event Reduction (TRA*CER) trial to evaluate the safety and efficacy status for the treatment of acute coronary syndrome (Bonaca & Morrow, 2009; CER & The TRA● CER Executive and Steering Committees, 2009). Rivaroxaban and enoxaparin represent the direct oral inhibitor of factor Xa recommended against DVT and PE in the first instance and for managing recurrent DVT and PE. In patients with DVT or PE, rivaroxaban is safe and well-tolerated. Compared to enoxaparin-vitamin K antagonist, rivaroxaban was linked with a considerably lower rate of severe bleeding (Burness & Perry,

2014). Betrixaban (PRT054021) is another direct antagonist of factor Xa with better safety and efficacy than enoxaparin for the treatment of venous thromboembolism (VTE) after the replacement of the total knee. Currently, this drug is in Acute Medically III VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX) trial to determine its safety and efficacy (Chan et al., 2014). American and European clinical practice guidelines emphasized bringing antiplatelet drugs into play for patients with cardiovascular diseases. Proper utilization of antiplatelet drugs can drop the mortality rate of CVD. This class of drugs, especially aspirin, is considered the primary prevention of CVD. This drug inhibits platelet aggregation by blocking the generation of TXA2 in platelet (by acetylation of COX in platelets) and blocks the prostaglandin synthesis in the vascular wall, which in turn causes vasorelaxation, preserves kidney function, and diminishes platelet adhesion to the vessel wall. Apart from antiplatelet activity, aspirin also exerts a direct effect on atheroma plaque in atherosclerosis patients (Chan et al., 2014; Patrono et al., 1985; Tendera & Wojakowski, 2003). Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) suggested the daily administration of low dose aspirin (75-100 mg) over no aspirin therapy, for the patients of 50 years or more without any symptomatic cardiovascular diseases. If maintained for ten years, aspirin brings down mortality modestly regardless of cardiovascular risk profile (Vandvik et al., 2012). These guidelines also recommended therapy for secondary prevention of patients with various diseases (Table 1). A diverse class of adjuvant treatments, including indirect antithrombin agents: heparin; direct thrombin inhibitors: hirudin, argatroban; antiplatelet agents: aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab, tirofiban, and eptifibatide are used with thrombolytic agents (Table 2) (Baker, 2005). Again, heparin-induced thrombocytopenia (HIT) is one of the most important drug-induced clinical complications in hospitalized patients. HIT is an immune-mediated prothrombotic disease caused by therapy with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). HIT is performed using antibodies that bind to macromolecular complexes formed by platelet autoprotein, platelet factor 4 (PF4), and heparin (Kelton, 2002). Agents used for adjuvant therapies are also present with a diverse class of adverse effects. Although the antithrombotic drugs possess potential side effects, including bleeding episodes, these drugs are widely used with adjuvant therapy to manage thrombus-induced CVDs.

6. PATHWAYS TO UNDERSTANDING THE ANTITHROMBOTIC EFFECTS OF NATURAL COMPOUNDS FROM BOTH PLANT AND ANIMAL SOURCES

From ancient times, human civilization has been reclined on the medicinal plant to alleviate major and minor ailments; medicinal plants and plant-derived bioactive compounds have always been suitable for treating various communicable and non-communicable diseases. Since ancient times, people have primarily dependent on natural heals to cure various communicable and non-communicable diseases (Shrivastava et al., 2022). It is well established that the pharmacological activity of natural medicine is attributed to the presence of various bioactive compounds, including phenolics, flavonoids, polysaccharides, proteins, peptides, terpenes, alkaloids, and several others. Multiple lines of evidence demonstrated that plant-derived bioactive compounds gradually became the first treatment choice for impeding thrombus formation and thrombus-induced cardiovascular and cerebrovascular diseases (Shaito et al., 2020). Phenolics or phenolic compounds are recognized as secondary metabolites ubiquitously distributed in various plant species. These compounds have the same chemical structure: an aromatic ring with one or more -OH (hydroxyl) substituents. Phenolic compounds can be classified into several groups, including flavonoids, tannins, stilbenes, lignans, and phenolic acids. These compounds are most prominently distributed in medicinal plants and exert various pharmacological roles (Alu'datt et al., 2017). Flavonoids represent the largest group of phenolic compounds, composed of fifteen carbon atoms in order in three rings (C6–C3–C6) marked as A, B, and C, respectively. Flavonoids can be subdivided into various groups, including flavones, flavonols, dihydrochalcones, isoflavones, aurones, flavanones, flavanones, chalcones, flavans, anthocyanins, and proanthocyanidins based on C-ring substituents and degree of saturation (Xu et al., 2017). On the other hand, terpenes or isoprenoids represent the single largest group of essential oils, consisting of isoprene molecules where each molecule contains five carbon atoms with double bonds. Based on the number of isoprene molecules, terpenes can be classified as monoterpenes (2 isoprene molecules), sesquiterpenes (3 isoprene molecules), and diterpenes (4 isoprene molecules) (Hanuš & Hod, 2020). Alkaloids are cyclic organic compounds with heterocyclic tertiary nitrogen in the structure. But caffeine, paclitaxel, and colchicine are the exception to this definition. The molecular skeleton can classify alkaloids into various vital groups, including indole alkaloids, isoquinoline alkaloids, tropane alkaloids, steroidal alkaloids, and pyridine and pyrrolizidine alkaloids. Multiple studies proved that alkaloids isolated from medicinal plants demonstrated antiplatelet activity in different experimental models (Ain et al., 2016).

Agents against thrombus formation exert their activity through multiple mechanisms, including inhibiting platelet aggregation and thrombus formation (antiplatelet agents), preventing the coagulation system, and interfering with further plaque expansion (anticoagulants). Natural phenolics, including polyphenols and flavonoids, have demonstrated effectiveness as a preventive and alternative medicine to manage thrombus-induced cardio and cerebrovascular complications. They are reported to exhibit antiplatelet and antithrombotic action via the reduction of oxidative stress, (Ciumărnean et al., 2020; Freedman, 2008) decreases intracellular Ca2+ mobilization,(Lutz et al., 2019) inhibit platelet phospholipase C,(Hsiao et al., 2005) ameliorate intraplatelet cyclic adenosine monophosphate (cAMP) level,(Oh et al., 2012) antagonize

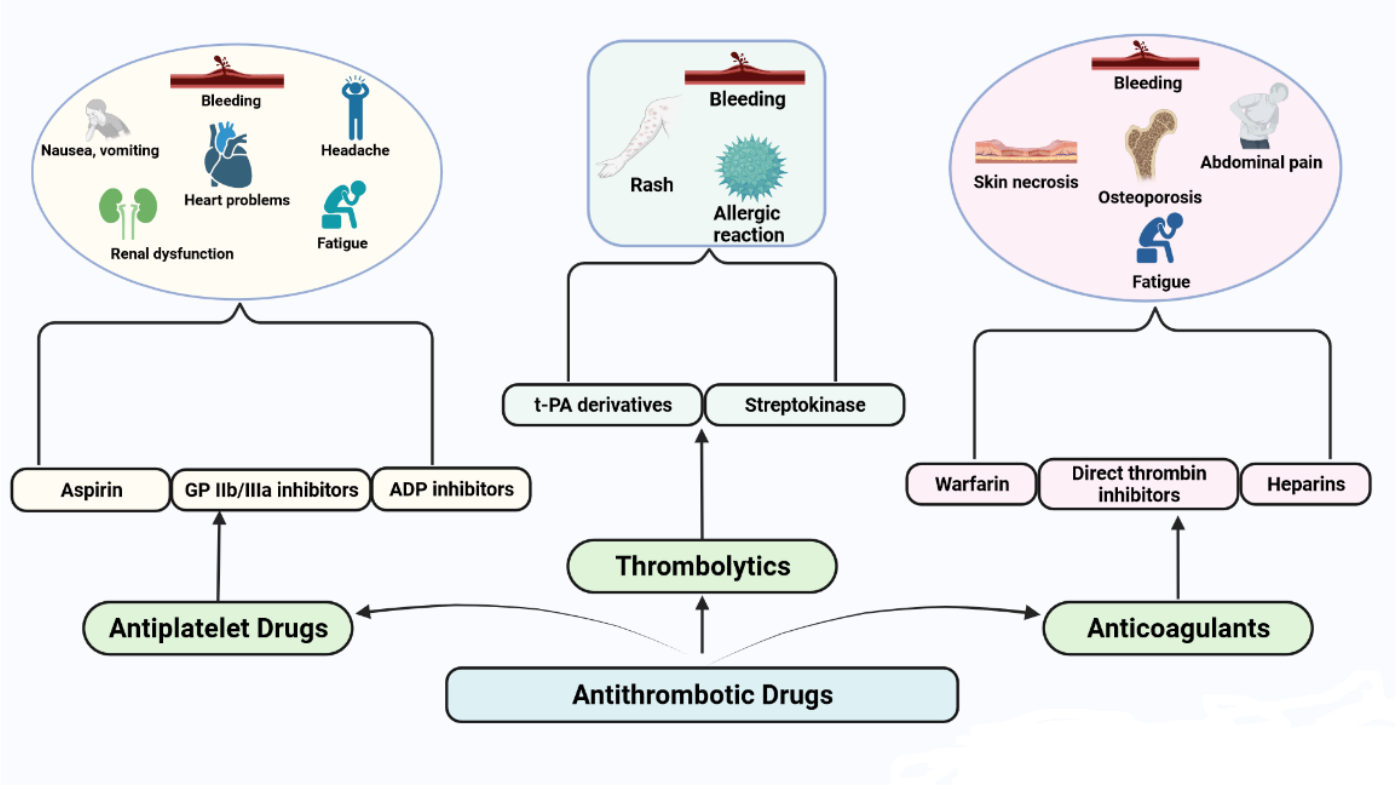

Figure 4. Common adverse effects of traditionally used antithrombotic drugs.

TXA2 receptor, (Guerrero et al., 2005) and antagonize thrombin receptor (Navarro-Núñez et al., 2008).

The generation of ROS and RNS (reactive nitrogen species) within the body promotes oxidative stress, generating various physiological consequences, including platelet hyperactivation and risk of thrombus formation. It is well established that phenolics have tremendous potential to scavenge free radicals and act as a potent antioxidants (Santhakumar et al., 2014). For instance, ascorbate or vitamin C is the best example of an antioxidant that possesses tremendous capability in scavenging ROS and reducing oxLDL (oxidized LDL) cholesterol in atherosclerotic conditions (Aguirre & May, 2008). Cinnamtannin B-1 is a proanthocyanidin isolated from bay wood that has been reported to reserve the generation of oxidants and reduce platelet aggregation in type-2 diabetic models (Bouaziz et al., 2007). Olive leaves and olive oil polyphenols demonstrate tremendous antioxidant activity through activating phospholipase C and promoting the metabolism of arachidonic acid (AA), reducing H2O2 levels. These events not only prolong atherosclerosis but also inhibit platelet aggregation (Singh et al., 2008). Grape seed extract and resveratrol (polyphenol in grape) were reported to reduce the blood platelet function by decreasing P-selectin expression, inhibiting platelet signaling pathways, and decreasing the production of superoxide anions in blood platelet (Olas et al., 2012). Therefore, quotidian consumption of phenolic-rich foods might protect against CVDs and antithrombotic action by inhibiting platelet hyperactivation or aggregation. Platelets release a spike of H2O2 in response to collagen stimulation, which stimulates phospholipase C and AA metabolism. Stimulation of AA promotes the release of prostaglandin H2 (PGH2) and TXA2, which are thought to activate the platelet intracellular signaling pathway and play a significant role in platelet activation (Figure 5). Polyphenolic antioxidants target H_2O_2 to neutralize this pernicious free radical and put a pivotal role in impeding platelet activation (Pignatelli et al., 1998; Santhakumar et al., 2014). Free radicals scavenging capacity of polyphenols impart numerous beneficial effects within the body, and it has been reported that a polyphenolic-rich diet vastly reduces cardiovascular mortality and thrombotic diseases (Massimo et al., 2004). Carnevale et al. (2012) reported that in smokers, polyphenols-rich dark chocolate down-regulates platelet ROS production, Nox2 (NADPH oxidase) activation, inhibits platelet activity by reducing the formation of platelet 8-ISO-prostaglandin F2α. Platelet 8-ISO-prostaglandin F2α is a bioactive product of AA peroxidation, responsible for enhancing platelet response to agonists through the stimulation of glycoprotein IIb-IIIa (GP IIb-IIIa) (Carnevale et al., 2012).

An increase in platelet activation dramatically raises intracellular Ca2+ to near macromolecular level and promotes the release of phospholipases Cβ and Cγ, which directly control the Ca2+ mobilization into the cytosol (Fuentes & Palomo, 2014). Various phenolic compounds, including rutin, α-naphthoflavone, obovatol, and rutaecarpine, downregulate AA. Serotonin liberation, phosphorylation of P47, and intracellular

Table 1
Therapeutic recommendation as secondary prevention of cardiovascular diseases for patients with various disease condition according to Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).

Patient's condition	Recommended therapy
Patients with established coronary artery disease (CAD) including one-year prior coronary artery bypass graft (CABG) surgery and/or post-acute coronary syndrome (ACS).	Daily aspirin 75-100 mg or clopidogrel 75 mg for long term. Single over dual antiplatelet therapy with aspirin plus clopidogrel
Patients with ACS but have not undergone percutaneous coronary intervention (PCI).	90 mg ticagrelor daily twice + daily 75-100 mg aspirin or daily 75 mg clopidogrel + daily 75-100 mg aspirin over single antiplatelet therapy. Daily 90 mg ticagrelor + low-dose aspirin over daily 75 mg clopidogrel + low-dose aspirin.
Patients with ACS and have subjected to PCI	Two times daily 90 mg ticagrelor + daily 75-100 mg aspirin, 75 mg clopidogrel daily + 75-100 mg aspirin, or 10 mg prasugrel daily + 75-100 mg aspirin over single antiplatelet therapy.
Patients with left ventricular (LV) thrombus and anterior MI or at high risk for LV thrombus who do not undergo stenting.	For the first 3 months, warfarin (INR 2.0-3.0) + daily 75 to 100 mg aspirin over single antiplatelet therapy or dual antiplatelet therapy. For up to 12 months, cessation of warfarin and keeping up of dual antiplatelet therapy. Single antiplatelet therapy is recommended after 12 months.
Patients with anterior MI and LV thrombus, or at high chance for LV thrombus who subjected to bare metal stents (BMS) placement.	For 1 month warfarin [INR 2.0-3.0], 75-100 mg aspirin, daily 75 mg clopidogrel over dual antiplatelet therapy. 2nd and 3rd month after bare metal stents (BMS) warfarin (INR 2.0-3.0) and single antiplatelet therapy over changing regimens and time frames for warfarin use. For up to 12 months cessation of warfarin and dual antiplatelet therapy. Antiplatelet therapy after 12 months.
Patients suffering from anterior MI and LV thrombus or at high jeopardy for LV thrombus who undergo drug-eluting stent (DES) placement.	For 3–6-month, warfarin [INR 2.0-3.0], 75-100 mg aspirin, daily 75 mg clopidogrel over over alternative time frame and regimens of warfarin therapy. For up to 12 months cessation of warfarin and carrying on dual antiplatelet therapy. Antiplatelet therapy after 12 months.
Patients who have Subjected to elective PCI with placement of BMS.	Daily aspirin 75-325 mg and daily 75 mg clopidogrel over single antiplatelet therapy. for the subsequent 11 months dual antiplatelet therapy composed of daily 75-100 mg aspirin and daily 75 mg clopidogrel over single antiplatelet therapy Single antiplatelet therapy is recommended over keeping up of dual antiplatelet therapy after 12 months.
Patients who have experienced elective PCI with placement of DES.	First 3-6 months, we recommend Dual antiplatelet therapy consist of 75-325 mg daily aspirin and 75 mg clopidogrel daily over single antiplatelet therapy. Then after 3-6 months, dual antiplatelet therapy is suggested with aspirin 75-100 mg and daily75 mg clopidogrel up till one year over single antiplatelet therapy. After 1-year, single antiplatelet therapy is recommended over carrying on of dual antiplatelet therapy. Thereafter, single antiplatelet therapy.
Patients who have subjected to elective BMS or DES stent placement.	Daily 75-100 mg aspirin and 75 mg clopidogrel alone rather than cilostazol in addition to these drugs. Dual antiplatelet therapy design with daily aspirin 75 to 100 mg and 75 mg clopidogrel is recommended rather than the use of either drug with cilostazol. Patients sensitive to allergy or other drugs, cilostazol 100 mg two times daily can be used as the substitute of either two drugs.
Patients suffering from CAD undergoing elective PCI but no stent placement.	Dual antiplatelet therapy design with daily 75-325 mg aspirin and 75 mg clopidogrel over single antiplatelet therapy. Thereafter, single antiplatelet therapy.
Patients with systolic LV abnormality without established and LV thrombus and CAD.	Antiplatelet therapy or warfarin recommend not to use.
Patients with systolic LV abnormality with no CAD, with identified acute LV thrombus.	For at least three months, moderate-intensity warfarin (INR 2.0-3.0) is recommended.
Patients with systolic LV abnormality and established CAD.	75-100 mg aspirin daily or 75 mg clopidogrel daily over no antiplatelet therapy is recommended for long term. Single over dual antiplatelet therapy with aspirin + clopidogrel.

Ca^{2+} mobilization through the inhibition of phospholipase C activity, PKC (protein kinase C) activation, and TXA2 formation, therefore produce antiplatelet activity (Hsiao et al., 2005; E.S. Park et al., 2011; Sheu et al., 2004). cAMP downregulates intracellular Ca2+ level in human platelet through the cAMP-dependent protein kinase a (PKA), which is involved in the inhibition of cytoskeletal reorganization (Rosado et al., 2001). cAMP exerts a modulatory role over Phospholipase C mediated secretion and human platelet aggregation Huzoor-Akbar et al. (1982). Epigallocatechin gallate (EGCG), a polyphenolic compound, raises cAMP levels in the collagen-platelet interaction, potentially preventing platelet activity and aggregation (Ok et al., 2012). Previously, we mentioned that TXA2 is produced as a sequential result of AA metabolism. Upon activation with the help of agonists like ADP, thrombin, and collagen, TXA2 acts as a potent unstable inducer of platelet aggregation and activation. After vascular damage, TXA2 recruits and activates surrounding platelets of the vascular damage site (Arita et al., 1989). So, inhibition of the TXA2 receptor can be an excellent therapeutic approach against

Table 2
List of drugs for the treatment of thrombosis in cardiovascular disorder and their adverse effects.

Drug name	Mechanism of action	Dose with dosage regimen	Side effects	Toxicity	References
Aspirin	Through irreversible acetylation of COX 1 Ser529 protein.	Adult dose: 75-300 mg daily Child dose: 60-100 mg orally.	Heartburn, bleeding, digestion complications.	Hyperventilation, dehydration, fever, double vision, and feeling faint.	C. Li et al. (2019); Stern and Lebowitz (2010)
Ticlopidine	Through irreversible suppression of P2Y12 receptor.	Adult dose: 250 mg two times daily for coronary artery stent thrombosis.	Bleeding, indigestion, heartburn, rash, neutropenia, TTP (thrombotic thrombocytopenic purpura).	Aplastic anaemia, agranulocytosis which can be accompanied by liver laceration.	Michelson (2008); Quinn and Fitzgerald (1999)
Clopidogrel	Through irreversible suppression of P2Y12 receptor.	Adult dose: 75mg daily orally.	Bleeding, rash, neutropenia and in rare case TTP.	Prostration, difficult breathing, and gastrointestinal haemorrhage in animals.	Balamuthusamy and Arora (2007); Michelson (2008); Quinn and Fitzgerald (1999)
Prasugrel	The active metabolite irreversibly inhibits the P2Y12 receptor	Adult dose: 10 mg daily orally.	Heartburn, indigestion, nausea, vomiting.	Gastrointestinal bleeding and thrombocytopenia.	Jakubowski et al. (2007); Nanau et al. (2014)
Abciximab	Integrin αIIbβ3 antagonist	Adult dose: injection solution 2mg/ml 0.125 μg/kg/min once via IV for unstable angina.	Heartburn, indigestion, nausea, vomiting.	Gastrointestinal bleeding and thrombocytopenia	Coller (1997); Mukherjee and Roffi (2008)
Eptifibatide	Integrin αIIbβ3 antagonist.	Adult dose: injection solution 2 mg/ml or 0.75 mg/ml once (180μg/kg) via IV for the acute coronary syndrome.	Bleeding, pseudo thrombocytopenia, hypotension.	Renal insufficiency, increase the risk of bleeding and heart failure.	Hongo and Brent (2001); O'shea et al. (2001)
Dipyridamole	Through the inhibition of adenosine uptake and cyclic nucleotide phosphodiesterase.	The adult dose: 75-100 mg two or three times orally.	Hypotension and inconsistent blood pressure, dizziness, flushing, diarrhea and abdominal discomfort, headache, rash etc.	Increases the risk of bleeding.	Henzlova et al. (2016); S. Lee et al. (2017); W. Lee et al. (2017); Patrono et al. (2008)
Cilostazol	Through the inhibition of adenosine uptake and cyclic nucleotide phosphodiesterase 3.	The adult dose: 100 mg twice daily orally.	Bleeding, headache, diarrhea, palpitations, dizziness, rash, pancytopenia	Severe hypotension, tachycardia, and possibly cardiac arrhythmia	Ahmad et al. (2012); Rogers et al. (2015)
Warfarin	Abolish the synthesis of active clotting factors through the inhibition of VKORC1 (vitamin K epoxide reductase complex 1).	Depends on guidelines; usually 5 mg per day.	Haemorrhage and bleeding, abdominal discomforts, flatulence, bloating, skin necrosis and altered sense of taste.	Increases the risk of bleeding.	Kuruvilla and Gurk-Turner (2001); Teles et al. (2012)
Rivaroxaban	Inhibits Factor Xa through reversible and direct binding with Factor Xa via the S1 and S4 pockets.	Adult dose: 10/20 mg orally once daily.	Haemorrhage, dizziness, insomnia, fatigue, depression, anxiety, abdominal pain.	Bleeding episode.	Kreutz (2012); Perzborn et al. (2010)
Heparin	Inhibits the FXa and thrombin in the coagulation cascade, thereby suppress the transformation of fibrinogen to fibrin.	Adult dose: 5,000-10,000 units every 4-6 hours (intravenous injection)	Bleeding, thrombocytopenia. Chronic use of aspirin generates osteoporosis and osteopenia.	Severe bleeding episodes.	Mulloy et al. (2015)
Ticagrelor	Through antagonism of P2Y12 receptor.	50 mg twice/day, 100 mg twice/day, 200 mg twice/day, or 400 mg/day	Bleeding, dyspnea, increase in ventricular pauses,	Risk of severe bleeding.	Dobesh and Oestreich (2014)

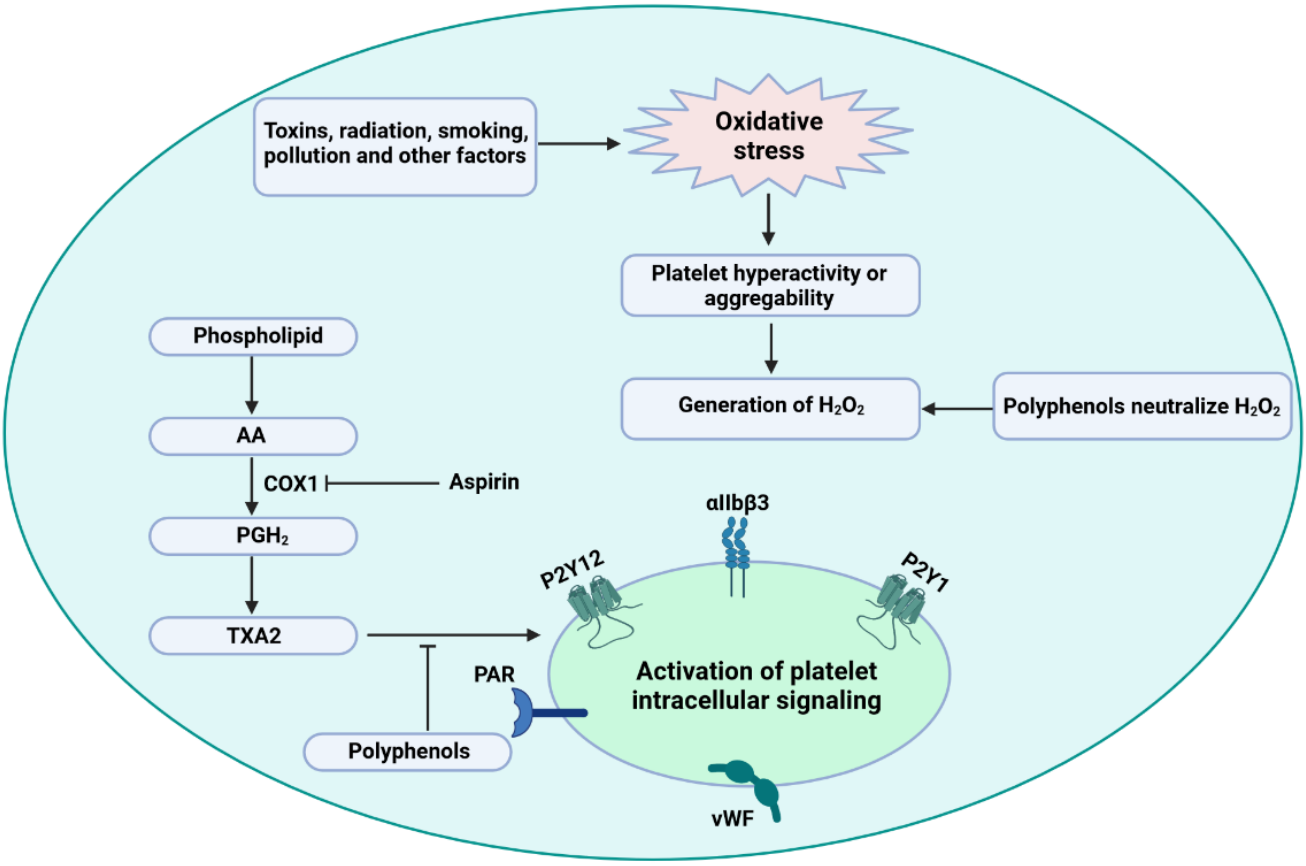

Figure 5. Dietary polyphenols inhibit oxidative stress-induced platelet aggregation through impeding H_2O_2 generation and activation of platelet intracellular signaling. AA= arachidonic acid; PGH_2= prostaglandin H_2; TXA2= thromboxane A2; COX1= cyclooxygenase 1; PAR= protease-activated receptor; VWF= von Willebrand factor.

thrombus-induced physiological consequences. A diverse class of flavonoids says genistein, apigenin, and luteolin inhibit collagen and ADP-induced platelet activation; reduce the extent of TXA2 secretion in collagen and ADP-stimulated platelets through binding with TXA2 receptor. It can be simplified that genistein, apigenin, and luteolin antagonize TXA2 receptors and inhibit platelet aggregation and activation Guerrero et al. (2005). Berberine and clausine-D alkaloids were reported to produce antiplatelet action through inhibiting ADP, AA, and collagen-induced TXA2 generation (Ain et al., 2016). Thrombin is an enzyme derived from the family of serine protease, known as active plasma coagulation factor II. It is a critical enzyme that regulates the second phase of the blood coagulation cascade by generating TF-bearing cells (responsible for blood platelet activation) and stimulating other plasma coagulation factors, including FXI and FVIII FV on the platelet's surface. Recently, a study conducted on eleven isoquinoline alkaloids revealed seven of them: jatrorrhizine, 8-trichloromethyl-dihydroberberine, berberine, acetonyl-berberine, palmatine, L tetrahydropalmatine, and L-corydalmine significantly inhibited the activity of TF. Further, berberine, L-corydalmine, L tetrahydropalmatine, and jatrorrhizine also stably bonded with the active site of the TF/FVIIa complex in the molecular docking study, which validates their potentiality in the treatment of cardiovascular diseases (He et al., 2021). So, agents that can inhibit thrombin from binding to thrombin receptors can be a lead compound for developing antithrombotic drug therapy. Various phenolics like silybin, cyanidin, (+) catechin quercetin, cyanin, and (-) epicatechin can directly inhibit thrombin amidolytic activity or change the proteolytic activity of thrombin (Bijak et al., 2014).

Plant-derived proteins, peptides, and polysaccharides produce antithrombic effects through several mechanisms. Peptides from a stable thrombin-antithrombin complex and the active site of peptide slow down the thrombin and fibrinogen activity, where fibrinogen is transformed into fiber protein to achieve the antithrombotic activity. It has been reported that three protein fractions (water-, salt- and acid-soluble) of *Mytilus edulis* showed antithrombotic efficacy in both *in vitro* and *in-silico* studies (Figure 6) (Qiao et al., 2018). Polysaccharides have been described as the most therapeutically investigated metabolites, and isolation of polysaccharides from natural sources may become an excellent approach for developing new and orally effective antithrombotic therapies; piquing the

interest of researchers looking to develop new antithrombotic therapies from natural polysaccharides. It has been reported that polysaccharides from natural sources, especially marine-derived polysaccharides, demonstrate tremendous potential through several mechanisms, including; enhancement of thrombin time (TT) and activated partial thromboplastin time (APTT), reduction of PAI-1 level, inhibition of thrombin and FXa activity, inhibition of thrombus formation, and inhibition of platelet aggregation (Figure 6). Prolongation of APTT occurs due to the scarcity of factors VIII, IX, XI, XII, and V or Willebrand's factors. On the other hand, prolonging prothrombin time (PT) represents the extrinsic coagulation pathway and occurs due to the lack of coagulation factors like V, VII, and X. However, polysaccharides isolated from various species of sea cucumber including *Cucumaria frondosa*, *Cucumaria japonica*, and *Massinium magnum*, brown algae including *Sargassum aquifolium*, and *Hormophysa cuneiformis*; sea urchin including *Echinometra lucunter*, and *Strongylocentrotus franciscanus*, showed antithrombotic activity in the various experimental setup (Carvalhal et al., 2019).

Apart from medicinal plants, animal sources like snake venoms, leeches, and bats' saliva are also enriched with antithrombotic compounds, which proved their potentiality in the various experimental set up with similar mechanisms to other antithrombotic therapeutics (Figure 6). Species of leeches cover most animal-derived antithrombotic bioactive compounds, and some of them are under investigation as pharmaceutical drugs. For instance, decorsin is a polypeptide isolated from the *Macrobdella decora* leech, acting as a platelet aggression inhibitor by potentially blocking the activity of glycoprotein IIb-IIIa (Table 3). This leech-derived peptide is under the investigation of Genentech, South San Francisco, California, the United States, as a pharmaceutical drug (Sawyer, 1991).

6.1. *In vitro* and *in vivo* antithrombotic investigation of different plant extracts

Research is still searching for safe compounds to treat thrombus-induced cardiovascular and cerebrovascular disorders. Medicinal plants extract from diverse families, and their active metabolites gradually become potential candidates for this purpose. They have been reported to produce a significant antithrombotic effect in various experimental models or produce a synergistic impact without major episodes of adverse effects when administered in combination with traditional drugs. For instance, *Rhus verniciflua* Stokes belongs to the family of Anacardiaceae and is well recognized for its antiplatelet activity. The active compounds (Fisetin, Butein, and Sulfuretin) were isolated from the bark of this auspicious plant; among them, Fisetin inhibited platelet aggregation by preventing collagen-induced ERK (extracellular signal-regulated kinase) and MAPK (mitogen-activated protein kinase) activation (J.H. Lee et al., 2014). *Ginkgo biloba* L. under the family Ginkgoaceae is one of the most widely used commercial medicinal plants, various parts of this plant have been included in ancient herbal medicine.

Flavonoid glycosides (kaempferol, quercetin, and isorhamnetin), biflavones, terpenoids (ginkgolides and bilobalides), and various organic acids are the active phytoconstituents of this plant which are strongly involved in various pharmacological activities (Shaito et al., 2020). Studies reported that different doses of *G. biloba* L. extract could potentiate the effect of cilostazol; a combination of these two can more efficiently inhibit platelet aggregation without increasing side effects (Ryu et al., 2009). Polyphenols, monoterpenes, flavones, flavonoids, and polyphenolic polysaccharide conjugates are the most active constituents of the medicinal plants belonging to various families. *Crataegus pinnatifida* Bge (Hawthorn), *Rubus chingii* Hu, *Chaenomeles sinensis* (Thunb.) Koehne, *Filipendula ulmaria* L., *Rubus plicatus* W. et N. *Fragaria vesca* L., are several major species of the Rosaceae family showing antithrombotic activity by various mechanisms.

Kaempferol, quercetin, polysaccharides, and polyphenolics are the leading active players responsible for platelet aggregation or anticoagulation activity (Han et al., 2012; Pawlaczyk et al., 2009). Asteraceae is another affluent plant family with antithrombotic activity. It has been reported that *Erigeron canadensis* L. is a rich source of polyphenolic-polysaccharide conjugates, which produce antiplatelet and anticoagulant effects through AA-induced cyclooxygenase pathway as well as by inhibiting thrombin and factor Xa activation (Pawlaczyk et al., 2011). Flowering parts of *Solidago virgaurea* L., *Echinacea purpurea* L. Moench. and *Arnica montana* L., are exuberant with various polysaccharides, monosaccharides (Rha, Ara, Man, Glc, Gal), and polyphenolics. These plants have been reported to completely inhibit plasma clot formation in APTT study models at a low concentration, proving the anticoagulation evidence in favor of these plants (Pawlaczyk et al., 2009). *Leonotis leonurus* L. from the Lamiaceae family and its isolated active compound Marrubiin showed anticoagulant action by increasing APTT and suppressing platelet aggregation, inflammatory markers, and coagulation markers in various *in vitro* and *in vivo* study models. Both plant extract and its active compound dose-dependently reduce protein secretion, intracellular Ca2+ mobilization, platelet adhesion, fibrin formation, and inhibit thromboxane B2 (TXB2) generation (Mnonopi et al., 2011). Active compounds of *Thymus vulgaris* L. and three different extracts of various parts of *Salvia deserta* Schang produced antiplatelet aggregation effects in the different experimental setups Kasimu et al. (2018); Okazaki et al. (2002). Numerous medicinal plants and plant-derived bioactive compounds derived from Poaceae, Cucurbitaceae, Araliaceae, Euphorbiaceae, Apiaceae, and Piperaceae families have also been reported to produce thrombus-induced cardioprotective activity by various mechanisms (Emon et al., 2021; Félix-Silva et al., 2014; Gadi et al., 2009; K.H. Kim et al., 2008; C.T. Li et al., 2013; Osoniyi & Onajobi, 2003; Rajput et al., 2014; Song et al., 2011; Yogeswari et al., 2020). Table 4 and Table 5 represent the antithrombotic activity of different plant extracts in the experiment set up with their possible mechanism of action.

Table 3
List of antithrombotic natural compounds isolated from various animal sources with their possible mechanisms.

Name	Source	Anti-thrombotic mechanism	References
Lufaxin	Saliva of *Lutzomyia longipalpis* fly	Inhibitor of factor Xa (FXa). Stop up prothrombinase. Enhance PT and APT.	Collin et al. (2012)
Tick anticoagulant peptide	*Ornithodoros moubata* soft tick extract	Produce anticoagulant effect through inhibiting factor Xa.	Waxman et al. (1990)
Hirudin, Antistasin, Ghilanten	Leeches	Produce anticoagulant effect through inhibiting factor Xa.	Sawyer (1991)
Decorsin	Leech (*Macrobdella decora*)	Inhibit platelet aggression through antagonizing glycoprotein IIb/IIIa.	Sawyer (1991)
Anticoagulant peptide	*Ancylostoma caninum*	Inhibit factor Xa and produce anticoagulation effect.	Cappellott et al. (1995)
Haemadin Thromin	*Haemadipsa sylvestri*, *Theromyzon tessulatum*	Generate anticoagulation through inhibiting thrombin.	Salzet et al. (2000); Strube et al. (1993)
Dipetalogastin	*Dipetalogaster maximus*	Inhibit thrombin and extend cloting time.	Mende et al. (1999)
Rhodniin Infestin Brasiliensin	*Rhodnius prolixus*, *Triatoma infestans*, *Triatoma brasiliensis*	Thrombin specific anticoagulation effect.	Araujo et al. (2007); Campos et al. (2002); Friedrich et al. (1993)
Peptides	*Glossina morsitans* morsitans	Suppress tsetse thrombin.	Cappello et al. (1998)
Thrombostasin Savignin Amblin	*Haematobia irritans*, *Ornithodoros savignyi*, *Amblyomma hebraeum*	Inhibit thrombin induced blood coagulation.	Lai et al. (2004); Nienaber et al. (1999); D. Zhang et al. (2002)
Proteins	*Boophilus microplus*	Inhibit thrombin induced platelet aggregation. Inhibit both intrinsic and extrinsic coagulation pathways.	Horn et al. (2000)
Bothrojaracin	*Bothrops jararaca*	Suppress the secretion and aggregation of platelet.	Zingali et al. (1993)
ACH-11 peptide	*Agkistrodon acutus* Venom	Suppress ADP induced platelet aggregation. Block the catalytic role of FXa	M. Chen et al. (2015)

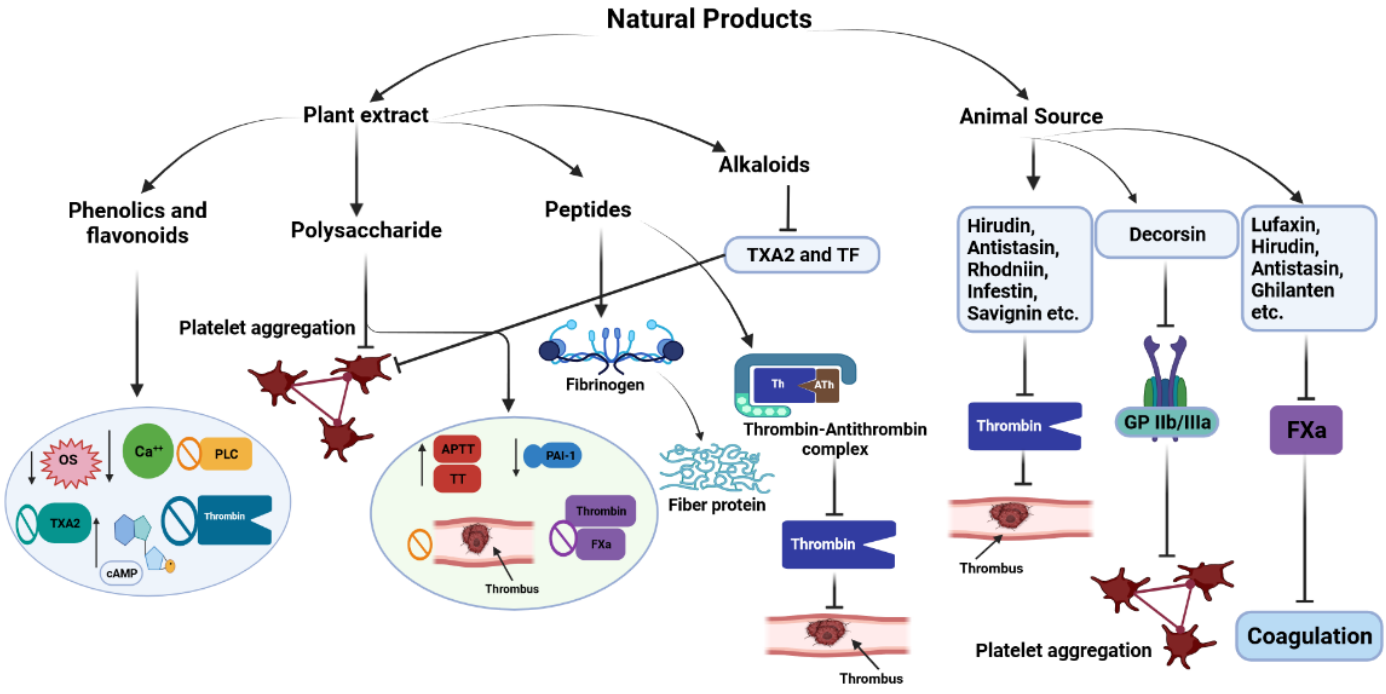

Figure 6. Antithrombotic mechanisms of various bioactive natural compounds from both plant and animal sources. cAMP= cyclic adenosine monophosphate; TXA2= thromboxane A2; OS= oxidative stress; TF= tissue factor; TT= thrombin time; APTT= activated partial thromboplastin time; PAI-1= plasminogen activator inhibitor-1;FXa= factor Xa.

Table 4
In vitro investigation of plants and natural medicinal compounds extract for antithrombotic effects.

Name	Medicinal uses	Active compounds	Name of the extract and dose or conc. used	Experimental setup	Results	Possible mechanism of action	References
Celastrus orbiculatus Thunb	To assuage pain, improve blood circulation, allay excitement, and used as tranquilizer.	Kaempferol, quercetin, kaempferol-3-O-α-L rhamnoside, kaempferol-7-O-α-L-rhamnopyranoside, etc.	NST-50 (an effective fraction of C. orbiculatus); Dose: 21.4, 42.9 and 85.7 mg/mL.	Fresh blood was collected from rats and platelet aggregation was determined.	42.9 mg/ml dose significantly inhibited platelet aggregation.	Prolong plasma recalcification time (PRT), APTT and TT. Abolish TXB2 while upregulate 6-keto-PGF1α.	J. Zhou et al. (2019)
Spatholobus suberectus Dunn	To improve blood circulation, and treat various blood diseases.	Vanillic acid, daidzein, and genistein	Ethanol extract; Dose: 50, 100, 200, and 400 μg/mL	Human platelet-rich plasma (PRP) was collected and platelet aggregation was measured.	400 μg/mL dose inhibited platelet aggregation.	Prolong the plasma clotting times, APTT and PT. Inhibit platelet aggregation. Inhibit fibrinogen binding to GP IIb/IIIa receptor.	B.J. Lee et al. (2011)
Radix Paeoniae Rubra	To treat blood stasis, to relieve pain, and to clear pathogenic heat from blood.	Albiflorin, paeoniflorin, benzoyl paeoniflorin, oxypaeoniflora, protocatechuic acid, and pentagalloylglcose.	Ethanolic, petroleum ether, ethyl acetate, and n-butanol extract; Dose: 25 L	Blood was collected from rabbit's auricular vein and coagulation time was measured.	All extract prolonged APTT, PT, and TT.	Produce antithrombotic effect through regulating TXA2 and PGI_2.	Xie et al. (2017)
Artemisia princeps Pampanini	To treat irregular uterine bleeding, colic, and diarrhea.	Jaceosidin, eupatilin, vitamins, minerals, and essential oils, etc.	Subcritical water extract; Dose: 10 μL	Blood sample was collected form healthy volunteer and antithrombotic effect was determined with a four-channel coagulometer.	The extract prolonged PT and APTT, also delayed blood coagulation time.	Block ICAM-1 and VCAM-1 at the transcriptional level. Interfere with the blood clotting factors.	K.J. Kim et al. (2019)
Fagonia Arabica L. (Dhamasa)	Used for cancer treatment, and in liver empowerment.	Flavonoids, saponin, tannin, carbohydrate, triterpenoids, monosaccharide, and reducing sugar.	Multisolvent Extract; Dose: 1, 2, 3, 4, 5, 10, 20 mg/mL.	Plasma was separated from human blood and anticoagulant activity was determined.	Aqueous extract at 20 mg/mL dose increased the time of clot formation.	Increase PRT. Phytochemicals might interfere with the extrinsic and intrinsic coagulation pathways.	Chourasia et al. (2014); Prasad et al. (2007)

Table 5
In vivo investigation of plants and natural medicinal compounds extract for antithrombotic effects.

Name	Medicinal uses	Active compounds	Name of the extract and dose or conc. used	Experimental setup	Results	Possible mechanism of action	References
Vitis labrusca L.	Used as neuroprotective, hepatoprotective, cardioprotective, renal-protective, and anticarcinogenic.	Quercetin, rutin, and isorhamnetin.	Ethanol and acetic acid extract; Dose: 10, 30, 100 mg/kg	Male Sprague Dawley rat tail bleeding model.	100 mg/kg dose increased bleeding time.	Suppress platelet aggregation. Generate antiplatelet activity via the downregulation of TXB2, and serotonin.	Kwon et al. (2016)
Ziziphus jujuba Mill.	To promote blood circulation and prolong sleep duration.	Jujuboside A and Jujuboside B.	Ethanolic extract; Dose: 30, 100 and 300 mg/kg	Mouse tail bleeding time and acute pulmonary thromboembolism model.	300 mg/kg dose prolonged bleeding time and protected against a thromboembolism attack.	Jujuboside B inhibits collagen-induced TXA2 production. Jujuboside B inhibits platelet aggregation.	Seo et al. (2013)
Eruca sativa Mill. Leaves	Used as anti-secretory, anti-inflammatory, cytoprotective, anti-ulcer, and to lessen the risk of CVDs.	Quercetin, kaempferol, and isorhamnetin-3,4 diglucoside.	Aqueous extract; Dose: 200 mg/kg	Murine thrombosis model and mouse tail bleeding time model.	200 mg/kg extract prolonged vessel occlusion and decreased maximum occlusion.	Inhibit various platelet inflammatory mediators (TGF-β1, IL-1β and CCL5). Inhibit NF-κB activation.	Fuentes et al. (2014)
Gardenia jasminoides J. Ellis	To treat hypertension and hepatic disorders, jaundice, fever, inflammation, and headaches.	Geniposide, aglycone genipin.	Ethanolic extract; Dose: 67, 133 and 266 mg/kg	Mouse tail thrombosis model induced by carrageenan, and arteriovenous shunt model on rat.	133 and 266 mg/kg markedly inhibited thrombosis and thrombus formation in both models.	Inhibit platelet aggregation. Geniposide and genipin inhibit thrombin stimulated VWF release and translocation of P-selectin.	H.Y. Zhang et al. (2013)

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Table 5 continued

Ophiopogon japonicus (Thunb.) Ker Gawl.	Used to abolish blood glucose levels and to treat diabetes, cancer, and inflammation.	Ruscogenin, cordycepin and ophiopogonin.	Fermented extract; Dose: 2, 6 and 12 mg/kg	Carrageenan-induced thrombosis model.	6 and 12 mg/kg produced a significant antithrombotic effect.	Increase clotting and bleeding times. Increases PT, APTT.	Y.L. Zhang et al. (2017)
Dendropanax morbifera Leveille	To ameliorate blood circulation.	Rutin and other phenolic and flavonoid compounds.	Fermented extract; Dose: Different dose for different model.	$FeCl_3$ stimulated arterial thrombosis model and thrombin-induced acute thromboembolism model.	200 mg/kg dose showed 40.67% inhibition of occlusion, on the other hand 100 mg/kg dose reduced the no. of paralyzed or dead occurrence.	Inhibit fibrin clot. Inhibit pro-coagulation factor FXa. Prolong APTT and PT through the inhibition of common coagulation factor XIII.	Choi and Kim (2019)
Campomanesia xanthocarpa (Mart.) O. Berg	To treat inflammatory diseases and hypercholesterolemia.	Tannins and flavonoids (rutin, myricetin, quercetin and quercitrin.).	Aqueous extract; Dose: 10, 30 and 100 mg/kg	Mouse tail bleeding and acute pulmonary thromboembolism model.	100 mg/kg extract significantly increased blood loss from the tail and provided 80% protection from being paralyzed.	Inhibit platelet aggregation and promotes fibrinolytic activity. Prolong APTT.	Klafke et al. (2012)
Salvia miltiorrhiza Bunge (Danshen)	To treat hypertension, stroke, atherosclerosis, and hyperlipidemia.	Tanshinones, including cryptotanshione, dihydrotanshinone I, tanshinone I, tanshinone IIA, and tanshinone IIB.	Supercritical CO2 extract; Dose: 7.5, 15 and 30 mg/kg.	Arteriovenous shunt thrombosis, ADP induced pulmonary thromboembolism model, tail cutting bleeding time, and rat platelet aggregation test.	Treatment with extract reduced both dry and wet weight of thrombosis, reduced recovery time of pulmonary embolism. 30 mg/kg dose inhibit platelet aggregation and prolonged bleeding time.	Inhibit ADP induced TXA2 release. Reduce the expression of PLCβ3 and p-PKC protein.	Fei et al. (2017)

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Table 5 continued

Bulnesia sarmienti (Gaiac wood or Paraguay-lignum-vitae)	Used to treat pain, inflammation, tumor, and bacterial infections.	Catechin, epigallocatechin, epicatechin, and epicatechin gallate.	Aqueous extract; Dose: 100 mg/kg	Rat extracorporeal shunt model and mouse tail bleeding model.	100 mg/kg dose inhibited thrombus formation by 40% and prolonged bleeding time and blood coagulation.	Inhibit platelet aggregation and Ca^{2+} mobilization. Reduce p38 MAPK, c-JNK1 and ERK2 phosphorylation.	Kamruzzaman et al. (2010)
Spatholobus suberectus Dunn	To ameliorate blood circulation. To treat anaemia, menoxenia, inflammation on peripheral blood vessels, and thrombotic changes in vessels.	Vanillic acid, daidzein, emodin, epicatechin, syringic acid, rhein, and genistein.	Ethanolic extract; Dose: 100 and 200 mg/kg	Mouse thromboembolism model.	200 mg/kg dose provided 87.5% protection from thrombotic death or paralysis.	Inhibit platelet aggregation. Suppress fibrinogen binding to the GP IIb/IIIa receptor. Impede the production of TXA2.	B.J. Lee et al. (2011)
Crataegus Orientalis Pall. ex M. Bieb. leaves	To prevent cardiovascular diseases including angina, congestive heart failure, and arrhythmias.	Flavonoids, proanthocyanidins, organic acids, and some amines.	Ethanolic extract; Dose: 100, 200, and 300 mg/kg	Thrombosis was induced by carrageenan in mouse and antithrombotic activity was evaluated.	200 and 300 mg/kg doses produced significant antithrombotic activity.	The presence of flavonoids in the extract are responsible for the suppression of platelet aggregation.	Arslan et al. (2011)
Crataegus aronia syn. Azarolus L.	To prevent diabetes, cardiovascular diseases, cancer, and sexual weaknesses.	Flavonoids and oligomeric proanthocyanidins.	Aqueous extract; Dose: 100, 200, 500, 1,000, and 2,000 mg/kg.	Tail cutting bleeding time model.	200 mg/kg extract significantly increased bleeding time	Inhibit platelet function. Inhibit TXB2.	Shatoor et al. (2012)
Ocimum basilicum L.	Used as cardiotonic, abdominal pain reliever, and antidiarrheal.	Essential oils are the main constituents.	Aqueous extract; Dose: 15, 75, 375 mg/kg	Rat arteriovenous shunt thrombosis model.	375 mg/kg decreased the weight of the thrombus.	Suppress platelet aggregation.	Tohti et al. (2006)

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Table 5 continued

Capparis ovata Desf. buds (CBE) and fruits (CFE)	Used to cure inflammation, pain, wound, rheumatism, and diuresis.	Phenolics, flavonoids, tannins and reducing sugars.	Methanolic extract; Dose: 100, 200 and 300 mg/kg	Carrageenan stimulated mouse tail thrombosis model.	300 mg/kg decreases the length of thrombosis.	Suppress thrombus generation which may be due to the presence of phytochemicals.	Bektas et al. (2012)
Ginkgo biloba L.	To treat various cerebral and peripheral arterial diseases like dementia, and claudication.	3,3'-dimethoxy-4,4'-dihydroxy-stilbene, ginkgolide A, B and C.	Prepared Ginkgo biloba extract; Dose: 20 and 40 mg/kg	$FeCl_3$ and epinephrine were induced arterial thrombosis and pulmonary thrombosis respectively and antithrombotic effect was determined.	40 mg/kg dose significantly extended arterial occlusion time; 20 and 40 mg/kg doses also increased the survival rate.	Impede platelet aggregation without prolonging bleeding time and occlusion time.	Ryu et al. (2009)
Lagenaria siceraria (Molina) Standl.	Used as cardioprotective, cardiotonic, antipyretic, antidote, diuretics, analgesic, antiulcer, to treat asthma, and other bronchial disorders.	Kaempferol, flavonoids, saponins, cucurbitacins, pectin, sterols, cardiotonic aglycones, and proteins.	Ethanolic extract; Dose: Different doses for two models	Mouse tail bleeding time model and acute pulmonary thrombosis model.	250 mg/kg dose significantly increased and provided 83.33% protection in the pulmonary thrombosis model.	Inhibit platelet aggregation. Antithrombotic potential attribute to various non-cellular chemical mediators of blood.	Rajput et al. (2014)

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Table 5 continued

Cydonia oblonga Mill.	To prevent diabetes, hyperlipidemia cardiovascular diseases, and oxidation.	Flavonoids, alkaloids, glycosides, organic acids, tannins, etc.	Aqueous extract; Dose: 20, 40 and 80 mg/kg	Mouse bleeding time, pulmonary thrombosis was induced by collagen-epinephrine antithrombotic effect was determined, rat carotid arterial thrombosis model.	80 mg/kg dose delayed the bleeding and clotting time. This dose increased the survival rate to 53.3% in the pulmonary thrombosis model. Also prolonged the thrombosis occlusion time, reducing the weight of the thrombus.	Promote plasmin activation through decreasing euglobulin lysis time. Decrease the plasma concentrations of TXB_2 and increases 6-keto-PGF1α which interfere with the formation of venous thrombosis.	W. Zhou et al. (2014)
Orbignya phalerata Mart. (Babassu)	To treat inflammations, pains, rheumatism, constipation, leukemia, obesity, tumors, ulcerations, and venous diseases.	Saponins, tannins, steroids, sugars and triterpenes.	Aqueous extract; Dose: 500 mg/kg	Carrageenan-induced thrombosis model	500 mg/kg dose treatment for 240 days decreased the percentage (88.9%) of necrosis area.	Increase the potentiality of the macrophage to generate NO. Increase PT and APTT which contribute in delaying coagulation process.	Azevedo et al. (2007)

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Table 5 continued

Rubia cordifolia L.	To treat various vascular diseases and neuroprotection.	Several types of anthraquinones, cyclic hexapeptides and arborinane type triterpenoids.	Aqueous extract; Dose: 12.5, 25, 50, 100, and 200 μg/mL	Phenylhydrazine induced AB strain zebrafish thrombosis model.	200 μg/mL extract reduced the formation of thrombus in the caudal vein.	The presence of anthraquinones and naphtho-quinones prevents thrombus formation through transferring electron in biological redox reaction which promotes or interfere with certain biochemical reactions.	Y. Chen et al. (2018)
Onion peel extract (OPE)	To suppress obesity, infections, and high blood pressure.	Dietary flavonoids including quercetin and kaempferol, organosulfur compounds, etc.	Aqueous extract; Dose: 2 mg and 10 mg solution	Ferric chloride-induced rats arterial thrombus formation model.	10 mg OPE dose significantly increased the time for arterial thrombus formation.	Diminish thrombin-induced expression of TF which is a coagulation initiator. Prevent the activation of ERK and JNK signaling pathways.	S.M. Lee et al. (2013)

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Table 6
Bioactive compounds that show *in vitro* antithrombotic activity.

Compound name	Compound class	Source	Dose/ conc. used	Experimental setup	Dose/conc. showed the significant effect	Possible mechanism of action	References
α-Naphthoflavone (α-NF)	Prototype flavone	Common in diet.	5-20 μM	Human platelet suspensions were prepared and platelet aggregation was measured by turbidimetric method.	5 and 10 μM doses inhibited platelet aggregation.	Inhibit the activation of phospholipase C, which leads to the inhibition of intracellular Ca^{2+} mobilization. Activate the formation of cyclic GMP which in consequence suppress platelet aggregation.	Hsiao et al. (2005)
Rutin	Bioflavonoid	Common in diet.	250 and 290 μM	Human platelet aggregation was measured by turbidimetric method.	290 μM dose inhibited collagen induced platelet aggregation.	Inhibit Ca^{2+} mobilization which in consequence suppress platelet aggregation. Impede TXA2 formation.	Sheu et al. (2004) (Sheu et al., 2004)
Epigallocatechin Gallate	Flavonoid	Green tea	25–200 μM	Platelet rich plasma was prepared from the blood of rabbit and platelet aggregation was determined.	200 μM dose inhibited collagen induced platelet aggregation.	Block phosphorylation of collagen mediated protein tyrosine and phospholipase (PL) Cγ2. Decrease serotonin secretion, cytosolic calcium mobilization and AA liberation. Block Ca^{2+}–ATPase inhibitor. Elevate AA-mediated PGD2 formation.	Jin et al. (2008)

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Table 6 continued

Quercetin, Apigenin and Catechin	Flavonoid, Flavone and Phenolic compound respectively.	Dietary source	Different concentrations.	Human platelets were prepared to conduct aggregation and 5-HT secretion experiments.	Apigenin at 10 μM and 40 μM doses inhibit platelet aggregation. Quercetin at 40 μM dose completely abolish aggregation. They also inhibited 5-HT secretion.	Impede platelet aggregation and 5-HT release. Inhibit the phosphorylation of total protein, PLCγ2 tyrosine and Syk. Inhibit Fyn kinase activity.	Wright et al. (2010)
Quercetin	Flavonoid	Fruits, vegetable, red wine, and tea.	12.5–100 μM	Blood was retrieved from the abdominal artery of 8$\sim$10 weeks old rats and platelet aggregation was determined.	25 μM inhibits platelet aggregation by 50%.	Suppress platelet aggregation. Inhibit collagen-induced P-selectin expression, $[Ca^{2+}]_i$ mobilization, ATP release and integrin-αIIbβ3 activation. Ameliorate cAMP and vasodilator-stimulated phosphoprotein (VASP) levels. Inhibit platelet aggregation by reducing p38 MAPK, PI3K, Akt, JNK1 and ERK2 activations.	Oh et al. (2012)
Genistein	Phytoestrognic isoflavone		1-30 μg/mL	Human platelet suspension was prepared and platelet aggregation was measured.	10 μg/mL dose inhibited U466lP induced platelet aggregation and serotonin release.	Inhibit tyrosine kinases. Inhibit serotonin secretion. Inhibit phospholipase C activity. Inhibit protein kinase C activity.	Mcnicol (1993)

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Table 6 continued

Equol	Soy isoflavones	Soy-based foodstuffs.	5, 10, 30 μmol/L	Human washed platelet was prepared and platelet aggregation was evaluated.	Produced dose dependent platelet aggregation.	Antagonize thromboxane A2 receptor.	Muñoz et al. (2009)
Orientin and isoorientin	C-glycosidic flavonoids	Vaccinium bracteatm Thunb.	Different doses	Washed human platelets were prepared, platelet aggregation and APTT and PT was measured.	Orientin and isoorientin at 5 and 20 μM dose prolonged APTT and PT. They inhibited thrombin and U46619 induced platelet aggregation in concentration dependent manner.	Impede platelet aggregation and thrombin-catalyzed fibrin polymerization. Suppress calcium mobilization and PKC activation. Decrease the PAI-1 to t-PA ratio.	W. Lee et al. (2017)
Pelargonidin	Anthocyanidin	Found as red pigment in plants.	0, 2, 5, 10, 20, 30 μM	Human platelets from healthy volunteers were prepared and platelet aggregation and APTT and PT was measured.	10 μM or higher dose prolonged APTT and PT. Pelargonidin inhibited reptilase and U46619 induced platelet aggregation in concentration dependent manner.	Decrease fibrin polymerization. Decrease human platelet aggregation. Decrease the amidolytic activity of thrombin. Inhibit the activation and production of FX and thrombin. Abolish the ration of PAI-to t-PA.	Ku et al. (2016)

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Table 6 continued

Scolymoside	Flavonoid	*Cyclopia subternata*	0-30 μM	Washed platelets from syngeneic donor mice and platelet aggregation was determined.	29.4 μM (IC_{50} for inhibition of platelet aggregation).	Impede platelet aggregation and thrombin-catalyzed fibrin polymerization. Abolish the ration of PAI-to t-PA.	Yoon et al. (2015)
Zingerone	A phenolic alkanone	*Zingiber officinale* Roscoe.	1, 5, 10, 25, 50 μM	Purified human PRP was prepared and platelet aggregation was determined by aggregometer.	19.94 μM doubled the clotting time. Suppressed platelet aggregation in a dose dependent manner.	Inhibit the catalytic activity of FXa. Inhibit phosphorylation of MARCKS (myristoylated alanine-rich C-kinase substrate), platelet P-selectin and PAC-1 expression.	W. Lee et al. (2017)
Cyclo(L-Pro-L-Tyr) and N-acetyltyramine	Diketopiperazine and Phenylethanoid respectively	*Tenebrio molitor* (insect)	1, 5, and 10 μM	Clotting time was measured from mice blood and platelet aggregation was determined from human PRP.	At 2.43, and 3.40 μM respectively doubled the clotting time and both inhibited platelet aggregation in a concentration dependent manner.	Impede FXa and platelet aggregation activities. Prolongs APTT.	W. Lee et al. (2017)
Pinnatifidanoside F	Sesquiterpenoid	*Crataegus pinnatifida* Bunge	0.25 mg/mL	PRP was prepared from rat and platelet aggregation activity was measured.	0.25 mg/mL concentration inhibited platelet aggregation by 84%.	Impede ADP induced platelet aggregation. Increase the time to form thrombocytes.	Gao et al. (2017)

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Table 6 continued

Geniposide	Iridoid glycoside	*Gardenia jasminoides* Ellis	2.6, 7.7, 26 and 77 mM	Platelet aggregation was measured by 4 channel aggregometer.	Geniposide inhibited collagen induced platelet aggregation by 84%.	Inhibit collagen-induced platelet aggregation. Inhibit phospholipase A2 (PLA2) activity.	Suzuki et al. (2001)
Nuzhennoside and Nuzhennoside G13	Secoiridoid glucosides	*Osmanthus fragrans* Lour.	0.7, 1.4 and 2.8 mg/kg	Platelet aggregation was measured from rabbit PRP.	Nuzhennoside G13 at 2.8 mg/kg showed greatest inhibition of platelet aggregation.	Inhibit ADP and collagen induced platelet aggregation.	Tang et al. (2015)
Ambinine	Alkaloid	*Corydalis ambigua* var.	0.5, 1 or 2 mg/mL	Plasma recalcification time (PRT) and blood clot assay was performed with fresh rat blood.	2 mg/mL dose prolonged PRT and degraded the blood clot.	Prolong PRT. Degrade blood clot through interfering with intrinsic coagulation cascade.	S. Chang et al. (2018)
Ferulic acid	Hydroxycinnamic acid	Various medicinal plants.	Different doses for different model	*In vitro* anticoagulation and aggregation study was performed with rat platelet.	200 μM dose inhibited thrombin, ADP, U46619 and collagen induced platelet aggregation.	Inhibit platelet aggregation. Reduce intracellular $Ca2^{+}$ mobilization and TXB2 production. Increase cAMP level.	Hong et al. (2016)

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Table 6 continued

Epi-sesamin	Lignan	Asarum sieboldii	0.5, 1, 2, 5, 10 and 20 μM	Anticoagulation study was performed with citrated normal human plasma and platelet aggregation assay was performed with mouse PRP.	Greater than 2 μM dose significantly prolonged APTT and PT. Inhibited platelet aggregation in concentration dependent manner.	Impede the functions and production of FXa and thrombin. Impede platelet aggregation fibrin polymerization. Decrease the PAI-1 to t-PA ratio.	Ku et al. (2013)

Table 7
Bioactive compounds that show *in vivo* antithrombotic activity.

Compound name	Compound class	Source	Dose/ conc. used	Experimental setup	Dose/conc. showed the significant effect	Possible mechanism of action	References
Fucoidan	A sulfated polysaccharide	*Undaria pinnatifida* sporophylls *Fucus vesiculosus*	0.1, 1.25, 2.5, 5.0, 10, 25, or 50 mg/kg	Ferric chloride-induced arterial thrombus mouse model.	5 or 50 mg/kg (UPS); 25 mg/kg (for Fucus fucoidan)	Inhibit thrombin formation.	Min et al. (2012)
Chikusetsusaponin IVa	A triterpenoid saponin	*Ilex paraguariensis*	15 and 50 mg/kg	Rat deep venous thrombosis model.	50 mg/kg reduced the thrombus size by 91.2%.	Inhibit thrombus formation. Prolong PT.	Dahmer et al. (2012)
Glycyrrhizin	Saponin	*Glycyrrhiza glabra* L.	Different doses for different model	Stasis induced thrombus formation model, arteriovenous shunt model and mouse tail bleeding time model.	75 mg/kg and 230 mg/kg dose decreased the thrombus weight in stasis and arteriovenous shunt model respectively. 360 mg/kg dose produced strong hemorrhagic effect in tail bleeding model.	Generate a direct effect on thrombin exosite I.	Mendes-Silva et al. (2003)
Withaferin A	A steroidal lactone	*Withania somnifera*	Different doses	The $FeCl_3$-induced thrombosis mice model and mouse tail bleeding time.	4.7 μg/mouse increased tail bleeding time and 4.7 μg/mouse increased time for large thrombus formation but slowed the growth of thrombi.	Inhibit thrombin-catalyzed fibrin polymerization. Impede the functions and generation of FXa and thrombin. Suppress PAI-1 production.	Ku and Bae (2014a)

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Table 7 continued

Wogonin and Wogonoside	Flavonoid	*Scutellaria baicalensis* Georgi	Wogonin: 5.7 or 11.4 μg/mouse Wogonoside: 9.2 and 18.4 μg/mouse	Mouse tail bleeding time model.	11.4 and 18.4 μg/mouse for prolonged the bleeding time of wogonin and wogonoside respectively.	Inhibit thrombin-catalyzed fibrin polymerization. Reduce PAI-1 to t-PA ratio.	Ku and Bae (2014b)
Tanshinone IIA	Diterpenoid	*Salvia milthorriza* Bunge	10 mg/kg	Mouse tail bleeding time model.	10 mg/kg dose significantly increased bleeding time.	Modulate tubulin acetylation. Suppress Erk-2 phosphorylation. Ameliorate bleeding time.	Maione et al. (2014)
Borneol	A bornane monoterpenoid	Various medicinal plants, like *Rosmarinus officinalis*.	35 and 70 mg/kg	Rat venous thrombosis model and rat arterio-venous shunt silk thread model.	35 mg/kg reduced the weight of thrombus by 37.9% and 28.7% in two models respectively.	Influence the level of 5-HT in platelet, which in turn affect platelet aggregation. Prolongs PT and TT. Produce thrombolytic activities might be due to anticoagulant activity.	Y.H. Li et al. (2008)
Glaucocalyxin A	An ent-kauranoid diterpene	*Rabdosia japonica* (Burm. f.)	Different concentrations for different model	$FeCl_3$-induced carotid artery injury model and mouse tail bleeding model.	10 mg/kg dose increased the average time of occlusion. 15 mg/kg extended mouse tail bleeding time.	Enhance the time for complete occlusion without perturbing bleeding time.	W. Li et al. (2013)
Curdione	Sesquiterpene	*Curcuma wenyujin*	50 mg/kg, 100 mg/kg, 200 mg/kg.	Carrageenan-induced Tail Thrombosis Model.	200 mg/kg dose significantly reduced the length of thrombosis.	Impede P-selectin expression in PAF induced activated platelets. Increase cAMP levels and decrease intracellular Ca^{2+} mobilization.	Xia et al. (2012)

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Table 7 continued

Hydroxychavicol	Phenolic	*Piper betle* leaf	Various doses (100-500 nmol/mouse)	*In vivo* thrombus formation and mouse tail bleeding model.	500 nmol/mouse elevates microvessel occlusion time but showed little effect in bleeding time.	Suppress COX1 and COX2 activity. Inhibit ROS production and Ca^{2+} mobilization. Inhibit TXB2 production.	M. Chang et al. (2007)
Fucosylated chondroitin sulfate (FCS) and depolymerized fragment (dFCS).	Polysaccharide	*Cucumaria frondosa*	0.1 and 1 mg/kg (FCS); 1 and 2 mg/kg (dFCSc)	Electrical induced arterial thrombosis rat model and mouse tail bleeding time.	1 mg/kg (FCS) produced higher inhibitory effect on thrombus formation and 2 mg/kg (dFCS) prolonged the occlusion time. Both samples prolonged the bleeding time.	Inhibit FIIa and FXa. Prolongs APTT.	Liu et al. (2016)
Vicenin-2	A flavonoid glycoside	*Cyclopia subternata*	11.9, 23.8, 35.7 μg/mouse	Tail bleeding time measured in male C57BL/6 mice model.	35.7 μg/mouse significantly prolonged the tail bleeding time.	Prolong APTT and PT. Inhibit thrombin and FXa activities. Suppress TNF-α stimulated PAI-1 secretion. Reduce the ratio of PAI-1 to t-PA.	W. Lee and Bae (2015)
Syringaresinol	Lignan	*Piper wallichii*	30 μM	Zebrafish thrombus model.	30 μM concentration produced 37% inhibitory effect on thrombus formation.	Inhibit platelet aggregation.	Shi et al. (2015)

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Table 7 continued

Allyl isothiocyanate	Isothiocyanate	Mustard	0.3, 1, 3 mg/kg	Mouse pulmonary thromboembolism and tail bleeding model.	3 mg/kg produced 63% protective effect from pulmonary thromboembolism, same dose prolonged tail bleeding time.	Inhibit cellular Ca^{2+}. Impede the phosphorylation of PKCδ, ERK, p38, and Akt pathways.	D.S. Lee et al. (2014)
Sesamol	Phenolic	Sesame oil	5 and 10 mg/kg	Observed fluorescein sodium-induced thrombus formation in mice mesenteric microvessel.	10 mg/kg dose increased occlusion time and 5 mg/kg dose prolonged platelet plug formation.	Suppress TXA2 formation and $[Ca^{2+}]i$ mobilization. Suppress the phosphorylation of (PLC)γ2, MAPK and PKC. Increase cAMP and cGMP levels.	C.C. Chang et al. (2010)
α-Linolenic acid	Essential fatty acid.	Flaxseed oil	High (7.3%) and low (0.03%) α-Linolenic acid conc.	Mouse carotid artery thrombosis model.	High conc (7.3%) increased occlusion time.	Inhibit thrombin-induced platelet aggregation. Decrease p38 MAPK activation in platelets. Inhibit TF expression and activity.	Holy et al. (2011)
Hinokitiol	A natural monoterpenoid	*Chymacyparis taiwanesis*	2.5 and 5 mg/kg	Observed fluorescein sodium-induced thrombus formation in mice mesenteric microvessel.	5 mg/kg dose significantly prolonged occlusion time.	Inhibit the phosphorylation of (PLC)γ2, PKC, MAPKs, and Akt. Reduce hydroxyl radical (OH•) formation and intracellular Ca^{2+} mobilization.	Lin et al. (2013)

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Table 7 continued

N-caffeoyldopamine	Clovamide-type phenyl-propenoic acid	*Theobroma cacao*	50 and 100 μg	*In vivo* determination of platelet leukocyte interaction and P-selectin expression.	100 μg reduced P-selectin expression and platelet-leukocyte interactions.	Inhibit platelet aggregation. Reduce P-selectin expression and platelet-leukocyte interactions.	J.B. Park and Schoene (2006)
Magnolol	Lignan	*Magnolia officinalis*	15 mg/kg	Observed fluorescein sodium-induced thrombus formation in mice mesenteric microvessel and mouse tail bleeding time.	15 mg/kg dose suppressed platelet plug formation and decreased the diameter of microvessel. This dose also prolonged bleeding time.	Upregulate the activity and intracellular level of platelets PPAR-β/γ. Inhibit intracellular Ca^{2+} mobilization.	Shih and Chou (2012)
Resveratrol	Stilbenoid polyphenol	Peanuts, grapes, mulberries.	2 and 5 mg/kg	Observed fluorescein sodium-induced thrombus formation in mice mesenteric microvessel.	5 mg/kg significantly prolonged occlusion time and inhibited platelet plug formation.	Impede TXA2 formation, $[Ca^{+2}]$i mobilization, PKC activation and phosphoinositide breakdown. Inhibits p38 MAPK in platelets and reduces hydroxyl radical (OH^-) formation.	Shen et al. (2007)

6.2. *In vitro* and *in vivo* screening of probable active compounds having the antithrombotic effect

Plant-derived active metabolites gradually become the main target of a safe agent that can satisfy clinical outcomes with little or no side effects. They already have proven significant antithrombotic effects in previous *in vitro* and *in vivo* setups. Hence would be a probable solution to treat cardiovascular disorders alone or in combination with current therapy to produce a synergistic effect without any chance of having severe adverse reactions. In this part, we have listed the bioactive compounds studied in different experimental sets to explore their possibility of becoming effective for better managing thrombotic episodes in cardiovascular disorders (Table 6 and Table 7).

7. CURRENT USE OF NATURAL ANTITHROMBOTIC COMPOUNDS AND COMPOUNDS IN THE CLINICAL TRIAL

Gradually natural bioactive compounds are becoming mainstream to treat thrombus-induced cardiovascular and cerebrovascular diseases. For example, Danhong injection (DHI) is one of the most prescribed Chinese medicine injections, prepared from the aqueous extracts of two widely used Chinese medicinal plants named *Salvia miltiorrhiza* Bunge and *Carthamus tinctorius* L., which generate synergistic therapeutic effects due to their multi-components and multi-targets. A bunch of seven salvianolic acids are the primary ingredients of this injection and have a remarkable impact on managing pernicious diseases, including cardiovascular and cerebrovascular complications in Chaina. It has been reported that the combination of salvianolic acids A and C synergistically inhibit platelet aggregation *in vitro* experimental models (Zhao et al., 2017). Guanxinning Tablet is another modern Chinese drug made from two traditional Chinese medicinal herbs named *Ligusticum striatum* DC and *Salvia miltiorrhiza* Bunge., which are reported to produce a synergistic effect in improving blood circulation and suppressing thrombus formation. Senkyunolide I and cryptotanshinone, two bioactive compounds isolated from these herbs, also produce a synergistic antithrombotic effect (B.X. Li et al., 2021). Administration of *Ginkgo biloba* extract in combination with cilostazol has been reported to enhance the antithrombotic activity of cilostazol without any episode of adverse impacts (Ryu et al., 2009). In another study, it has been found that *Campomanesia xanthocarpa* extract produces a synergistic effect when administered in combination with acetylsalicylic acid and increases the potentiality of acetylsalicylic acid to inhibit platelet aggregation (Otero et al., 2017). Natural bioactive compounds can be considered medicinal agents for treating cardiovascular and cerebrovascular complications with pathological clotting.

Apart from administration with other drugs, various antithrombotic therapy derived from natural sources (plants and animals) were tested in clinical trials to investigate their safety and efficacy. Although the number of attempts at natural antithrombotic compounds is still not significant, initiatives are gradually taken to insert natural compounds into human trials (B.X. Li et al., 2021; Wang et al., 2015). The more substantial number of tests will be conducted, more opportunities will create to discover safer antithrombotic therapies. Table 8 demonstrates the outcome of clinical trials conducted on natural compounds from plant and animal sources to determine their safety and efficacy in the human model.

It is well known that currently available antithrombotic drugs have substantial side effects (i.e., internal hemorrhages), which demand more extensive research to discover a safe and efficient one. Because of their ability to preserve normal hemostasis while lowering internal bleeding and avoiding unexpected clot formation, the mechanism of action of antiplatelet and anticoagulant natural compounds has been the research focus. However, little has been known regarding how therapies from natural products possess lower risk than traditional therapy. But human trials on several natural compounds revealed their safe therapeutic profile. For instance, desirudin is an analog of hirudin, when administered subcutaneously, produces direct thrombin inhibitory effect without significant bleeding episodes. In 1997 European medicines agency approved the administration of desirudin to manage DVT in patients' surgery like total knee replacement or total hip replacement. So extensive research is required to discover the novel mechanisms of natural antithrombotic compounds regarding how they are comparatively safer than traditional therapy.

8. SAFETY OF NATURAL ANTITHROMBOTIC DRUGS IN CONTEXT OF CURRENT THERAPY

Due to the life-threatening bleeding risk of conventional antithrombotic drugs, researchers are now inclined to discover safer therapy from natural sources. Therapies target various receptors, majorly COX1, P2Y12, ADP, thrombin, thromboxane, integrin αIIbβ3, cAMP, calcium, VKORC1, PDE, prostacyclin, and prostaglandin to produce antiplatelet and anticoagulant action (L. Zhang et al., 2021) . Most antithrombotic drugs are multitargeted and non-specific drugs. For instance, low molecular weight heparin and unfractionated heparin work on several coagulation factors. Combination therapy for the management of thrombus-induced cardiovascular diseases may potentiate the risk of bleeding. Although the reduction of the bleeding mechanism by natural antithrombotic therapies is still not apparent, these agents may target specific coagulation factors. Rigorous research is necessary to uncover their exact mechanism.

9. CONCLUSION AND FUTURE DIRECTION

In developed countries, the increasing pattern of sedentary lifestyles is responsible for developing various pernicious diseases, including CVDs and thrombosis, recognized as the primary cause of global death and disability. The death rate from these diseases is increasing alarmingly, and researchers are still working onerously to uncover the possible solution to this emergency, including the development of complementary

Table 8
Clinical trial of antithrombotic natural compounds from both plant and animal source to investigate their safety and efficacy.

Name and source	Study design	Outcomes	References
Anfibatide (*Deinagkistrodon acutus* venom)	Randomized, and open-label phase I clinical trial on 94 healthy volunteers.	Inhibited VWF-mediated platelet aggregation without any noticeable adverse reactions.	B.X. Li et al. (2021)
Danhong injection (*Salvia miltiorrhiza* Bunge and *Carthamus tinctorius* L.)	Randomized multicenter, double-blind, placebo-controlled, adaptive clinical trial on 870 patients.	This is an ongoing trial to investigate the safety and efficacy of DHI against chronic stable angina.	Wang et al. (2015)
Guanxinning Tablet (*Salvia miltiorrhiza* and *Ligusticum chuanxiong*)	Randomized, Multicenter, Placebo-Controlled Trial on 160 patients.	This tablet was found be safe and effective at a dose of 4 tablets three times daily in the treatment of stable angina.	(Ming-yue et al., 2019)
Nematode anticoagulant protein c2 (NAPc2) (*Ancylostoma caninum*)	Randomized, double-blinded, dose-escalation, multicenter trial on 154 patients receiving various doses of NAPc2.	NAPc2 inhibited TF/FVIIa complex and up to 7.5 μg/kg doses was found safe and effective administered in combination with unfractionated heparin clopidogrel, and aspirin.	Moons et al. (2003)
Isoquercitin (various plant species)	Multicenter phase II trial	This compound inhibited protein disulfide isomerase (PDI) and improved coagulation markers.	Zwicker et al. (2019)
Desirudin (*Hirudo medicinalis*)	Multicenter, open-label, single-arm study on 516 hospitalized patients.	Desirudin didn't observe any major bleeding and the trial ended up without any VTE related death.	Bergese et al. (2013)
Lumbrokinase (earthworms)	Human trial on 60 pulmonary thromboembolism patients to investigate the efficacy of the combinational therapy of lumbrokinase, heparin, and sequential warfarin.	This combination was found safe and effective to manage acute and moderate risk pulmonary thromboembolism.	Jiang et al. (2017)

therapeutic agents, search for natural bioactive compounds with maximum therapeutic efficacy and minimal adverse effects, formulation of functional foods to increase blood circulation and finally changes in lifestyle pattern. Isolation of bioactive compounds from natural sources with antithrombotic activity might produce promising alternatives to current treatments and replace the conventional therapies with potentially adverse effects. As the therapy has been recognized for its auspicious role in thrombotic disorders, more research should be conducted to isolate potential compounds and drive them in human trials to determine their safety and efficacy. Administration of these compounds with traditional drugs can also improve the therapeutic efficacy of the drug. Therefore, continuous investigation of natural products with antithrombotic properties can yield new insights into new drugs with better safety and efficacy.

ABBREVIATIONS

5HT, 5-hydroxytryptamine receptors; AA, arachidonic acid; ADP, adenosine diphosphate; APTT- activated partial thromboplastin time; cAMP, cyclic adenosine monophosphate; CVDs, cardiovascular diseases; ERK, extracellular-signal-regulated kinase; ICAM, intercellular adhesion molecule; IHD, ischemic heart disease; JNK, c-Jun N-terminal kinase; HMWK-high molecular weight kininogen; MAPK, mitogen-activated protein kinases; PGH2, prostaglandin H2; PGI2, prostaglandin I2; PT, prothrombin time; ROS, reactive oxygen species; TF, tissue factor; TT, thrombin time; TXA2, thromboxane A2, TXB2, thromboxane B2.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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M.S.H. and T.M. developed the conception of the presented idea and developed the theoretical framework; T.M., M.A.S., S.M., and S.H. contributed to the final version of the manuscript. M.S.H. did the overall supervision and critic review for the manuscript. Authors have accepted responsibility for the entire content of this manuscript and approved its submission.

REFERENCES

Aguirre, R., May, J.M., 2008. Inflammation in the vascular bed: Importance of vitamin C. Pharmacology and Therapeutics. 119, 96–103. https://doi.org/10.1016/j.pharmthera.2008.05.002

Ahmad, F., Degerman, E., Manganiello, V.C., 2012. Cyclic nucleotide phosphodiesterase 3 signaling complexes. Hormone and Metabolic Research. 44(10), 776–785. https://doi.org/10.1055/s-0032-1312646

Ain, Q.U., Khan, H., Mubarak, M.S., Pervaiz, A., 2016. Plant alkaloids as antiplatelet agent: Drugs of the future in the light of recent developments. Frontiers in Pharmacology. 7(28), 292. https://doi.org/10.3389/fphar.2016.00292

Alu'datt, M.H., Rababah, T., Alhamad, M.N., Al-Mahasneh, M.A., Almajwal, A., Gammoh, S., Ereifej, K., Johargy, A., Alli, I., 2017. A review of phenolic compounds in oil-bearing plants: Distribution, identification and occurrence of phenolic compounds. Food Chemistry. 218, 99–106. https://doi.org/10.1016/j.foodchem.2016.09.057

Araujo, R.N., Campos, I.T.N., Tanaka, A.S., Santos, A., Gontijo, N.F., Lehane, M.J., Pereira, M.H., 2007. Brasiliensin: A novel intestinal thrombin inhibitor from *Triatoma brasiliensis* (Hemiptera: Reduviidae) with an important role in blood intake. International Journal for Parasitology. 37(12), 1351–1358. https://doi.org/10.1016/j.ijpara.2007.04.017

Arauna, D., Furrianca, M., Espinosa-Parrilla, Y., Fuentes, E., Alarcón, M., Palomo, I., 2019. Natural bioactive compounds as protectors of mitochondrial dysfunction in cardiovascular diseases and aging. Molecules. 24(23), 4259. https://doi.org/10.3390/molecules24234259

Arita, H., Nakano, T., Hanasaki, K., 1989. Thromboxane A2: Its generation and role in platelet activation. Progress in Lipid Research. 28(4), 90002–90009. https://doi.org/10.1016/0163-7827(89)90002-7

Arslan, R., Bor, Z., Bektas, N., Meriçli, A.H., Ozturk, Y., 2011. Antithrombotic effects of ethanol extract of *Crataegus orientalis* in the carrageenan-induced mice tail thrombosis model. Thrombosis Research. 127(3), 210–213. https://doi.org/10.1016/j.thromres.2010.11.028

Asada, Y., Yamashita, A., Sato, Y., Hatakeyama, K., 2018. Thrombus formation and propagation in the onset of cardiovascular events. Journal of Atherosclerosis and Thrombosis. 25(8), 653–664. https://doi.org/10.5551/jat.rv17022

Azevedo, A.P.S., Farias, J.C., Costa, G.C., Ferreira, S.C.P., Aragão-Filho, W.C., Sousa, P.R.A., Pinheiro, M.T., Maciel, M.C.G., Silva, L.A., Lopes, A.S., Barroqueiro, E.S.B., Borges, M.O.R., Guerra, R.N.M., Nascimento, F.R.F., 2007. Anti-thrombotic effect of chronic oral treatment with *Orbignya phalerata* Mart. Journal of Ethnopharmacology. 111, 155–159. https://doi.org/10.1016/j.jep.2006.11.005

Baker, W.F., 2005. Thrombolytic therapy: Current clinical practice. Hematology/Oncology Clinics of North America. 19(1), 147–181. https://doi.org/10.1016/j.hoc.2004.09.008

Balamuthusamy, S., Arora, R., 2007. Hematologic adverse effects of clopidogrel. American Journal of Therapeutics. 14, 106–112. https://doi.org/10.1097/01.mjt.0000212708.81034.22

Bektas, N., Arslan, R., Goger, F., Kirimer, N., Ozturk, Y., 2012. Investigation for anti-inflammatory and anti-thrombotic activities of methanol extract of *Capparis ovata* buds and fruits. Journal of Ethnopharmacology. 142, 48–52. https://doi.org/10.1016/j.jep.2012.04.011

Bergese, S.D., Minkowitz, H.S., Arpino, P.A., Sane, D.C., Levy, J.H., 2013. Multicenter trial of desirudin for the prophylaxis of thrombosis: An alternative to heparin-based anticoagulation (DESIR-ABLE). Clinical and Applied Thrombosis. 19(4), 418–423. https://doi.org/10.1177/1076029612452779

Berndt, M.C., Shen, Y., Dopheide, S.M., Gardiner, E.E., Andrews, R.K., 2001. The vascular biology of the glycoprotein Ib-IX-V com-

plex. Thrombosis and Haemostasis. 86, 178–188. 10.1055/s-0037-1616216

Bijak, M., Ziewiecki, R., Saluk, J., Ponczek, M., Pawlaczyk, I., Krotkiewski, H., Wachowicz, B., Nowak, P., 2014. Thrombin inhibitory activity of some polyphenolic compounds. Medicinal Chemistry Research. 23(5), 2324–2337.

Bivard, A., Lin, L., Parsonsb, M.W., 2013. Review of Stroke Thrombolytics. Journal of Stroke. 15(2), 90–98.

Bonaca, M.P., Morrow, D.A., 2009. SCH 530348: A novel oral thrombin receptor antagonist. Future Cardiology. 5(5), 435–442. https://doi.org/10.2217/fca.09.27

Borne, P.A.K.V.D., Meijers, J.C.M., Bouma, B.N., 1995. Feedback activation of factor XI by thrombin in plasma results in additional formation of thrombin that protects fibrin clots from fibrinolysis. Blood. 86(8), 3035–3042. https://doi.org/10.1182/blood.V86.8.3035.3035

Bouaziz, A., Salido, S., Linares-Palomino, P.J., Sanchez, A., Altarejos, J., Bartegi, A., Salido, G.M., Rosado, J.A., 2007. Cinnamtannin B-1 from bay wood reduces abnormal intracellular Ca2+ homeostasis and platelet hyperaggregability in type 2 diabetes mellitus patients. Archives of Biochemistry and Biophysics. 457(2), 235–242. https://doi.org/10.1016/j.abb.2006.10.020

Bouma, B.N., Griffin, J.H., 1977. Human blood coagulation factor XI. Purification, properties, and mechanism of activation by activated factor XII. The Journal of Biological Chemistry. 252(18), 39977–39982. https://doi.org/10.1016/S0021-9258(17)39977-5

Brummel, K.E., Paradis, S.G., Butenas, S., Mann, K.G., 2002. Thrombin functions during tissue factor-induced blood coagulation. Blood. 100(1), 148–152. https://doi.org/10.1182/blood.V100.1.148

Bugge, T.H., Xiao, Q., Kombrinck, K.W., Flick, M.J., Holmback, K., Danton, M.J.S., Colbert, M.C., Witte, D.P., Fujikawa, K., Davie, E.W., 1996. Fatal embryonic bleeding events in mice lacking tissue factor, the cell-associated initiator of blood coagulation. Proceedings of the National Academy of Sciences of the United States of America. 93(13), 80146–80155. https://doi.org/10.1073/pnas.93.13.6258

Burness, C.B., Perry, C.M., 2014. Rivaroxaban: A review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. Drugs. 74(2), 243–262. https://doi.org/10.1007/s40265-013-0174-4

Campos, I.T.N., Amino, R., Sampaio, C.A.M., Auerswald, E.A., Friedrich, T., Lemaire, H.G., Schenkman, S., Tanaka, A.S., 2002. Infestin, a thrombin inhibitor presents in Triatoma infestans midgut, a Chagas' disease vector: Gene cloning, expression and characterization of the inhibitor. Insect Biochemistry and Molecular Biology. 32(9), 35–43.

Cappello, M., Li, S., Chen, X., Li, C., Ben, Harrison, L., Narashimhan, S., Beard, C.B., Aksoy, S., 1998. Tsetse thrombin inhibitor: Bloodmeal-induced expression of an anticoagulant in salivary glands and gut tissue of *Glossina morsitans* morsitans. Proceedings of the National Academy of Sciences of the United States of America. 95(24), 14290–14295. https://doi.org/10.1073/pnas.95.24.14290

Cappellott, M., Vlasuk, G.P., Bergum, P.W., Huang, S., Hotezt, P.J., 1995. Ancylostoma caninum anticoagulant peptide: A hookworm- derived inhibitor of human coagulation factor Xa. Proceedings of the National Academy of Sciences. 92(13), 6152–6156. https://doi.org/10.1073/pnas.92.13.6152

Carnevale, R., Loffredo, L., Pignatelli, P., Nocella, C., Bartimoccia, S., Santo, S.D., Martino, F., Catasca, E., Perri, L., Violi, F., 2012. Dark chocolate inhibits platelet isoprostanes via NOX2 down-regulation in smokers. Journal of Thrombosis and Haemostasis. 10, 125–132. https://doi.org/10.1111/j.1538-7836.2011.04558.x

Carvalhal, F., Cristelo, R.R., Resende, D.I.S.P., Pinto, M.M.M., Sousa, E., Correia-Da-Silva, M., 2019. Antithrombotics from the sea: Polysaccharides and beyond. Marine Drugs. 17(3), 170. https://doi.org/10.3390/md17030170

Cate, H.T., Hemker, H.C., 2016. Thrombin Generation and Atherothrombosis: What Does the Evidence Indicate? Journal of the American Heart Association. 5(8). https://doi.org/10.1161/jaha.116.003553

CER, T., The TRA● CER Executive and Steering Committees., 2009. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA● CER) trial: study design and rationale. American Heart Journal. 158(3), 327–334. https://doi.org/10.1016/j.ahj.2009.07.001

Chan, N.C., Hirsh, J., Ginsberg, J.S., Eikelboom, J.W., 2014. Betrixaban (PRT054021): Pharmacology, dose selection and clinical studies. Future Cardiology. 10(1), 43–52. https://doi.org/10.2217/fca.13.98

Chang, C.C., Lu, W.J., Chiang, C.W., Jayakumar, T., Ong, E.T., Hsiao, G., Fong, T.H., Chou, D.S., Sheu, J.R., 2010. Potent antiplatelet activity of sesamol in an in vitro and in vivo model: Pivotal roles of cyclic AMP and p38 mitogen-activated protein kinase. Journal of Nutritional Biochemistry. 21(12), 1214–1221. https://doi.org/10.1016/j.jnutbio.2009.10.009

Chang, M., Uang, B., Tsai, C., Wu, H., Lin, B., Lee, C., Chen, Y., Chang, C., Tsai, Y., Kao, C., Jeng, J., 2007. Hydroxychavicol, a novel betel leaf component, inhibits platelet aggregation by suppression of cyclooxygenase, thromboxane production and calcium mobilization. British Journal of Pharmacology. 152, 73–82. https://doi.org/10.1038/sj.bjp.0707367

Chang, S., Yang, Z., Han, N., Liu, Z., Yin, J., 2018. The antithrombotic, anticoagulant activity and toxicity research of ambinine, an alkaloid from the tuber of *Corydalis ambigua* var. amurensis. . Regulatory Toxicology and Pharmacology. 95, 175–181. https://doi.org/10.1016/j.yrtph.2018.03.004 https://doi.org/10.1016/j.yrtph.2018.03.004

Che, C.T., George, V., Ijinu, T.P., Pushpangadan, P., Andrae-Marobela, K., 2017. Traditional Medicine, S. Badal, R. Delgoda, et al., (Eds.), Pharmacognosy Fundamentals, Applications and Strategies. Elsevier Inc, pp. 15–30. https://doi.org/10.1016/B978-0-12-802104-0.00002-0

Chen, C., Yang, F.Q., Zhang, Q., Wang, F.Q., Hu, Y.J., Xia, Z.N., 2015. Natural products for antithrombosis. Evidence-Based Complementary and Alternative Medicine. 2015, 876426. https://doi.org/10.1155/2015/876426 https://doi.org/10.1155/2015/876426

Chen, M., Ye, X., Ming, X., Chen, Y., Wang, Y., Su, X., Su, W., Kong, Y., 2015. A novel direct factor Xa inhibitory peptide with anti-platelet aggregation activity from *Agkistrodon acutus* venom hydrolysates. Scientific Reports. 2(5), 10846. https://doi.org/10.1038/srep10846

Chen, Y., Chen, P.D., Bao, B.H., Shan, M.Q., Zhang, K.C., Cheng, F.F., Cao, Y.D., Zhang, L., Ding, A.W., 2018. Anti-thrombotic and pro-angiogenic effects of *Rubia cordifolia* extract in zebrafish. Journal of Ethnopharmacology. 219, 152–160. https://doi.org/10.1016/j.jep.2017.11.005

Choi, J.H., Kim, D.W., Park, S.E., Lee, H.J., Kim, K.M., Kim, K.J., Kim, M.K., Kim, S.J., Kim, S., 2015. Anti-thrombotic effect of rutin isolated from *Dendropanax morbifera* Leveille. Journal of Bioscience and Bioengineering. 120(2), 181–186. https://doi.org/10.1016/j.jbiosc.2014.12.012

Choi, J.H., Kim, S., 2019. Antioxidant and antithrombotic properties of *Dendropanax morbifera* Léveille (Araliaceae) and its ferments produced by fermentation processing. Journal of Food Biochemistry(12), 43–43. https://doi.org/10.1111/jfbc.13056

Chourasia, S.R., Kashyap, R.S., Deopujari, J.Y., Purohit, H.J.,

Taori, G.M., Daginawala, H.F., 2014. Effect of aqueous extract and fractions of *Fagonia arabica* on in vitro anticoagulant activity. Clinical and Applied Thrombosis. 20(8), 844–850.

Cines, D.B., Pollak, E.S., Buck, C.A., Loscalzo, J., Zimmerman, G.A., Mcever, R.P., Pober, J.S., Wick, T.M., Konkle, B.A., Schwartz, B.S., Barnathan, E.S., Mccrae, K.R., Hug, B.A., Schmidt, A., Stern, D.M., 1998. Endothelial Cells in Physiology and in the Pathophysiology of Vascular Disorders. The Journal of The American Society of Hematology. 91(10), 3527–3561. https://doi.org/10.1182/blood.V91.10.3527

Ciumărnean, L., Milaciu, M.V., Runcan, O., Vesa, S.C., Răchisan, A.L., Negrean, V., Perné, M.G., Donca, V.I., Alexescu, T.G., Para, I., Dogaru, G., 2020. The effects of flavonoids in cardiovascular diseases. Molecules. 25(18), 4320–4320. https://doi.org/10.3390/molecules25184320

Coller, B.S., 1997. Platelet GPIIb/IIIa antagonists: The first anti-integrin receptor therapeutics. Journal of Clinical Investigation. 99(7), 1467–1471. https://doi.org/10.1172/jci119307

Collin, N., Assumpção, T.C.F., Mizurini, D.M., Gilmore, D.C., Dutra-Oliveira, A., Kotsyfakis, M., Sá-Nunes, A., Teixeira, C., Ribeiro, J.M.C., Monteiro, R.Q., Valenzuela, J.G., Francischetti, I.M.B., 2012. Lufaxin, a novel factor Xa inhibitor from the salivary gland of the sand fly *Lutzomyia longipalpis* blocks protease-activated receptor 2 activation and inhibits inflammation and thrombosis in vivo. Arteriosclerosis, Thrombosis, and Vascular Biology. 32(9), 2185–2196. https://doi.org/10.1161/atvbaha.112.253906

Colman, R.W., Schmaier, A.H., 1997. Contact system: A vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. Blood. 90(10), 3819–3843. https://doi.org/10.1182/blood.V90.10.3819

Dahmer, T., Berger, M., Barlette, A.G., Reck, J., Segalin, J., Verza, S., Ortega, G.G., Gnoatto, S.C.B., Guimarães, J.A., Verli, H., Gosmann, G., 2012. Antithrombotic effect of chikusetsusaponin IVa isolated from *Ilex paraguariensis* (Maté). Journal of Medicinal Food. 15(12), 1073–1080. https://doi.org/10.1089/jmf.2011.0320

Davì, G., Patrono, C., 2007. Platelet Activation and Atherothrombosis. New England Journal of Medicine. 357(24), 2482–2494. https://doi.org/10.1056/nejmra071014

Dobesh, P.P., Oestreich, J.H., 2014. Ticagrelor: Pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. Pharmacotherapy. 34(10), 1077–1090. https://doi.org/10.1002/phar.1477

Emon, N.U., Alam, S., Rudra, S., Riya, S.R., Paul, A., Hossen, S.M.M., Kulsum, U., Ganguly, A., 2021. Antidepressant, anxiolytic, antipyretic, and thrombolytic profiling of methanol extract of the aerial part of *Piper nigrum*: In vivo, in vitro, and in silico approaches. Food Science and Nutrition. 9(2), 833–846. https://doi.org/10.1002/fsn3.2047

Fei, Y., Wang, S., Yang, L., Qiu, Y., Ying, Li, Y., Liu, W., Yuan, Xi, T., Fang, W., Li, Y.M., 2017. *Salvia miltiorrhiza* Bunge (Danshen) extract attenuates permanent cerebral ischemia through inhibiting platelet activation in rats. Journal of Ethnopharmacology. 207, 57–66. https://doi.org/10.1016/j.jep.2017.06.023

Feigin, V.L., Forouzanfar, M.H., Krishnamurthi, R., Mensah, G.A., Connor, M., Bennett, D.A., Moran, A.E., Sacco, R.L., Anderson, L., Truelsen, T., O'donnell, M., Venketasubramanian, N., Barker-Collo, S., Lawes, C.M.M., Wang, W., Shinohara, Y., Witt, E., Ezzati, M., Naghavi, M., 2014. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. The Lancet. 383(9913), 61953–61957. https://doi.org/10.1016/S0140-6736(13)61953-4

Félix-Silva, J., Souza, T., Camara, R.B., Arro, G., Cabral, B., Silva-Júnior, A.A., Rebecchi, I.M.M., Zucolotto, S.M., Rocha, H.A., Lexandr, O., Fernandes-Pedrosa, M., De, F., 2014. In vitro anticoagulant and antioxidant activities of *Jatropha gossypiifolia* L. (Euphorbiaceae) leaves aiming therapeutical applications. BMC Complementary and Alternative Medicine. 14, 405. https://doi.org/10.1186/1472-6882-14-405

Freedman, J.E., 2008. Oxidative stress and platelets. Arteriosclerosis, Thrombosis, and Vascular Biology. 28(3), 11–16. https://doi.org/10.1161/ATVBAHA.107.159178

Friedrich, T., Kroger, B., Bialojan, S., Lemaire, H.G., Hoffken, H.W., Reuschenbach, P., Otte, M., Dodt, J., 1993. A Kazal-type inhibitor with thrombin specificity from *Rhodnius prolixus*. Journal of Biological Chemistry. 268(22), 16216–16222. https://doi.org/10.1016/S0021-9258(19)85408-X

Fuentes, E., Alarcón, M., Fuentes, M., Carrasco, G., Palomo, I., 2014. A Novel Role of *Eruca sativa* Mill. (rocket) extract: Antiplatelet (NF-κB Inhibition) and antithrombotic activities. Nutrients. 6(12), 5839–5852. https://doi.org/10.3390/nu6125839

Furie, B., Furie, B.C., 2007. In vivo thrombus formation. Journal of Thrombosis and Haemostasis. 5, 12–17. https://doi.org/10.1111/j.1538-7836.2007.02482.x

Gachet, C., 2005. The platelet P2 receptors as molecular targets for old and new antiplatelet drugs. Pharmacology and Therapeutics. 108(2), 180–192. https://doi.org/10.1016/j.pharmthera.2005.03.009

Gadi, D., Bnouham, M., Aziz, M., Ziyyat, A., Legssyer, A., Legrand, C., Lafeve, F.F., Mekhfi, H., 2009. Parsley extract inhibits in vitro and ex vivo platelet aggregation and prolongs bleeding time in rats. Journal of Ethnopharmacology. 125, 170–174. https://doi.org/10.1016/j.jep.2009.05.014

Gailani, D., Broze, G.J., 1991. Factor XI activation in a revised model of blood coagulation. Science. 253, 909–912. https://doi.org/10.1126/science.1652157

Gale, A.J., 2011. Current Understanding of Hemostasis. Toxicologic Pathology. 39(1), 273–280.

Gao, P.Y., Li, L.Z., Liu, K.C., Sun, C., Sun, X., Wu, Y.N., Song, S.J., 2017. Natural terpenoid glycosides with in vitro / vivo antithrombotic profiles from the leaves of *Crataegus pinnatifida*. RSC Advances. 7, 48466–48474. https://doi.org/10.1039/c7ra10768d https://doi.org/10.1039/C7RA10768D

Gregson, J., Kaptoge, S., Bolton, T., Pennells, L., Willeit, P., Burgess, S., Bell, S., Sweeting, M., Rimm, E.B., Kabrhel, C., Zöller, B., Assmann, G., Gudnason, V., Folsom, A.R., Arndt, V., Fletcher, A., Norman, P.E., Nordestgaard, B.G., Kitamura, A., Meade, T., 2019. Cardiovascular Risk Factors Associated With Venous Thromboembolism. JAMA Cardiol.. 4, 163–173. 10.1001/jamacardio.2018.4537

Grover, S.P., Mackman, N., 2019. Intrinsic pathway of coagulation and thrombosis: Insights from animal models. Arteriosclerosis, Thrombosis, and Vascular Biology. 39(3), 331–338. https://doi.org/10.1161/atvbaha.118.312130

Guerrero, J.A., Lozano, M.L., Castillo, J., Benavente-García, O., Vicente, V., Rivera, J., 2005. Flavonoids inhibit platelet function through binding to the thromboxane A2 receptor. Journal of Thrombosis and Haemostasis. 3, 369–376. https://doi.org/10.1111/j.1538-7836.2004.01099.x

Hacke, W., Zoppo, G.J., Del, Harker, L.A., 1987. Thrombosis and cerebrovascular disease, K. Poeck, E. B., Ringelstein, W., Hacke, (Eds.), New Trends in Diagnosis and Management of Stroke. Springer, pp. 59–74. https://doi.org/10.1007/978-3-642-72996-6_4

Han, N., Gu, Y., Ye, C., Cao, Y., Liu, Z., Yin, J., 2012. Antithrombotic activity of fractions and components obtained from raspberry leaves (*Rubus chingii*). Food Chemistry. 132, 181–185. https://doi.org/10

.1016/j.foodchem.2011.10.051
Hansson, G.K., 2005. Inflammation, Atherosclerosis, and Coronary Artery Disease. The New England Journal of Medicine. 352(16), 1685–1695. https://doi.org/10.1056/nejmra043430
Hanuš, L.O., Hod, Y., 2020. Terpenes/Terpenoids in Cannabis: Are They Important? . Medical Cannabis and Cannabinoids. 3, 1–36. https://doi.org/10.1159/000509733
He, X., Zeng, Y., Jiang, W., 2021. Eleven isoquinoline alkaloids on inhibiting tissue factor activity: Structure-activity relationships and molecular docking. Zeitschrift Fur Naturforschung - Section C Journal of Biosciences. 76(1-2), 11–19. https://doi.org/10.1515/znc-2019-0223
Heemskerk, J.W.M., Bevers, E.M., Lindhout, T., 2002. Platelet activation and blood coagulation. Thrombosis and Haemostasis. 88(2), 186–193. 10.1055/s-0037-1613209
Hennekens, C.H., Sechenova, O., Hollar, D., Serebruany, V.L., 2006. Dose of aspirin in the treatment and prevention of cardiovascular disease: Current and future directions. Journal of Cardiovascular Pharmacology and Therapeutics. 11(3), 170–176. https://doi.org/10.1177/1074248406292263
Henzlova, M.J., Duvall, W.L., Einstein, A.J., Travin, M.I., Verberne, H.J., 2016. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. Journal of Nuclear Cardiology. 23(3), 606–639. https://doi.org/10.1007/s12350-015-0387-x
Herzig, V., Cristofori-Armstrong, B., Israel, M.R., Nixon, S.A., Vetter, I., King, G.F., 2020. Animal toxins - Nature's evolutionary-refined toolkit for basic research and drug discovery. Biochemical Pharmacology. 181, 114096. https://doi.org/10.1016/j.bcp.2020.114096
Holy, E.W., Forestier, M., Richter, E.K., Akhmedov, A., Leiber, F., Camici, G.G., Mocharla, P., Lüscher, T.F., Beer, J.H., Tanner, F.C., 2011. Dietary α-linolenic acid inhibits arterial thrombus formation, tissue factor expression, and platelet activation. Arteriosclerosis, Thrombosis, and Vascular Biology. 31(8), 1772–1780.
Hong, Q., Ma, Z.C., Huang, H., Wang, Y.G., Tan, H.L., Xiao, C.R., Liang, Q., De, Zhang, H.T., Gao, Y., 2016. Antithrombotic activities of ferulic acid via intracellular cyclic nucleotide signaling. European Journal of Pharmacology. 777, 1–8. https://doi.org/10.1016/j.ejphar.2016.01.005
Hongo, R.H., Brent, B.N., 2001. Association of eptifibatide and acute profound thrombocytopenia. American Journal of Cardiology. 88(4), 428–431. https://doi.org/10.1016/s0002-9149(01)01695-2
Horn, F., Santos, P.C.D., Termignoni, C., 2000. *Boophilus microplus* anticoagulant protein: An antithrombin inhibitor isolated from the cattle tick saliva. Archives of Biochemistry and Biophysics. 384(1), 68–73. https://doi.org/10.1006/abbi.2000.2076
Hsiao, G., Chang, C.Y., Shen, M.Y., Chou, D.S., Tzeng, S.H., Chen, T.F., Sheu, J.R., 2005. α-Naphthoflavone, a potent antiplatelet flavonoid, is mediated through inhibition of phospolipase C activity and stimulation of cyclic GMP formation. Journal of Agricultural and Food Chemistry. 53, 5179–5186. https://doi.org/10.1021/jf0500738
Huzoor-Akbar, Navran, S.S., Chang, J., Miller, D.D., Feller, D.R., 1982. Investigation of the effects of phospholipase C on human platelets: evidence that aggregation induced by phospholipase C is independent of prostaglandin generation, released ADP and is modulated by cyclic AMP. Thrombosis Research. 27(4), 405–417. https://doi.org/10.1016/0049-3848(82)90058-5
Jakubowski, J.A., Winters, K.J., Naganuma, H., Wallentin, L., 2007. Prasugrel: A novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. Cardiovascular Drug Reviews. 25(4), 357–374. https://doi.org/10.1111/j.1527-3466.2007.00027.x
Jiang, G., Zhang, W., Peng, M., Yan, W., 2017. Effect of lumbrokinase on serum neuron-specific enolase in patients with acute cerebral infarction. Journal of Central South University (Medical Sciences)(10), 1156–1162. https://doi.org/10.11817/j.issn.1672-7347.2017.10.005
Jin, Y.R., Im, J.H., Park, E.S., Cho, M.R., Han, X.H., Lee, J.J., Lim, Y., Kim, T.J., Yun, Y.P., 2008. Antiplatelet activity of epigallocatechin gallate is mediated by the inhibition of PLCγ2 phosphorylation, elevation of PGD2 production, and maintaining calcium-ATPase activity. Journal of Cardiovascular Pharmacology. 51(1), 45–54. https://doi.org/10.1097/fjc.0b013e31815ab4b6
Kamruzzaman, S.M., Endale, M., Oh, W.J., Park, S.C., Kim, K.S., Hong, J.H., Kwak, Y.S., Yun, B.S., Rhee, M.H., 2010. Inhibitory effects of *Bulnesia sarmienti* aqueous extract on agonist-induced platelet activation and thrombus formation involves mitogen-activated protein kinases. Journal of Ethnopharmacology. 130(3), 614–620. https://doi.org/10.1016/j.jep.2010.05.049
Kasimu, R., Wang, X., Wang, X., Hu, J., Wang, X., Mu, Y., 2018. Antithrombotic effects and related mechanisms of *Salvia deserta* Schang root EtOAc extracts. Scientific Reports. 8(1), 17753. https://doi.org/10.1038/s41598-018-36026-7
Kelton, J.G., 2002. Heparin-induced thrombocytopenia: An overview. Blood Reviews. 16(1), 77–80. https://doi.org/10.1054/blre.2001.0189
Kim, K.H., Lee, H.J., Lee, J.H., Jang, Y.S., Kim, D.K., Shim, B.S., Cho, K.H., Ko, S.G., Ahn, K.S., Kim, S.H., 2008. Blockade of glycoprotein IIb/IIIa mediates the antithrombotic activity of butanol fraction of *Actinostemma lobatum* Maxim. Journal of Ethnopharmacology. 116(3), 431–438. https://doi.org/10.1016/j.jep.2007.12.012
Kim, K.J., Kim, M.S., Seok, P.R., Shin, J.H., Kim, J.Y., 2019. Antithrombotic Effect of *Artemisia princeps* Pampanini Extracts in Vitro and in FeCl3-Induced Thrombosis Rats. Journal of Food Science. 84(10), 3037–3044. https://doi.org/10.1111/1750-3841.14786
Klafke, J.Z., Silva, M.A.D., Rossato, M.F., Trevisan, G., Walker, C.I.B., Leal, C.A.M., Borges, D., Schetinger, M.R.C., Moresco, R., Duarte, M.M.M.F., Santos, A.R.S.D., Viecili, P.R., Ferreira, J., 2012. Antiplatelet, antithrombotic, and fibrinolytic activities of *Campomanesia xanthocarpa*. Evidence-Based Complementary and Alternative Medicine. 2012, 954748. https://doi.org/10.1155/2012/954748 https://doi.org/10.1155/2012/954748
Kong, D.F., Califf, R.M., Miller, D.P., Moliterno, D.J., White, H.D., Harrington, R.A., Tcheng, J.E., Lincoff, A.M., Hasselblad, V., Topol, E.J., 1998. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation. 98(25), 2829–2835. https://doi.org/10.1161/01.cir.98.25.2829
Kreutz, R., 2012. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. Fundamental and Clinical Pharmacology. 26, 27–32. https://doi.org/10.1111/j.1472-8206.2011.00981.x
Ku, S.K., Bae, J.S., 2014a. Antiplatelet, anticoagulant, and profibrinolytic activities of withaferin A. Vascular Pharmacology. 60(3), 120–126. https://doi.org/10.1016/j.vph.2014.01.009
Ku, S.K., Bae, J.S., 2014b. Antithrombotic activities of wogonin and wogonoside via inhibiting platelet aggregation. Fitoterapia. 98, 27–35. https://doi.org/10.1016/j.fitote.2014.07.006
Ku, S.K., Kim, J.A., Han, C.K., Bae, J.S., 2013. Antithrombotic activities of Epi-Sesamin in vitro and in vivo. American Journal of Chinese Medicine. 41(6), 1313–1327. https://doi.org/10.1142/s0192415x13500882

Ku, S.K., Yoon, E.K., Lee, W., Kwon, S., Lee, T., Bae, J.S., 2016. Antithrombotic and antiplatelet activities of pelargonidin in vivo and in vitro. Archives of Pharmacal Research. 39(3), 398–408. https://doi.org/10.1007/s12272-016-0708-x

Kuruvilla, M., Gurk-Turner, C., 2001. A Review of Warfarin Dosing and Monitoring. . Proceedings (Baylor University Medical Center). 14(3), 305–306.

Kwon, S.U., Lee, H.Y., Xin, M., Ji, S.J., Cho, H.K., Kim, D.S., Kim, D.K., Lee, Y.M., 2016. Antithrombotic activity of *Vitis labrusca* extract on rat platelet aggregation. Blood Coagulation and Fibrinolysis. 27(2), 141–146. https://doi.org/10.1097/mbc.0000000000000394

Lai, R., Takeuchi, H., Jonczy, J., Rees, H.H., Turner, P.C., 2004. A thrombin inhibitor from the ixodid tick, *Amblyomma hebraeum*. Gene. 342(2), 243–249. https://doi.org/10.1016/j.gene.2004.07.012

Lee, B.J., Jo, I.Y., Bu, Y., Park, J.W., Maeng, S., Kang, H., Jang, W., Hwang, D.S., Lee, W., Min, K., Kim, J.I., Yoo, H.H., Lew, J.H., 2011. Antiplatelet effects of *Spatholobus suberectus* via inhibition of the glycoprotein IIb/IIIa receptor. Journal of Ethnopharmacology. 134(2), 460–467. https://doi.org/10.1016/j.jep.2010.12.039

Lee, D.S., Kim, T.H., Jung, Y.S., 2014. Inhibitory effect of allyl isothiocyanate on platelet aggregation. Journal of Agricultural and Food Chemistry. 62(29), 7131–7139. https://doi.org/10.1021/jf4041518

Lee, J.H., Kim, M., Chang, K.H., Hong, C.Y., Na, C.S., Dong, M.S., Lee, D., Lee, M.Y., 2014. Antiplatelet effects of *Rhus verniciflua* stokes heartwood and its active constituents -Fisetin, Butein, and Sulfuretin -In Rats. Journal of Medicinal Food. 18(1), 1–10. https://doi.org/10.1089/jmf.2013.3116

Lee, M.H., Son, Y.K., Han, Y.N., 2002. Tissue factor inhibitory flavonoids from the fruits of *Chaenomeles sinensis*. Archives of Pharmacal Research. 25(6), 842–850. https://doi.org/10.1007/bf02977002

Lee, S., Di, Huang, W.C., Peng, N.J., Hu, C., 2017. Dipyridamole-induced adverse effects in myocardial perfusion scans: Dynamic evaluation. . IJC Heart and Vasculature. 14, 14–19. https://doi.org/10.1016/j.ijcha.2016.11.002 https://doi.org/10.1016/j.ijcha.2016.11.002

Lee, S.M., Moon, J., Chung, J.H., Cha, Y.J., Shin, M.J., 2013. Effect of quercetin-rich onion peel extracts on arterial thrombosis in rats. Food and Chemical Toxicology. 57, 99–105. https://doi.org/10.1016/j.fct.2013.03.008

Lee, W., Bae, J.S., 2015. Antithrombotic and antiplatelet activities of vicenin-2. Blood Coagulation and Fibrinolysis. 26(6), 628–634. https://doi.org/10.1097/mbc.0000000000000320

Lee, W., Ku, S.K., Kim, M.A., Bae, J.S., 2017. Anti-factor Xa activities of zingerone with anti-platelet aggregation activity. Food and Chemical Toxicology. 105, 186–193. https://doi.org/10.1016/j.fct.2017.04.012

Li, B.X., Dai, X., Xu, X.R., Adili, R., Neves, M.A.D., Lei, X., Shen, C., Zhu, G., Wang, Y., Zhou, H., Hou, Y., Ni, T., Pasman, Y., Yang, Z., Qian, F., Zhao, Y., Gao, Y., Liu, J., Teng, M., Ni, H., 2021. In vitro assessment and phase I randomized clinical trial of anfibatide a snake venom derived anti-thrombotic agent targeting human platelet GPIbα. Scientific Reports. 11, 11663. https://doi.org/10.1038/s41598-021-91165-8

Li, C., Cai, C., Zheng, X., Sun, J., Ye, L., 2019. Orientin suppresses oxidized low-density lipoproteins induced inflammation and oxidative stress of macrophages in atherosclerosis. Bioscience, Biotechnology and Biochemistry. 84(4), 774–779. https://doi.org/10.1080/09168451.2019.1702871

Li, C.T., Wang, H.B., Xu, B.J., 2013. A comparative study on anticoagulant activities of three Chinese herbal medicines from the genus *Panax* and anticoagulant activities of ginsenosides Rg1 and Rg2. Pharmaceutical Biology. 51(8), 1077–1080. https://doi.org/10.3109/13880209.2013.775164

Li, W., Tang, X., Yi, W., Li, Q., Ren, L., Liu, X., Chu, C., Ozaki, Y., Zhang, J., Zhu, L., 2013. Glaucocalyxin A inhibits platelet activation and thrombus formation preferentially via GPVI signaling pathway. PLoS ONE. 8(12), e85120. https://doi.org/10.1371/journal.pone.0085120

Li, Y., Wang, N., 2010. Antithrombotic effects of Danggui, Honghua and potential drug interaction with clopidogrel. Journal of Ethnopharmacology. 128(3), 623–628. https://doi.org/10.1016/j.jep.2010.02.003

Li, Y.H., Sun, X.P., Zhang, Y.Q., Wang, N.S., 2008. The antithrombotic effect of Borneol related to its anticoagulant property. American Journal of Chinese Medicine. 36(4), 719–727. https://doi.org/10.1142/s0192415x08006181

Lin, K.H., Kuo, J.R., Lu, W.J., Chung, C.L., Chou, D.S., Huang, S.Y., Lee, H.C., Sheu, J.R., 2013. Hinokitiol inhibits platelet activation ex vivo and thrombus formation in vivo. Biochemical Pharmacology. 85(10), 1478–1485. https://doi.org/10.1016/j.bcp.2013.02.027

Lippi, G., Franchini, M., Targher, G., 2011. Arterial thrombus formation in cardiovascular disease. Nature Reviews Cardiology. 8(9), 502–512. https://doi.org/10.1038/nrcardio.2011.91

Liu, X., Hao, J., Shan, X., Zhang, X., Zhao, X., Li, Q., Wang, X., Cai, C., Li, G., Yu, G., 2016. Antithrombotic activities of fucosylated chondroitin sulfates and their depolymerized fragments from two sea cucumbers. Carbohydrate Polymers. 152, 343–350. https://doi.org/10.1016/j.carbpol.2016.06.106

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S.Y., Almazroa, M.A., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Barker-Collo, S., Bartels, D.H., Murray, C.J.L., 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 380(9859), 2095–2128. https://doi.org/10.1016/S0140-6736(12)61728-0

Lu, Y., He, Z., Shen, X., Xu, X., Fan, J., Wu, S., Zhang, D., 2012. Cholesterol-lowering effect of allicin on hypercholesterolemic ICR mice. Oxidative Medicine and Cellular Longevity. https://doi.org/10.1155/2012/489690

Mackman, N., 2008. Triggers, targets and treatments for thrombosis. Nature(7181), 914–918. https://doi.org/10.1038/nature06797

Maione, F., De Feo, V., Caiazzo, E., De Martino, L., Cicala, C., Mascolo, N., 2014. Tanshinone IIA, a major component of *Salvia milthorriza* Bunge, inhibits platelet activation via Erk-2 signaling pathway. Journal of Ethnopharmacology. 155, 1236–1242. https://doi.org/10.1016/j.jep.2014.07.010

Malaguarnera, M., Vacante, M., Avitabile, T., Malaguarnera, M., Cammalleri, L., Motta, M., 2009. L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes. American Journal of Clinical Nutrition. 89, 71–76. https://doi.org/10.3945/ajcn.2008.26251

Massimo, C., Scarpelli, P., Penco, M., Tozzi-Ciancarelli, M.G., 2004. Possible involvement of plasma antioxidant defences in training-associated decrease of platelet responsiveness in humans. European Journal of Applied Physiology. 91(4), 406–412. https://doi.org/10.1007/s00421-003-0998-9

Mcnicol, A., 1993. The effects of genistein on platelet function are due to thromboxane receptor antagonism rather than inhibition of tyrosine kinase. Prostaglandins, Leukotrienes and Essential Fatty Acids. 48(5), 379–384. https://doi.org/10.1016/0952-3278(93)90118-g

Meadows, T.A., Bhatt, D.L., 2007. Clinical aspects of platelet inhibitors and thrombus formation. Circulation Research. 100(9), 1261–1275. https://doi.org/10.1161/01.res.0000264509.36234.51

Mega, J.L., Simon, T., 2015. Pharmacology of antithrombotic drugs: An assessment of oral antiplatelet and anticoagulant treatments. The Lancet. 386(9990), 281–291. https://doi.org/10.1016/s0140-6736(15)60243-4

Mende, K., Petoukhova, O., Koulitchkova, V., Schaub, G.A., Lange, U., Kaufmann, R., Nowak, G., 1999. Dipetalogastin, a potent thrombin inhibitor from the blood-sucking insect Dipetalogaster maximus. cDNA cloning, expression and characterization. European Journal of Biochemistry. 266(2), 583–590. https://doi.org/10.1046/j.1432-1327.1999.00895.x

Mendes-Silva, W., Assafim, M., Ruta, B., Monteiro, R.Q., Guimarães, J.A., Zingali, R.B., 2003. Antithrombotic effect of Glycyrrhizin, a plant-derived thrombin inhibitor. Thrombosis Research. 112, 93–98. https://doi.org/10.1016/j.thromres.2003.10.014

Michelson, A.D., 2008. P2Y 12 Antagonism promises and challenges. Arteriosclerosis, Thrombosis, and Vascular Biology. 28(3), 33–38. https://doi.org/10.1161/atvbaha.107.160689

Min, S.K., Kwon, O.C., Lee, S., Park, K.H., Kim, J.K., 2012. An antithrombotic fucoidan, unlike heparin, does not prolong bleeding time in a murine arterial thrombosis model: A comparative study of *Undaria pinnatifida* sporophylls and *Fucus vesiculosus*. Phytotherapy Research. 26(5), 752–757. https://doi.org/10.1002/ptr.3628

Mnonopi, N., Levendal, R.A., Davies-Coleman, M.T., Frost, C.L., 2011. The cardioprotective effects of marrubiin, a diterpenoid found in *Leonotis leonurus* extracts. Journal of Ethnopharmacology. 138, 67–75. https://doi.org/10.1016/j.jep.2011.08.041

Mohamed, A.S., Ibrahim, W.M., Zaki, N.I., Ali, S.B., Soliman, A.M., 2019. Effectiveness of *Coelatura aegyptiaca* Extract Combination with Atorvastatin on Experimentally Induced Hyperlipidemia in Rats. Evidence-Based Complementary and Alternative Medicine. 2019, 9726137. https://doi.org/10.1155/2019/9726137 https://doi.org/10.1155/2019/9726137

Moons, A.H.M., Peters, R.J.G., Bijsterveld, N.R., Piek, J.J., Prins, M.H., Vlasuk, G.P., Rote, W.E., Büller, H.R., 2003. Recombinant nematode anticoagulant protein c2, an inhibitor of the tissue factor/factor VIIa complex, in patients undergoing elective coronary angioplasty. Journal of the American College of Cardiology. 41(12), 2147–2153. https://doi.org/10.1016/s0735-1097(03)00478-9

Morrissey, J.H., 2001. Tissue factor: An enzyme cofactor and a true receptor. Thrombosis and Haemostasis. 86, 66–74. 10.1055/s-0037-1616202

Mukherjee, D., Roffi, M., 2008. Glycoprotein IIb/IIIa receptor inhibitors in 2008: Do they still have a role. Journal of Interventional Cardiology. 21(2), 118–121. https://doi.org/10.1111/j.1540-8183.2007.00344.x

Mulloy, B., Hogwood, J., Gray, E., Lever, R., Page, C.P., 2015. Pharmacology of Heparin and Related Drugs. Pharmacological Reviews. 68, 76–141. https://doi.org/10.1124/pr.115.011247

Muñoz, Y., Garrido, A., Valladares, L., 2009. Equol is more active than soy isoflavone itself to compete for binding to thromboxane A2 receptor in human platelets. Thrombosis Research. 123(5), 740–744. https://doi.org/10.1016/j.thromres.2008.07.011

Nanau, R.M., Delzor, F., Neuman, M.G., 2014. Efficacy and safety of prasugrel in acute coronary syndrome patients. Clinical Biochemistry. 47, 516–528. https://doi.org/10.1097/mjt.0000000000000096

Navarro-Núñez, L., Lozano, M.L., Palomo, M., Martínez, C., Vicente, V., Castillo, J., Benavente-García, O., Diaz-Ricart, M., Escolar, G., Rivera, J., 2008. Apigenin inhibits platelet adhesion and thrombus formation and synergizes with aspirin in the suppression of the arachidonic acid pathway. Journal of Agricultural and Food Chemistry. 56(9), 2970–2976. https://doi.org/10.1021/jf0723209

Nienaber, J., Gaspar, A.R.M., Neitz, A.W.H., 1999. Savignin, a potent thrombin inhibitor isolated from the salivary glands of the tick *Ornithodoros savignyi* (Acari: Argasidae). Experimental Parasitology. 93(2), 82–91. https://doi.org/10.1006/expr.1999.4448

Norris, L.A., 2003. Blood coagulation. . Best Practice & Research Clinical Obstetrics & Gynaecology. 17(3), 369–383. https://doi.org/10.1016/s1521-6934(03)00014-2

Oh, W.J., Endale, M., Park, S.C., Cho, J.Y., Rhee, M.H., 2012. Dual roles of quercetin in platelets: Phosphoinositide-3-kinase and MAP kinases inhibition, and cAMP-dependent vasodilator-stimulated phosphoprotein stimulation. . Evidence-Based Complementary and Alternative Medicine. 2012, 485262. https://doi.org/10.1155/2012/485262

Ok, W.J., Cho, H., Kim, H.H., Lee, D.H., Kang, H.Y., Kwon, H.W., Rhee, M.H., Kim, M., Park, H.J., 2012. Epigallocatechin-3-gallate has an anti-platelet effect in a cyclic AMP-dependent manner. Journal of Atherosclerosis and Thrombosis. 19(4), 337–348. https://doi.org/10.5551/jat.10363

Okazaki, K., Kawazoe, K., Takaishi, Y., 2002. Human platelet aggregation inhibitors from thyme (*Thymus vulgaris* L.). Phytotherapy Research. 16(4), 398–399. https://doi.org/10.1002/ptr.979

Olas, B., Wachowicz, B., Stochmal, A., Oleszek, W., 2012. The polyphenol-rich extract from grape seeds inhibits platelet signaling pathways triggered by both proteolytic and non-proteolytic agonists. Platelets. 23(4), 282–289. https://doi.org/10.3109/09537104.2011.618562

O'shea, J.C., Hafley, G.E., Greenberg, S., Hasselblad, V., Lorenz, T.J., Kitt, M.M., Strony, J., Tcheng, J.E., 2001. Platelet Glycoprotein IIb/IIIa Integrin Blockade With Eptifibatide in Coronary Stent Intervention The ESPRIT Trial: A Randomized Controlled Trial. Clinical Research. 285(19), 2468–2473. https://doi.org/10.1001/jama.285.19.2468

Osoniyi, O., Onajobi, F., 2003. Coagulant and anticoagulant activities in *Jatropha curcas* latex. Journal of Ethnopharmacology. 89, 101–105. https://doi.org/10.1016/s0378-8741(03)00263-0

Otero, J.S., Hirsch, G.E., Klafke, J.Z., Porto, F.G., De Almeida, A.S., Nascimento, S., Schmidt, A., Silva, B.D., Pereira, R.L.D., Jaskulski, M., Parisi, M.M., Guarda, N.D.S., Moresco, R.N., Aita, C.A.M., Viecili, P.R.N., 2017. Inhibitory effect of *Campomanesia xanthocarpa* in platelet aggregation: Comparison and synergism with acetylsalicylic acid. Thrombosis Research. 154, 42–49. https://doi.org/10.1016/j.thromres.2017.03.020

Park, E.S., Lim, Y., Lee, S.H., Kwon, B.M., Yoo, H.S., Hong, J.T., Yun, Y.P., 2011. Antiplatelet activity of obovatol, a biphenolic component of magnolia obovata, in rat arterial thrombosis and rabbit platelet aggregation. Journal of Atherosclerosis and Thrombosis. 18(8), 659–669. https://doi.org/10.5551/jat.7427

Park, J.B., Schoene, N., 2006. Clovamide-type phenylpropenoic acid amides, N-coumaroyldopamine and N-caffeoyldopamine, inhibit platelet-leukocyte interactions via suppressing P-selectin expression. The Journal of Pharmacology and Experimental Therapeutics. 317(2), 813–819. https://doi.org/10.1124/jpet.105.097337

Patrono, C., Baigent, C., Hirsh, J., Roth, G., 2008. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 133(SUPPL. 6), 199–233. https://doi.org/10.1378/chest.08-0672

Patrono, C., Ciabarroni, G., Patrignani, P., Pugliese, F., Filabozzi, P., Catella, F., Davi, G., Forni, L., 1985. Clinical pharmacology of platelet cyclooxygenase inhibition. Circulation. 72(6), 1177–1184. https://doi.org/10.1161/01.cir.72.6.1177

Pawlaczyk, I., Czerchawski, L., Kuliczkowski, W., Karolko, B., Pilecki, W., Witkiewicz, W., Gancarz, R., 2011. Anticoagulant and anti-platelet

activity of polyphenolic-polysaccharide preparation isolated from the medicinal plant *Erigeron canadensis* L. Thrombosis Research. 127(4), 328–340. https://doi.org/10.1016/j.thromres.2010.11.031

Pawlaczyk, I., Czerchawski, L., Pilecki, W., Lamer-Zarawska, E., Gancarz, R., 2009. Polyphenolic-polysaccharide compounds from selected medicinal plants of Asteraceae and Rosaceae families: Chemical characterization and blood anticoagulant activity. Carbohydrate Polymers. 77(3), 568–575. https://doi.org/10.1016/j.carbpol.2009.01.030

Perzborn, E., Roehrig, S., Straub, A., Kubitza, D., Mueck, W., Laux, V., 2010. Rivaroxaban: A new oral factor xa inhibitor. . Arteriosclerosis, Thrombosis, and Vascular Biology. 30, 376–381. https://doi.org/10.1161/ATVBAHA.110.202978

Pifarre, R., 1998. Thrombosis and cardiovascular disease. Medical Clinics of North America. 82(3), 511–522. https://doi.org/10.1016/s0025-7125(05)70008-0

Pignatelli, P., Pulcinelli, F.M., Lenti, L., Gazzaniga, P.P., Violi, F., 1998. Hydrogen peroxide is involved in collagen-induced platelet activation. Blood. 91(2), 484–490. https://doi.org/10.1182/blood.V91.2.484

Prasad, S., Kashyap, R.S., Deopujari, J.Y., Purohit, H.J., Taori, G.M., Daginawala, H.F., 2007. Effect of *Fagonia Arabica* (Dhamasa) on in vitro thrombolysis. BMC Complementary and Alternative Medicine. 7, 36. https://doi.org/10.1186/1472-6882-7-36

Qiao, M., Tu, M., Wang, Z., Mao, F., Chen, H., Qin, L., Du, M., 2018. Identification and antithrombotic activity of peptides from blue mussel (*Mytilus edulis*) protein. International Journal of Molecular Sciences. 19(1), 138–138. https://doi.org/10.3390/ijms19010138

Quinn, M.J., Fitzgerald, D.J., 1999. Ticlopidine and clopidogrel. Circulation. 100(15), 1667–1672. https://doi.org/10.1161/01.cir.100.15.1667

Rajabi, A., Castro, A., Silva, G.S.F.D., Nelson, R.P., Thiesen, R.C., Vannucchi, A., Vine, H., Proctor, D.F., Field, S.D., Curtis, C.J., Jacobs, J.M., L, R., 2014. Choline supplementation protects against liver damage by normalizing cholesterol metabolism in Pemt/Ldlr knockout mice fed a high-fat diet. Journal of Nutrition. 144(3), 252–257. https://doi.org/10.3945/jn.113.185389

Rajput, M.S., Balekar, N., Jain, D.K., 2014. Inhibition of ADP-induced platelet aggregation and involvement of non-cellular blood chemical mediators are responsible for the antithrombotic potential of the fruits of *Lagenaria siceraria*. Chinese Journal of Natural Medicines. 12(8), 60091–60092. https://doi.org/10.1016/s1875-5364(14)60091-1

Rasche, H., 2001. Haemostasis and thrombosis: An overview. European Heart Journal Supplements. 3, 3–7. 10.1016/S1520-765X(01)90034-3

Raskob, G.E., Angchaisuksiri, P., Blanco, A.N., Buller, H., Gallus, A., Hunt, B.J., Hylek, E.M., Kakkar, A., Konstantinides, S.V., Mccumber, M., Ozaki, Y., Wendelboe, A., Weitz, J.I., 2014. Thrombosis: A Major Contributor to Global Disease Burden. Arteriosclerosis, Thrombosis, and Vascular Biology. 34(11), 2363–2371. https://doi.org/10.1161/atvbaha.114.304488

Richling, N., Herkner, H., Holzer, M., Riedmueller, E., Sterz, F., Schreiber, W., 2007. Thrombolytic therapy vs primary percutaneous intervention after ventricular fibrillation cardiac arrest due to acute ST-segment elevation myocardial infarction and its effect on outcome. American Journal of Emergency Medicine. 25(5), 545–550. https://doi.org/10.1016/j.ajem.2006.10.014

Rogers, K.C., Oliphant, C.S., Finks, S.W., 2015. Clinical efficacy and safety of cilostazol: A critical review of the literature. Drugs. 75(4), 377–395. https://doi.org/10.1007/s40265-015-0364-3

Rosado, J.A., Porras, T., Conde, M., Sage, S.O., 2001. Cyclic Nucleotides Modulate Store-mediated Calcium Entry through the Activation of Protein-tyrosine Phosphatases and Altered Actin Polymerization in Human Platelets. The Journal of Biological Chemistry. 276(19), 15666–15675. https://doi.org/10.1074/jbc.m009217200

Ryu, K.H., Han, H.Y., Lee, S.Y., Jeon, S.D., Im, G.J., Lee, B.Y., Kim, K., Lim, K.M., Chung, J.H., 2009. *Ginkgo biloba* extract enhances antiplatelet and antithrombotic effects of cilostazol without prolongation of bleeding time. Thrombosis Research. 124(3), 328–334. https://doi.org/10.1016/j.thromres.2009.02.010

Salzet, M., Chopin, V., Baert, J.L., Matias, I., Malecha, J., 2000. Theromin, a novel leech thrombin inhibitor. Journal of Biological Chemistry. 275(40), 30774–30780. https://doi.org/10.1074/jbc.m000787200

Santhakumar, A.B., Bulmer, A.C., Singh, I., 2014. A review of the mechanisms and effectiveness of dietary polyphenols in reducing oxidative stress and thrombotic risk. Journal of Human Nutrition and Dietetics. 27(1), 1–21. https://doi.org/10.1111/jhn.12177

Sawyer, R.T., 1991. Thrombolytics and anticoagulants from leeches. Bio/Technology. 9(6), 513–518. https://doi.org/10.1038/nbt0691-513

Seo, E.J., Lee, S.Y., Kang, S.S., Jung, Y.S., 2013. *Zizyphus jujuba* and its active component jujuboside B inhibit platelet aggregation. Phytotherapy Research. 27(6), 829–834. https://doi.org/10.1002/ptr.4809

Shaito, A., Thuan, D.T.B., Phu, H.T., Nguyen, T.H.D., Hasan, H., Halabi, S., Abdelhady, S., Nasrallah, G.K., Eid, A.H., Pintus, G., 2020. Herbal Medicine for Cardiovascular Diseases: Efficacy, Mechanisms, and Safety. Frontiers in Pharmacology. 11, 422. https://doi.org/10.3389/fphar.2020.00422

Shatoor, A.S., Soliman, H., Al-Hashem, F., Gamal, B., El, Othman, A., El-Menshawy, N., 2012. Effect of Hawthorn (*Crataegus aronia* syn. Azarolus (L)) on Platelet Function in Albino Wistar Rats. Thrombosis Research. 130, 75–80. https://doi.org/10.1016/j.thromres.2012.01.001

Shen, M.Y., Hsiao, G., Liu, C.L., Fong, T.H., Lin, K.H., Chou, D.S., Sheu, J.R., 2007. Inhibitory mechanisms of resveratrol in platelet activation: Pivotal roles of p38 MAPK and NO/cyclic GMP. British Journal of Haematology. 139(3), 475–485. https://doi.org/10.1111/j.1365-2141.2007.06788.x

Sheng, S., Wang, J., Wang, L., Liu, H., Li, P., Liu, M., Long, C., Xie, C., Xie, X., Su, W., 2014. Network pharmacology analyses of the antithrombotic pharmacological mechanism of Fufang Xueshuantong Capsule with experimental support using disseminated intravascular coagulation rats. Journal of Ethnopharmacology. 154(3), 735–744. https://doi.org/10.1016/j.jep.2014.04.048

Sheu, J.R., Hsiao, G., Chou, P.H., Shen, M.Y., Chou, D.S., 2004. Mechanisms involved in the antiplatelet activity of rutin, a glycoside of the flavonol quercetin, in human platelets. Journal of Agricultural and Food Chemistry. 52(14), 4414–4418. https://doi.org/10.1021/jf040059f

Shi, Y.N., Shi, Y.M., Yang, L., Li, X.C., Zhao, J.H., Qu, Y., Zhu, H.T., Wang, D., Cheng, R.R., Yang, C.R., Xu, M., Zhang, Y.J., 2015. Lignans and aromatic glycosides from *Piper wallichii* and their antithrombotic activities. Journal of Ethnopharmacology. 162, 87–96. https://doi.org/10.1016/j.jep.2014.12.038

Shih, C.Y., Chou, T.C., 2012. The antiplatelet activity of magnolol is mediated by PPAR-β/γ. Biochemical Pharmacology. 84(6), 793–803. https://doi.org/10.1016/j.bcp.2012.06.022

Shrivastava, A.K., Chaudhary, D., Shrestha, L., Palikhey, A., Yaadav, C.K., Basyal, D., Joshi, B., Shekh, M.U., 2022. In silico Investigation of inhibitory characteristics of phytoconstituents from *Moringa oleifera* against SARS-CoV-2 viral proteins. Natural Resources for Human Health, 1–26. https://doi.org/10.53365/nrfhh/153401

Singh, I., Mok, M., Christensen, A.M., Turner, A.H., Hawley, J.A.,

2008. The effects of polyphenols in olive leaves on platelet function. Nutrition, Metabolism and Cardiovascular Diseases. 18, 127–132. j.numecd.2006.09.001

Sivanesan, S., Taylor, A., Zhang, J., Bakovic, M., 2018. Betaine and Choline Improve Lipid Homeostasis in Obesity by Participation in Mitochondrial Oxidative Demethylation. Frontiers in Nutrition. 5, 61. https://doi.org/10.3389/fnut.2018.00061

Song, Y., Yang, C.J., Yu, K., Li, F.M., 2011. In vivo Antithrombotic and Antiplatelet Activities of a Quantified *Acanthopanax sessiliflorus* Fruit Extract. Chinese Journal of Natural Medicines. 9(2), 141–145. https://doi.org/10.3724/SP.J.1009.2011.00141

Stern, C.S., Lebowitz, J., 2010. Latest drug developments in the field of cardiovascular disease. International Journal of Angiology. 19(3), 100–105. https://doi.org/10.1055/s-0031-1278379

Strube, K.H., Kroger, B., Bialojan, S., Otte, M., Dodt, J., 1993. Isolation, sequence analysis, and cloning of haemadin. An anticoagulant peptide from the Indian leech. Journal of Biological Chemistry. 268(12), 52916–52917. https://doi.org/10.1016/S0021-9258(18)52916-1

Suzuki, Y., Kondo, K., Ikeda, Y., Umemura, K., 2001. Antithrombotic effect of geniposide and genipin in the mouse thrombosis model. Planta Medica. 67(9), 807–810. https://doi.org/10.1055/s-2001-18842

Tang, W., Cao, J., Zhang, X., Zhao, Y., 2015. *Osmanthus fragrans* seeds, a source of secoiridoid glucosides and its antioxidizing and novel platelet-aggregation inhibiting function. Journal of Functional Foods. 14, 337–344. https://doi.org/10.1016/j.jff.2015.02.001

Tedgui, A., Mallat, Z., 2006. Cytokines in atherosclerosis: Pathogenic and regulatory pathways. Physiological Reviews. 86(2), 515–581. https://doi.org/10.1152/physrev.00024.2005

Teles, J.S., Fukuda, E.Y., Feder, D., 2012. Warfarin: pharmacological profile and drug interactions with antidepressants. . Einstein (São Paulo, Brazil). 10, 110–115. https://doi.org/10.1590/S1679-45082012000100024

Tendera, M.B., Wojakowski, W., 2003. Role of antiplatelet drugs in the prevention of cardiovascular events. Thrombosis Research. 110(5-6), 355–359. https://doi.org/10.1016/j.jacc.2017.08.037

Thornton, P., Douglas, J., 2010. Coagulation in pregnancy. Best Practice and Research: Clinical Obstetrics and Gynaecology. 24(3), 339–352. https://doi.org/10.1016/j.bpobgyn.2009.11.010

Tohti, I., Tursun, M., Umar, A., Turdi, S., Imin, H., Moore, N., 2006. Aqueous extracts of *Ocimum basilicum* L. (sweet basil) decrease platelet aggregation induced by ADP and thrombin in vitro and rats arterio-venous shunt thrombosis in vivo. Thrombosis Research. 118(6), 733–739. https://doi.org/10.1016/j.thromres.2005.12.011

Vandvik, P.O., Lincoff, A.M., Gore, J.M., Gutterman, D.D., Sonnenberg, F.A., Alonso-Coello, P., Akl, E.A., Lansberg, M.G., Guyatt, G.H., Spencer, F.A., 2012. Primary and secondary prevention of cardiovascular disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. Chest. 141(2), 637–668. https://doi.org/10.1378/chest.11-2306

Wang, P.Q., Li, D.D., Dong, W., Liu, J., Yu, Y.N., Shen, C.T., Chen, Q.G., Chen, B.W., Chen, Y.D., Wang, Z., 2015. Danhong injection in the treatment of chronic stable angina: Study protocol for a randomized controlled trial. Trials. 17(474), 474. https://doi.org/10.1186/s13063-015-0998-1

Watson, R.D.S., Chin, B.S.P., Lip, G.Y.H., 2002. Antithrombotic therapy in acute coronary syndromes. BMJ. 325(7376), 1348–1351. https://doi.org/10.1136/bmj.325.7376.1348

Waxman, L., Smith, D.E., Arcuri, K.E., Vlasuk, G.P., 1990. Tick Anticoagulant Peptide (TAP) is a novel inhibitor of blood coagulation factor Xa. Science. 248(4955), 593–596. https://doi.org/10.1126/science.2333510

Weitz, J.I., Linkins, L.A., 2007. Beyond heparin and warfarin: The new generation of anticoagulants. Expert Opinion on Investigational Drugs. 16(3), 271–282. https://doi.org/10.1517/13543784.16.3.271

Wright, B., Moraes, L.A., Kemp, C.F., Mullen, W., Crozier, A., Lovegrove, J.A., Gibbins, J.M., 2010. A structural basis for the inhibition of collagen-stimulated platelet function by quercetin and structurally related flavonoids. British Journal of Pharmacology. 159(6), 1312–1325. https://doi.org/10.1111/j.1476-5381.2009.00632.x

Xia, Q., Wang, X., Xu, D.J., Chen, X.H., Chen, F.H., 2012. Inhibition of platelet aggregation by curdione from *Curcuma wenyujin* essential Oil. Thrombosis Research. 130(3), 409–414. https://doi.org/10.1016/j.thromres.2012.04.005

Xie, P., Cui, L., Shan, Y., Kang, W.Y., 2017. Antithrombotic Effect and Mechanism of Radix Paeoniae Rubra. BioMed Research International. 2017, 9475074. https://doi.org/10.1155/2017/9475074 https://doi.org/10.1155/2017/9475074

Xu, C.C., Wang, B., Pu, Y.Q., Tao, J.S., Zhang, T., 2017. Advances in extraction and analysis of phenolic compounds from plant materials. Chinese Journal of Natural Medicines. 15(10), 30103–30109. https://doi.org/10.1016/S1875-5364(17)30103-6

Yang, Y.S., Su, Y.F., Yang, H.W., Lee, Y.H., Chou, J.I., Ueng, K.C., 2014. Lipid-lowering effects of curcumin in patients with metabolic syndrome: A randomized, double-blind, placebo-controlled trial. Phytotherapy Research. 28(12), 1770–1777. https://doi.org/10.1002/ptr.5197

Yogeswari, S., Bindu, K.H., Kamalraj, S., Ashokkumar, V., Jayabaskaran, C., 2020. Antidiabetic, Antithrombin and Cytotoxic bioactive compounds in five cultivars of *Piper betle* L. Environmental Technology and Innovation. 20, 101140. https://doi.org/10.1016/j.eti.2020.101140

Yokozawa, T., Nakagawa, T., Kitani, K., 2002. Antioxidative activity of green tea polyphenol in cholesterol-fed rats. Journal of Agricultural and Food Chemistry. 50(12), 3549–3552. https://doi.org/10.1021/jf020029h

Yoon, E.K., Ku, S.K., Lee, W., Kwak, S., Kang, H., Jung, B., Bae, J.S., 2015. Antitcoagulant and antiplatelet activities of scolymoside. BMB Reports. 48(10), 577–582. https://doi.org/10.5483/bmbrep.2015.48.10.044

Zhang, D., Cupp, M.S., Cupp, E.W., 2002. Thrombostasin: Purification, molecular cloning and expression of a novel anti-thrombin protein from horn fly saliva. Insect Biochemistry and Molecular Biology. 32(3), 93–98. https://doi.org/10.1016/s0965-1748(01)00093-5

Zhang, H.Y., Liu, H., Yang, M., Wei, S.F., 2013. Antithrombotic activities of aqueous extract from *Gardenia jasminoides* and its main constituent. Pharmaceutical Biology. 51(2), 221–225. https://doi.org/10.3109/13880209.2012.717088

Zhang, L., Li, Z., Ye, X., Chen, Z., Chen, Z.S., 2021. Mechanisms of thrombosis and research progress on targeted antithrombotic drugs. Drug Discovery Today. 26(10), 2282–2302. https://doi.org/10.1016/j.drudis.2021.04.023

Zhang, Y.L., Xi, M.Z., Choi, Y., Bin, Lee, B.H., 2017. Antithrombotic Effect of Fermented *Ophiopogon japonicus* in Thrombosis-Induced Rat Models. Journal of Medicinal Food. 20(7), 637–645. https://doi.org/10.1089/jmf.2016.3872

Zhao, T., Chang, L., Zhang, B., Lu, M., Wang, X., Orgah, J.O., Wang, Y., Tian, X., Yang, J., Fan, G., Zhang, B., Zhu, Y., 2017. Specific combination of salvianolic acids as core active ingredients of Danhong injection for treatment of arterial thrombosis and its derived dry gangrene. Frontiers in Pharmacology. 8, 361. https://doi.org/10.3389/fphar.2017.00361

Zhou, J., Zhai, J.X., Zheng, W., Han, N., Liu, Z., Lv, G., Zheng, X., Chang, S., Yin, J., 2019. The antithrombotic activity of the active fractions from the fruits of *Celastrus orbiculatus* Thunb through the anti-coagulation, anti-platelet activation and anti-fibrinolysis pathways. Journal of Ethnopharmacology, 111974. https://doi.org/10.1016/j.jep.2019.111974

Zhou, W., Abdurahman, A., Umar, A., Iskander, G., Abdusalam, E., Berké, B., Bégaud, B., Moore, N., 2014. Effects of *Cydonia oblonga* Miller extracts on blood hemostasis, coagulation and fibrinolysis in mice, and experimental thrombosis in rats. Journal of Ethnopharmacology. 154, 163–169. https://doi.org/10.1016/j.jep.2014.03.056

Zingali, R.B., Jandrot-Perrus, M., Guillin, M.C., Bon, C., 1993. Bothrojaracin, a New Thrombin Inhibitor Isolated from *Bothrops jararaca* Venom: Characterization and Mechanism of Thrombin Inhibition. Biochemistry. 32(40), 10794–10802. https://doi.org/10.1021/bi00091a034

Zwicker, J.I., Schlechter, B.L., Stopa, J.D., Liebman, H.A., Aggarwal, A., Puligandla, M., Caughey, T., Bauer, K.A., Kuemmerle, N., Wong, E., Wun, T., Mclaughlin, M., Hidalgo, M., Neuberg, D., Furie, B., Flaumenhaft, R., 2019. Targeting protein disulfide isomerase with the flavonoid isoquercetin to improve hypercoagulability in advanced cancer. JCI Insight. 4, e125851. https://doi.org/10.1172/jci.insight.125851