

Review Article

A Review of Antiplatelet Activity of Traditional Medicinal Herbs on Integrative Medicine Studies

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Thrombotic events mainly occurred by platelet activation and aggregation. The vascular occlusion causes serious disease states such as unstable angina, ischemic stroke, and heart attack. Due to the pervading of thrombotic diseases, new antiplatelet drugs are necessary for preventing and treating arterial thrombosis without adverse side effects. Traditional medicinal herbs have been used for the treatment of human ailments for a long time. The clinically useful and safe products from traditional medicinal herbs were identified and developed in numerous pharmacological approaches. A complementary system of traditional medicinal herbs is a good candidate for pharmacotherapy. However, it still has a limitation in its function and efficacy. Thus, it is necessary to study the mode of action of traditional medicinal herbs as alternative therapeutic agents. In this review, we focused on our current understanding of the regulatory mechanisms of traditional medicinal herbs in antiplatelet activity and antithrombotic effect of traditional medicinal herbs on platelet function.

1. Introduction

Thrombosis is one of the leading pathological causes of morbidity and mortality in a wide range of cardiovascular diseases [1]. Thrombus formation is initiated by the adhesion of circulating platelets to the damaged blood vessel walls [2]. Vasoocclusive events are a major cause of death and involve serious vascular diseases such as unstable angina, ischemic stroke, and myocardial infarction [3]. Activation of platelet effector responses (exocytosis and other response independent of exocytosis) triggers the adhesion of platelets to the exposed subendothelial matrix and induces morphological changes, thromboxane A₂ (TxA₂) synthesis, and exteriorization of phosphatidylserine [4, 5]. Due to the high prevalence of thrombotic diseases [6], several studies are being carried out on new antithrombotic drugs, which inhibit platelet function, and upstream elements in the signaling cascades that activate platelets [7]. P₂Y₁₂ antagonists are a good example of extensively used in the treatment and prevention of cardiovascular diseases [8]. Although these drugs inhibit the effect of adenosine diphosphate (ADP) and attenuate almost all platelet responses, the predisposing of

bleeding is the main off-target effect [9]. Thus, there is a need to develop novel alternative antithrombotic remedies that have limited adverse effects. Traditional medicinal herbs (TMHs) have been considered as an alternative remedy in pharmaceutical industries [10]. Recently, several studies have been demonstrated the antiplatelet, fibrinolytic, and anticoagulant activities of plant extracts or natural products, such as coumarins, xanthenes, alkaloids, flavonoids, anthraquinones, naphthalenes, and stilbenes [11–20]. Indeed, the extensive experience with TMHs positions them as good candidates for novel pharmacotherapeutic agents [20, 21]. According to the World Health Organization (WHO) estimates, approximately 80% of the world's population uses TMHs for their primary healthcare [22, 23]. In this review, we focus on the antithrombotic effects of TMHs that regulate platelet activation and aggregation and summarize the mechanisms by which TMHs influence platelet thrombus formation.

2. Currently Available Antithrombotic Agents

Three classes of antithrombotic agents, including cyclooxygenase-1 (COX-1) inhibitor (aspirin), adenosine diphosphate

(ADP) P₂Y₁₂ receptor antagonists (ticlopidine, clopidogrel, prasugrel, and ticagrelor), and glycoprotein (GP) IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban), are currently approved for clinical events in patients undergoing arterial thrombosis [24–27].

2.1. COX-1 Inhibitor (Aspirin). Aspirin is a prototypic antiplatelet agent for treatment of patients with various atherosclerotic diseases [55]. It exerts its effects by inhibiting the activation of COX-1 enzyme which blocks the synthesis of TxA₂ from arachidonic acid [56]. Aspirin is more effective in the prevention of arterial thrombosis than venous thrombosis [57]. This is attributable to the important role of platelets in the causation of arterial thrombosis. Clinical trials of high-dose aspirin have shown that the antithrombotic efficacy of aspirin can be blunted [58]. Given that thromboxane receptors are expressed in all vascular tissues, including inflammatory cells, endothelial cells, atherosclerotic plaques, and platelets, most of the high doses of aspirin inhibit the activity of COX-1 in all tissues, indicating that the antithrombotic efficacy of high doses of aspirin might have an independent of platelet COX-1 inhibition [59, 60]. Further, numerous studies have shown the risks associated with the use of aspirin for primary prevention of peripheral vascular disease, polycythemia vera, diabetes, end-stage renal disease, and carotid stenosis [61–63]. In addition, long-term aspirin therapy is associated with a modest increase in the incidence of gastrointestinal bleeding [64]. Thus, despite the distinct antithrombotic efficacy of aspirin, its clinical use continues to be suboptimal.

2.2. P₂Y₁₂ Receptor Antagonists (Ticlopidine, Clopidogrel, Prasugrel, and Ticagrelor). Ticlopidine and clopidogrel are prodrugs. These irreversibly bind and inhibit the P₂Y₁₂ receptor for the lifespan of the platelet after *in vivo* bioactivation via the cytochrome P450 (CYP) enzyme system in the liver [65, 66]. Ticlopidine (Ticlid) is an antiplatelet drug in the first thienopyridine that was received by the US Food and Drug Administration (FDA) in 1991 to reduce the incidence of ischemic events in coronary artery disease (CAD) patients. Treatment of ticlopidine (250 mg per twice daily) showed an efficacious antithrombotic effect in patients with peripheral artery bypass surgery, unstable angina, claudication, and cerebrovascular disease [65]. However, in a few cases, treatment of ticlopidine is associated with a high incidence of neutropenia and it is irreversible and potentially fatal [67]. Clopidogrel (Plavix) is an orally available second generation of thienopyridine that was approved by the FDA in 1997 to reduce the ischemic events in patients with atherosclerotic vascular diseases following the results of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial [68]. Although clopidogrel represents an advance in antithrombotic therapy compared with ticlopidine, thrombotic thrombocytopenic purpura (TTP) occurs [69, 70]. Prasugrel (Effient) is a prodrug and orally available third-generation of thienopyridine [71]. Similar to clopidogrel, its active metabolites is regulated by CYP system in the liver and it irreversibly binds to platelet P₂Y₁₂ receptor. However, it is quickly hydrolyzed by intestinal and blood esterases and

oxidized more efficiently to its active metabolites through a single CYP-dependent step [71]. In patients with stable coronary disease and elective percutaneous coronary intervention (PCI), prasugrel has a more effective in platelet aggregation compared with clopidogrel [72, 73]. However, its metabolites directly inhibit the function of neutrophils and its use is associated with an increased risk of bleeding [74, 75]. Ticagrelor (Brillinta), also known as AZD6140, is an oral compound belonging to the class of cyclopentyl triazolopyrimidine. It is also metabolized via hepatic bioconversion to form an active metabolite [76]. Like the thienopyridines, ticagrelor also directly but reversibly binds to the P₂Y₁₂ receptor on platelet. In this case, the drug displayed only ~30–40% of the antiplatelet effect [77, 78]. This may be because ticagrelor interacts with plasma proteins in the circulation [79]. Similar to prasugrel, ticagrelor has been shown to produce a more effective antithrombotic effect compared with clopidogrel in patients irrespectively of genetic differences [80–83]. However, the incidence of dyspnea and hemorrhagic strokes was increased in the ticagrelor-treated group [84, 85]. Given that ticlopidine, clopidogrel, prasugrel, and ticagrelor display a good antithrombotic activity, the treatment of drugs should be defined in the clinical setting and events.

2.3. GPIIb/IIIa Inhibitors (Abciximab, Eptifibatide, and Tirofiban). Abciximab (ReoPro) is the first GPIIb/IIIa antagonist that was approved by the FDA in 1994 for the prevention of ischemic complications of angioplasty [86, 87]. Later, it was approved for PCI with stents and as medical therapy for unstable angina [88, 89]. Most of the administrated abciximab binds to GPIIb/IIIa on platelet with high affinity, but not irreversible, thereby preventing platelet aggregation and thrombus formation. However, long-term treatment of abciximab has shown a quite remarkable mortality in patients with PCI [90, 91]. Abciximab was shown to reduce the risk of death, myocardial infarction, repeat angioplasty, and bypass surgery. However, it may potentially cause fatal bleeding [86, 87]. Eptifibatide (integrilin) is a synthetic cyclic heptapeptide of <1 kDa that was approved by the FDA in 1998. Its design was reliant on a Lys-Gly-Asp (KGD) motif from snake venom disintegrin barbourin that was shown to have potent antiplatelet activity [92]. Eptifibatide acts as a highly potent inhibitor of fibrinogen binding to GPIIb/IIIa and rapidly and reversibly inhibits platelet aggregation with modest prolong bleeding time [93–95]. Eptifibatide has a relatively long plasma half-life but it is primarily removed by kidneys [96]. Although the safety and efficacy of eptifibatide were conducted in different clinical trials, it must be dose reduced in patients with kidney failure and not given to patients receiving dialysis [97–100]. Tirofiban (Aggrastat) is a small molecule based on an RGD-peptidomimetic analog of tyrosine that was approved by the FDA in 1998 [101, 102]. Tirofiban specifically and reversibly binds to GPIIb/IIIa on resting platelets and inhibits the platelet aggregation [101, 102]. The advantages of tirofiban are recovering from platelet aggregation to 50% of the baseline value within 4 hours when an infusion is stopped. Further, it is also removed by kidneys and biliary excretion [103]. Therefore, it is required to dose adjustment of tirofiban in patients with kidney

TABLE 1: The list of traditional medicinal herbs (TMHs).

| Species | Vernacular name | Species | Vernacular name |
|---------------------------------|-----------------|-------------------------------------|-----------------|
| <i>Glycyrrhiza uralensis</i> | Kamcho | <i>Trogopterus xanthipes</i> | Oryunggi |
| <i>Curcuma aromatica</i> | Kanghwang | <i>Vaccaria segetalis</i> | Wangbuluhaeng |
| <i>Rhus verniciflua</i> | Kunchil | <i>Achyranthes bidentate</i> | Usul |
| <i>Spatholobus suberectus</i> | Kaehyuldeung | <i>Curcuma aromatica</i> | Ulgum |
| <i>Sophora flavescens</i> | Kosam | <i>Artemisia anomala</i> | Uukino |
| <i>Eriocaulon sieboldianum</i> | Kokjungcho | <i>Cinnamomum cassia</i> | Yukkye |
| <i>Sophora japonica</i> | Keuigak | <i>Leonurus sibiricus</i> | Ickmocho |
| <i>Selaginella tamariscina</i> | Kwonbaek | <i>Paeonia lactiflora</i> | Chokchayak |
| <i>Lonicera japonica</i> | Kumunhwa | <i>Lyceum chinense</i> | Ghigolpi |
| <i>Phragmites communis</i> | Nogun | <i>Viola yedoensis</i> | Chahwagijeong |
| <i>Phaseolus radiates</i> | Nokdu | <i>Lithospermum erythrorhizon</i> | Chacho |
| <i>Rhaponticum uniflorum</i> | Nuro | <i>Eupolyphaga sinensis</i> | Chachung |
| <i>Salvia miltiorrhiza</i> | Dansam | <i>Panax notoginseng</i> | Cheonchil |
| <i>Lophatherum gracile</i> | Damchukyup | <i>Citrus unshiu</i> | Chinpi |
| <i>Isatis indigotica</i> | Daechongyup | <i>Gleditsia sinensis</i> | Chogakcha |
| <i>Glycine max</i> | Daeduhwangkwon | <i>Anemarrhena asphodeloides</i> | Chimo |
| <i>Rheum palmatum</i> | Daehwang | <i>Phyllostachys nigra, henonis</i> | Chukyup |
| <i>Prunus persica</i> | Doin | <i>Cnidium officinale</i> | Chunking |
| <i>Lasiosphaera fenzlii</i> | Mabal | <i>Manis pentadactyla</i> | Chunsangap |
| <i>Portulaca oleracea</i> | Machihyun | <i>Artemisia annua</i> | Chungho |
| <i>Verbena officinalis</i> | Mapyuncho | <i>Gentian scabra</i> | Choyoungdam |
| <i>Tabanus bivittatus</i> | Mangchung | <i>Leonurus sibiricus</i> | Chungulcha |
| <i>Erigeron canadensis</i> | Mangcho | <i>Patrinia villosa</i> | Paechangkun |
| <i>Paeonia suffruticosa</i> | Mokdanpi | <i>Taraxacum mongolicum</i> | Pogongyoung |
| <i>Buddleja officinalis</i> | Milmonghwa | <i>Smilax glabra</i> | Tobokrung |
| <i>Pulsatilla koreana</i> | Baekduong | <i>Lycopus lucidus</i> | Taklan |
| <i>Dictamnus dasycarpus</i> | Baeksunpi | <i>Scrophularia buergeriana</i> | Hyunsam |
| <i>Oldenlandia diffusa</i> | Baekwhasasulcho | <i>Corydalis turtschaninovii</i> | Hyunhosak |
| <i>Belamcanda chinensis</i> | Sakan | <i>Coptis chinensis</i> | Hwangnyon |
| <i>Sophora tonkinensis</i> | Sandukeon | <i>Carthamus tinctorius</i> | Honghwa |
| <i>Cremastra appendiculata</i> | Sanchako | <i>Polygonum cuspidatum</i> | Hojangkun |
| <i>Sparganium stoloniferum</i> | Samneong | <i>Prunella vulgaris lilacina</i> | Hagocho |
| <i>Whitmania pigra</i> | Suchil | <i>Scutellaria baicalensis</i> | Hwangkun |
| <i>Rehmannia glutinosa</i> | Sukchihwang | <i>Caesalpinia sappan</i> | Somok |
| <i>Massa Medicate Fermentat</i> | Singok | <i>Nelumbo nucifera</i> | Yeonchayuk |
| <i>Curcuma zedoaria</i> | Achul | <i>Lonicera japonica</i> | Indong |
| <i>Chrysanthemum indicum</i> | Yaguk | <i>Stellaria dichotoma</i> | Ensiho |
| <i>Houttuynia cordata</i> | Erseoungcho | | |

insufficiency. As established by extensive clinical trials and usage of GPIIb/IIIa inhibitors [104], ongoing trials should be required to focus primarily on reduction of side effects including reduction of bleeding and dosage optimization in patients with kidney failure.

3. The Benefits of Traditional Medicinal Herbs on Platelet Function

Traditional medicinal herbs (TMHs) are a part of East-Asian medical systems and have been used for the treatment of various diseases [105]. TMHs are now being manufactured

as drugs containing ingredients of standardized quality and quantity. Most of the TMHs are relatively low cost, are effective and abundant resources, and have minimized adverse effects in clinical research [106, 107]. Particularly, several studies have demonstrated that most of TMHs showed a positive impact on thrombotic diseases [108]. However, the antithrombotic effect of TMHs on platelet function is relatively unknown. In this review, we will focus on our current understanding of the regulatory mechanisms and the antithrombotic effect of TMHs on platelet function. We judiciously selected total 75 candidates (Table 1) from our database (unpublished data). Among these, only eleven plants

have been investigated with respect to their antiplatelet activity, i.e., *Rhus verniciflua*, *Salvia miltiorrhiza*, *Caesalpinia Sappan*, *Curcuma zedoaria*, *Curcuma aromatic*, *Cinnamomum cassia*, *Paeonia lactiflora*, *Panax ginseng*, *Anemarrhena as-pho-de-loid-es*, *Coptis chinensis*, and *Carthamus tinctorius* (Table 2).

3.1. *Rhus Verniciflua* (*Toxicodendron vernicifluum*). *Rhus verniciflua*, formerly known as the *Toxicodendron vernicifluum*, is a deciduous tree from Anacardiaceae family, which is widely cultivated in Korea, China, and Japan [109]. Since 15th century AD, *R. verniciflua* has been used as an herbal therapy for the stomach problems, liver detoxification, promoting blood circulation, and removing blood stasis [105, 110, 111]. Although the scientific evidence of *R. verniciflua* is lacking in health remedies, *in vitro* studies, recently, have shown the potential of antithrombotic, antioxidant, antiobesity, anti-inflammatory, antimutagenic, and anticancer activities [28, 29, 111–117]. Particularly, the extracts of *R. verniciflua* exhibit a potent antithrombotic effect in human platelets. A study showed that eight urushiol-type compounds extracted from *R. verniciflua* inhibited ADP- or arachidonic acid- (AA-) induced human platelet aggregation in a dose-dependent manner (IC₅₀ value of ~ 5 to 15 μmol/L) [116]. Also, the isomaltol and pentagalloyl glucose from *R. verniciflua* inhibited ADP-, AA-, and collagen-induced human platelet aggregation and relative platelet surface receptors [28]. These results demonstrated that *R. verniciflua* has a potential in antiplatelet activity. Therefore, future study should be suggested to further explore the effects.

3.2. *Salvia Miltiorrhiza* (Asian Red Sage). *Salvia miltiorrhiza*, also known as Asian red sage, is a medicinal herb for the circulatory system. It is traditionally used for ameliorating the symptoms of cardiovascular and cerebrovascular diseases in Korea, China, and Japan [118–121]. A study has shown that the extract from *S. miltiorrhiza* has beneficial effects on ischemia-induced symptoms including cellular damage and low blood flow [120]. Further, the treatment of *S. miltiorrhiza* in human vein endothelial cells displayed a significant decrease of IL-6 and IL-8, which reflects the effects of *S. miltiorrhiza* on inflammatory responses [122]. The main focus of the predominant bioactivity compounds in *S. miltiorrhiza* is laid on the cardioprotective mechanisms during atherosclerosis, thrombosis, and myocardial infarction by reperfusion [123]. Specifically, the extracts of *S. miltiorrhiza*, including 15, 16-dihydrotanshinone I, lipid-soluble tanshinone I, tanshinone IIA, cryptotanshinone, dihydrotanshinone, water-soluble danshensu, and salvianolic acid B, displayed potent antiplatelet activity via suppression of platelet aggregation and promotion of fibrinolysis [30, 31, 119, 124]. Further, the treatment of *S. miltiorrhiza* successfully prevented blood stasis and ameliorated blood flow from cerebral infarction and hemorrhage [32]. According to clinical studies and the wide range of case studies with *S. miltiorrhiza* after many years of use in Korea, China, and Japan, no major side effects of *S. miltiorrhiza* have been reported, which is extremely safe [31, 125].

3.3. *Caesalpinia Sappan* (Brazilin). *Caesalpinia sappan*, commonly known as Brazilin or Sappan wood, belongs to the family of Leguminosae. Its dried heartwood has been used as a traditional medicine [126]. Studies have shown that *C. sappan* possesses various pharmacological efficacies such as analgesia, antibacterial, anti-inflammatory antiplatelet activity, promoting blood circulation, and preventing blood stasis [127–130]. The main bioactive component of *C. sappan* is brazilin [7,11b-dihydrobenz(b)indeno[1,2-d]pyran-3,6a,9,10(6H)-tetrol], which has been studied the diverse biological activities such as hypoglycemic, antibacterial, anti-hepatotoxicity, anti-inflammatory, and anticancer activities [131–134]. A study has shown that brazilin (0.1 to 1 mM) significantly inhibited thrombin-, collagen-, and ADP-induced aggregation of washed rat platelets through a regulation of Ca²⁺ mobilization and phospholipase (PLA₂) activity [135]. Thus, brazilin may be a useful molecule for the development of a new natural drug for remedying of thrombosis.

3.4. *Curcuma Zedoaria* and *Curcuma Aromatic* (Turmeric). *Curcuma zedoaria* (white turmeric) and *Curcuma aromatic* (wild turmeric) are perennial herbs and member of the genus *Curcuma* belonging to the family of Zingiberaceae. These have been used for a traditional medicine in Asia for a long time [33, 136]. Several studies have shown that the drugs of *Curcuma* possess pharmacological effects such as antitumor, anti-inflammatory, antibacterial, immunological activity, cytotoxicity, and antifungal activities [137–142]. Traditionally, *Curcuma* drugs have been used for ameliorating the obstruction of blood circulation. Among them, curcumin (polyphenolic diferuloylmethane) is a major component of *Curcuma* plant [143]. It has a wide range of beneficial effects in cardiovascular disease including antioxidant and anti-inflammatory [144–146]. Intriguingly, curcumin is regarded as a safe compound, because oral administration of curcumin (8g per day) did not show an off-target effect in patients with high-risk or premalignant lesions [147]. Further, *in vitro* studies have shown that curcumin has a significant inhibitory effect in ADP-, AA-, collagen-, platelet activation factor- (PAF-) induced platelet aggregation [34, 35, 148]. Thus, curcumin has a potential in the reduction of platelet aggregation and activation.

3.5. *Cinnamomum cassia* (Cinnamon). *Cinnamomum cassia*, also known as cinnamon, is an evergreen tree distributed mostly in Asia and member of genus *Cinnamomum* belonging to the family of Lauraceae [36]. The extract of cinnamon is used as a traditional medicine for the alleviation of fever, inflammation, chronic bronchitis, and improving blood circulation [149–151]. The most important constituents of cinnamon are cinnamaldehyde and trans-cinnamaldehyde and other derivatives such as cinnamic acid, coumarins, diterpenoids, and cinnamate [36, 152–154]. These are contributing to the fragrance and various biological activities, including antifungal, antipyretic, antioxidant, and antimicrobial [155–158]. In addition, the extracts of *C. cassia* have found effective inhibition of platelet activation and coagulation [159]. Among the thirteen compounds, eugenol, amygdalactone, cinnamic alcohol, 2-hydroxycinnamaldehyde,

TABLE 2: The active constituents of TMHs.

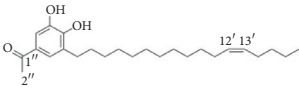
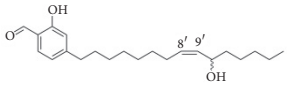
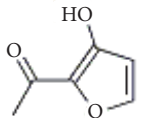
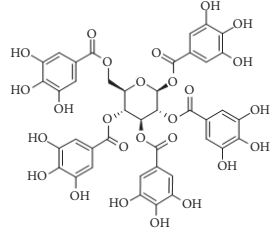
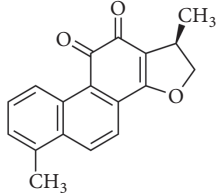
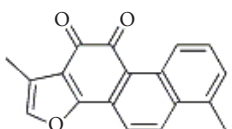
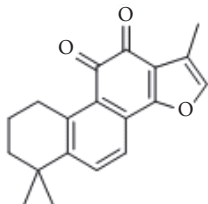
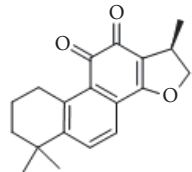
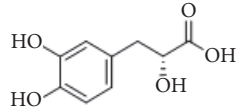
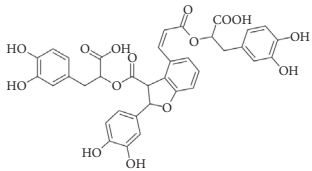
| Scientific name | Active compound | Structure | Results | Ref. |
|----------------------------|--|---|---|---------|
| <i>Rhus verniciflua</i> | 3-(8'R,9'R-dihydroxypentadecyl)-phenol |  | Inhibition of platelet aggregation induced by ADP and AA. | [28] |
| | 1-[3,4-dihydroxy-5-(12'Z)-12-heptadecen-1-ylphenyl]-ethanone |  | | |
| | Isomaltol |  | | |
| | Pentagalloyl glucose |  | Inhibition of platelet aggregation induced by ADP, AA, collagen. | [29] |
| <i>Salvia miltiorrhiza</i> | 15,16-dihydrotanshinone I |  | | |
| | Tanshinone I |  | | |
| | Tanshinone IIA |  | Inhibited collagen-induced platelet aggregation via Ca ²⁺ mobilization and TxA ₂ generation, Inhibited AA metabolism. | [30–32] |
| | Cryptotanshinone |  | | |
| | Danshensu |  | | |
| | Salvianolic acid B |  | | |

TABLE 2: Continued.

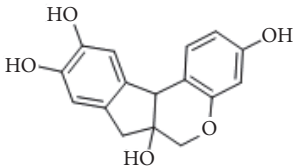
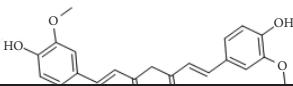
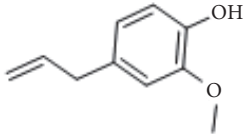
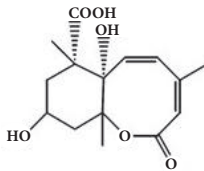
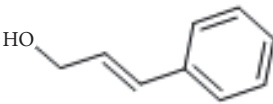
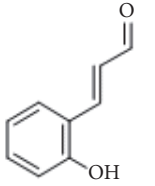
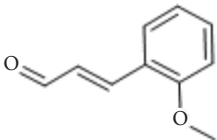
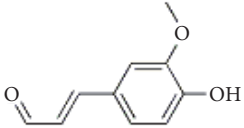
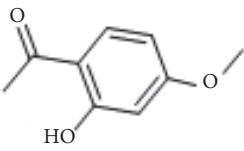
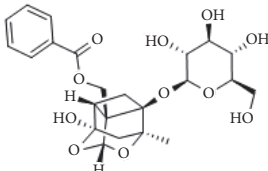
| Scientific name | Active compound | Structure | Results | Ref. |
|--|-------------------------|---|---|----------|
| <i>Caesalpinia sappan</i> | Brazilin |  | Inhibited platelet aggregation activity induced by thrombin, collagen, and ADP. | [33] |
| <i>Curcuma zedoaria</i> <i>Curcuma aromatic</i> | Curcumin |  | Inhibitory effect in ADP-, AA-, collagen-, platelet activation factor (PAF)-induced platelet aggregation. | [34–36] |
| | Eugenol |  | | |
| | Amygdalactone |  | | |
| <i>Cinnamomum cassia</i> | Cinnamic alcohol |  | Inhibition of ADP-, collagen-, AA-induced platelet activation and aggregation. Inhibitory effect in TxA ₂ formation and Ca ²⁺ mobilization. | [37–39] |
| | 2-Hydroxycinnamaldehyde |  | | |
| | 2-Methoxycinnamaldehyde |  | | |
| | Coniferaldehyde |  | | |
| | Paeonol |  | Inhibited ADP-, AA-, and collagen-induced platelet aggregation via the inhibition of TxA ₂ and PGD ₂ formation. | [40, 41] |
| <i>Paeonia lactiflora</i> | Paeoniflorin |  | Improving blood circulation through anti-platelet aggregation and blood coagulation. | [42] |

TABLE 2: Continued.

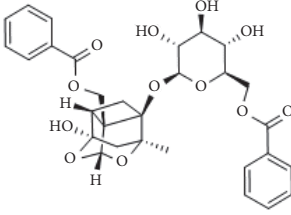
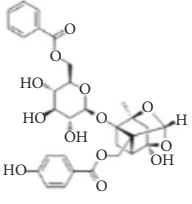
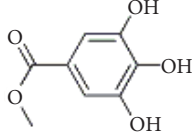
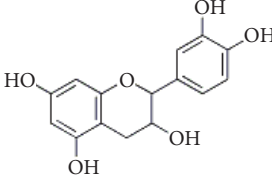
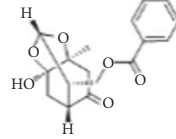
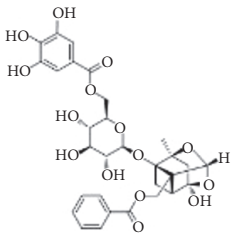
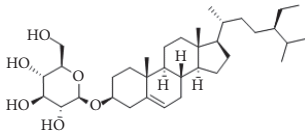
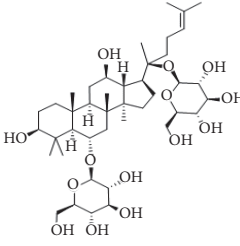
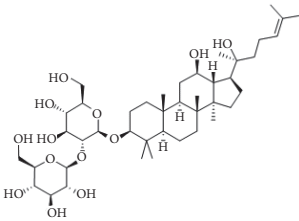
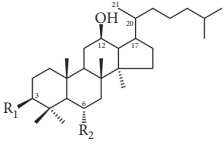
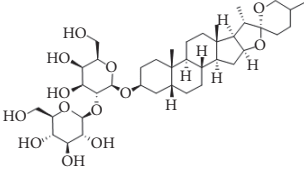
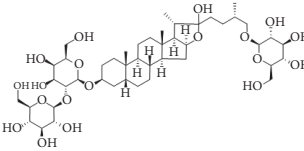
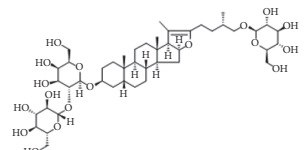
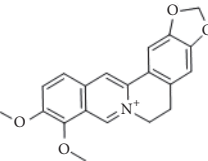
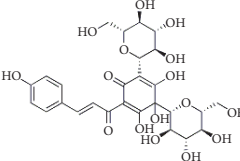
| Scientific name | Active compound | Structure | Results | Ref. |
|----------------------|------------------------|---|---|------|
| | Benzoylpaeoniflorin |  | | |
| | Benzoyloxypaeoniflorin |  | | |
| | Methyl gallate |  | | |
| | Catechin |  | | |
| | Paeoniflorigenone |  | | |
| | Galloylpaeoniflorin |  | | |
| | Daucosterol |  | | |
| <i>Panax ginseng</i> | Ginsenoside Rg1 |  | Inhibition of platelet activation and aggregation induced by thrombin, ADP, collagen, and U46619. | [43] |

TABLE 2: Continued.

| Scientific name | Active compound | Structure | Results | Ref. |
|----------------------------------|-------------------------|---|--|----------|
| | Ginsenoside Rg3 |  | | [44] |
| | Ginsenoside Rp4 |  | | [45] |
| <i>Anemarrhena asphodeloides</i> | Timosaponin A-III |  | | |
| | Timosaponin B-II |  | Remarkably inhibited ADP-induced platelet aggregation and delayed thromboplastin time. | [46–49] |
| | Anemarsaponin B |  | | |
| <i>Coptis chinensis</i> | Berberine |  | Inhibited ADP, collagen, AA-induced platelet aggregation and TxA ₂ synthesis. | [50, 51] |
| <i>Carthamus tinctorius</i> | Hydroxysafflor yellow A |  | Inhibited ADP, PAF induced platelet aggregation and delated PT, TT and APTT | [52–54] |

2-methoxycinnamaldehyde, and coniferaldehyde showed a significant inhibitory activity in platelet activation and aggregation compared to acetylsalicylic acid (ASA)[159]. Further, eugenol was previously reported to inhibit platelet activation and aggregation through the suppression of TxA₂ formation [37, 38]. Thus, the extract of *C. cassia* has a potential for antiplatelet activity.

3.6. *Paeonia lactiflora* (Peony). *Paeonia lactiflora*, also known as garden peony, is an herbaceous perennial flowering plant in the family of Paeoniaceae and is widespread in Asia [39]. The roots of *P. lactiflora* have long been used under the traditional names of *Paeoniae Radix* in Korea, China, and Japan [160]. It

is used as a source of traditional medicine for various diseases such as antipyretic, anti-inflammatory, and analgesic [40, 42, 161]. Particularly, the extract of *Paeoniae Radix* has been used as remedies for cardiovascular diseases for improving blood circulation [162, 163]. Biochemical studies showed that paeonol, a representative component of *Paeonia*, inhibited ADP-, AA-, and collagen-induced platelet aggregation via the inhibition of TxA₂ and PGD₂ formation [42, 164]. Further, the extract of *Paeoniae Radix*, including paeoniflorin, benzoylpaeoniflorin, benzoyloxypaeoniflorin, methyl gallate, catechin, paeoniflorigenone, galloylpaeoniflorin, and daucosterol, showed an improving blood circulation through their inhibitory effects on both platelet aggregation and blood

coagulation [160]. However, the role of each constituent and their overall effects *in vivo* still remain elusive.

3.7. *Panax Ginseng* (Ginseng). Ginseng is the root of plants in the genus *Panax*, which includes several species such as Korean ginseng (*Panax ginseng*), South China ginseng (*Panax notoginseng*), and American ginseng (*Panax quinquefolius*) [41]. Ginseng is regarded as a valuable traditional medicine for treatment of different ailments and enhancing immunity. Although ginseng acts as a panacea and heals all kinds of illnesses for a long time, there is little evidence from clinical research [41, 107]. Recently, several studies have focused on the effects of ginseng in vasorelaxant, antioxidant, anti-inflammatory, and antiplatelet properties [41, 165–168]. Particularly, the oral administration of *P. ginseng* extract (daily at doses of 250 and 500 mg/kg) significantly inhibited ADP- and collagen-induced aggregation and granules secretion in rat platelets [169]. Also, the extract of *P. notoginseng* inhibited collagen-induced platelet aggregation by 60% at 3 mg/ml [168]. Biochemical studies showed that ginseng contains various active constituents including ginsenosides, peptides, polysaccharides, mineral oils, and fatty acids [170]. Among them, single ginsenosides, such as Rg1, Rg3, and Rp4, showed a significant reduction of platelet aggregation and Ca²⁺ mobilization via the regulation of PI3K/Akt signaling pathway [44, 45, 171]. Thus, the constituents of ginseng are important for regulating platelet activation and aggregation.

3.8. *Anemarrhena asphodeloides* (Liliaceae). *Anemarrhena asphodeloides* is an herbaceous plant and member of genus *Anemarrhena* belonging to Asparagaceae family and mainly distributed in Korea, China, and Mongolia [43]. It has been commonly used in traditional medicine for thousands of years [108]. The curative properties of *A. asphodeloides* have been known to have an antidiabetic, antiplatelet, and diuretic activities [172–174]. Further, biochemical studies have shown that the extract of *A. asphodeloides* displayed beneficial effects on the central nervous system, gastric cancer, and inflammation [43, 108, 175]. The primarily compounds isolated from *A. asphodeloides* are xanthenes, steroidal saponins, flavonoids, norlignans, and polysaccharides [43, 46, 172, 176]. Particularly, the series of steroidal saponins, including timosaponin A-III, timosaponin B-II, and anemarsaponin B, remarkably inhibited ADP-induced platelet aggregation and delayed thromboplastin times [47, 48, 176, 177]. These results suggested that the steroidal saponins isolated from *A. asphodeloides* might be used as a novel antithrombotic therapeutic agent.

3.9. *Coptis chinensis* (Goldthread). *Coptis chinensis* is a low-growing plant belonging to Ranunculaceae family. It is indigenous to the mountainous regions of Korea, China, and Japan [49]. The rhizome of *C. chinensis* has been widely used as a tonic remedy for hepatic and cardiovascular disorders for a long time in traditional medicine [178]. Further, pharmacological studies have shown that *C. chinensis* possesses a wide range of beneficial effects in bacterial infection, cancer, and inflammation [179–181]. According to biochemical

studies, berberine (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolinium, BBR) is the major constituent of *C. chinensis* [182]. The beneficial effects of BBR have been reported in carbohydrate and lipid metabolism, inflammation, endothelial function, and cardiovascular system [49, 183–187]. BBR also has an antiplatelet effect that is mediated via the inhibition of arachidonic acid (AA) metabolism and Ca²⁺ mobilization [188]. A study examined that BBR (0.5 mol/L) inhibited collagen-, ADP-, and AA-induced TxA₂ synthesis in rabbit platelets [188]. Intriguingly, BBR directly interacted with thrombin (Kd value of 16.39 μM), thereby inhibiting thrombin-induced platelet aggregation [50]. Thus, BBR may be a considerable and potential candidate for the development of safe and effective antiplatelet agents.

3.10. *Carthamus tinctorius* (Safflower). *Carthamus tinctorius*, commonly known as safflower, is an herbaceous and thistle-like annual plant and belongs to the family of Compositae [51]. Its extract and oil are important for use in traditional medicines as a purgative, analgesic, antipyretic, and antidote to poisoning [51, 189]. In Korea, *C. tinctorius* is also known as Honghwain, and it has been clinically used to promote bone formation and prevent menstrual problems, postpartum hemorrhage, and osteoporosis [190, 191]. Further, several clinical studies have investigated the mechanisms of the therapeutic effect of *C. tinctorius* against a diverse range of diseases [192]. The extract of *C. tinctorius* was shown to inhibit platelet aggregation induced by ADP and platelet activating factor (PAF) stimulation, both *in vitro* and *in vivo* [52, 193]. The aqueous extract of *C. tinctorius* also displayed antithrombotic activity against venous thrombosis *in vivo* [53]. Further, the extracts of *C. tinctorius* prolonged the plasma thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (APTT) [52, 193]. Thus, the constituents of *C. tinctorius* are important for regulating thrombosis.

4. The Prescriptions of Korean Medicine on Platelet Function

Most Asian countries have their own traditional medicines and prescriptions for a long time. Korean traditional medicines (KTM) are widely used for the treatment of various diseases in clinics in Korea [54]. Due to the geomorphological characteristics, Korea has a plenty of herbal plant materials including about 3,400 species, 762 varieties, and 287 forms. Among them, 300 kinds of natural plants are currently used as traditional medicines [194]. Since 1991, the Korean government has attempted to establish the standard of KTM preparations such as manufacturing process, quality control, and handling of KTM [194]. The establishment of the Korean government policy framework and the efforts of the Korea Institute of Oriental Medicine (KIOM) institution have helped standardize the manufacture of KTM preparations using pharmaceutical approaches. In addition, the optimal prescriptions of KTM are studied based on the philosophy of ancient medical science and originated from eleven oriental books in Korea [194].

TABLE 3: The prescriptions of Korean traditional medicine.

| Prescription | Components | Literatures |
|-------------------------------|--|-------------------|
| On-Gyeong-Tang | Big blue lilyturf (8g), Korean Angelica (6g), Ginseng (4g), Pinellia (4g), white peony (4g), Cnidium (4g), Moutan (4g), Gelatinum (3g), licorice (3g), Evodia (2g), Cinnamon (2g) | Dong-Eu-Bo-Gam |
| Cheon-Geum-Jo-Gyeong-Tang | Big blue lilyturf (8g), Korean Angelica (6g), Ginseng (4g), Pinellia (4g), white peony (4g), Cnidium (4g), Moutan (4g), Gelatinum (2g), Evodia (2g), Cinnamon (2g), Ginger (2g) | Dong-Eu-Bo-Gam |
| Dae-Hwang-Mog-Dan-PI-Tang I | Moutan (10g), licorice (6g), Rhubarb (6g), Peach kernel (10g), Kirilowii (10g) | Dong-Eu-Bo-Gam |
| Dae-Hwang-Mog-Dan-PI-Tang II | Moutan (10g), licorice (6g), Rhubarb (6g), Peach kernel (10g), Gourd (10g) | Dong-Eu-Bo-Gam |
| Bog-Won-Hwal-Hyeol-Tang | Korean angelica (6.8g), licorice (4g), Rhubarb (10g), Peach kernel (10g), Bupleurum (6g), Pangolin (4g), Dogeun (4g), Safflower (2g) | Dong-Eu-Bo-Gam |
| Byeol-Gab-Jeon-Hwan | Peach kernel (20g), Safflower (20g), Amyda shell (40g), Bur-reed (20g), Curcuma (20g), Cyperus (20g), Nastsudaidai peal (20g), Nuruk (20g), Malt (20g), Shell powder (20g) | Dong-Eu-Bo-Gam |
| Gwi-Chul-Pa-Jing-Tang | white peony (3.75g), Safflower (1.87g), Bur-reed (3.75g), Curcuma (3.75g), Cyperus (5.62g), Nastsudaidai peal (3.75g), Peony (3.75g), Dong quai (3.75g), Lindera root (2.6g), Sappan (1.87g), Cinnamon (1.87g) | Je-Jung-Sin-Pyeon |
| Do-Haeg-Seung-Gi-Tang | licorice (3.7g), Cinnamon (7.5g), Rhubarb (11.2g), Peach kernel (10g), Glauber salt (7.5g) | Je-Jung-Sin-Pyeon |
| Tong-Gyeong-Tang | Korean angelica (2.6g), white peony (2.6g), Rhubarb (2.6g), Safflower (2.6g), Sappan (2.6g), Cinnamon (2.6g), Rehmania (2.6g), Machilia (2.6g), Citrus (2.6g), Poncirus (2.6g), Orpiment (2.6g), Mume fruit (2g), Ginger (3g), Jujube (2g) | Je-Jung-Sin-Pyeon |
| Tong-Gyeong-Tang + Hwanglyeon | Korean angelica (2.6g), white peony (2.6g), Rhubarb (2.6g), Safflower (2.6g), Sappan (2.6g), Cinnamon (2.6g), Rehmania (2.6g), Machilia (2.6g), Citrus (2.6g), Poncirus (2.6g), Orpiment (2.6g), Mume fruit (2g), Ginger (3g), Jujube (2g), Coptis (2.6g) | Je-Jung-Sin-Pyeon |
| Hwal-Hyeol-Tang | Cnidium (2.6g), Moutan (3.7g), licorice (0.75g), Cinnamon (1.87g), Ginger (1g), Peach kernel (3.7g), Safflower (2.6g), Cyperus (3.7g), Peony (3.75g), Dong Quai (3.75g), Lindera root (3.75g), Citrus (3.75g), Corydalis (3.75g), Elecampane (1.87g) | Je-Jung-Sin-Pyeon |
| Tong-Gyu-Hwal-Hyeol-Tang | Korean Angelica (6g), Ginseng (2g), licorice (2g), Bupleurum (4g), Nastsudaidai peal (1.2g), Milk Vetch root (4g), Atractylodes (4g), Cimicifuga (4g), Anemarrhena (4g), Ostericum (4g), Seseleos radix (2g), Angelica dahurica (2g), Orpiment (2g), Alisma (2g), Orange peel (1.2g), Coptis (1.2g), Elecampane (1.2g) | Dong-Eu-Bo-Gam |
| Bo-Yang-Hwan-O-Tang, | Korean Angelica (1.2g), Ginseng (2g), licorice (2g), Bupleurum (6g), Peony (1.2g), Rehmannia (2g), Milk Vetch root (2g), Atractylodes (2g), Anemarrhena (1.2g), Ostericum (2g), Seseleos radix (1.2g), Alisma (1.2g), Orange peel (1.2g), Crudes (1.2g), White Poria cocos (1.2g), Cinnamon(1.2g) | Dong-Eu-Bo-Gam |
| Sil-So-San | <i>Trogopterorum faeces</i> (4g), <i>Typhae Pollen</i> (4g) | Dong-Eu-Bo-Gam |
| Gye-Ji-Bog-Lyeong-Hwan | Moutan (4g), Peach kernel (4g), Peony (4g), Red Poria cocos (4g), Cinnamon (4g) | Dong-Eu-Bo-Gam |
| Gyeong-Ha-Chul-Eo-Tang | Cnidium (7.5g) Moutan (7.5g), licorice (3.7g), Peach kernel (2.6g), Safflower (2.6g), Cyperus (2.6g), Peony (2.6g), Korean Angelica (2.6g), Lindera root (2.6g), Citrus (7.5g), Corydalis (3.75g), <i>Trogopterorum faeces</i> (3.75g) | Ui-Lim-Gae-Chag |
| Dae-Hwang-Ja-Chung-Hwan | licorice (75g), Rhubarb (37.5g), Safflower (3.75g) Peony (112.5g), Rehmania (375g), Orpiment (75g), Eupolyphaga (37.5g), Lacquer tree bark (37.5g), Hirudo (37.5g), Breeze (37.5g), Styra (37.5g), <i>Persicae Semen</i> (243.75g) | Geum-Gwe-Yo-Lag |

TABLE 3: Continued.

| Prescription | Components | Literatures |
|-------------------------|--|--------------------|
| Tal-Hwa-Jeon | Korean Angelica (26.2g), Cinnamon (3.75g), <i>Cnidii Rhizoma</i> (7.5g), <i>Achyranthes</i> (7.5g), <i>Psyllium</i> (5.62g) | Dong-Eu-Bo-Gam |
| So-Bog-Chug-Eo-Tang | Korean Angelica (11.2g), <i>Cnidium</i> (7.5g), Cinnamon (3.75g), Ginger (5g), Peony (7.5g), <i>Thphae Pollen</i> (11.2g), <i>Trogopterorum faeces</i> (7.5g), Myrrha (7.5g), <i>Foeniculi Fructus</i> (7.5g), <i>Corydaline</i> (3.75g), <i>Zingiberis Rhizoma</i> (3.75g) | Je-Jung-Sin-Pyeon |
| So-Pung-Hwal-Hyeol-Tang | Korean Angelica (3.7g), <i>Cnidium</i> (7.5g), Safflower (1.12g), <i>Atractylodes</i> (3.75g), <i>Angelica dahurica</i> (2g), Orpiment 3.75g, <i>Clematidis Radix</i> 3.75g), <i>Stephaniae TetrandraeRadix</i> (3.75g), <i>ArisamatisRhizoma</i> (3.75g), <i>OstericiiRadix</i> (3.75g), <i>Cinnamomi Ramulus</i> (3.75g) | Je-Jung-Sin-Pyeon |
| Hwal-Lag-Hyo-Lyeong-Dan | Korean Angelica (18.7g), Myrrha (18.7g), <i>Salvia miltiorrhiza</i> (18.7g), Frankincense (18.7g) | Je-Jung-Sin-Pyeon |
| So-Hwal-Lag-Dan | Myrrha (7.5g), <i>Aconiti Radix</i> (22.5g), <i>Aconiti Ciliare Tuber</i> (22.5g), <i>Arisamatis Rhizoma</i> (22.5g), <i>Lumbricus</i> (22.5g), <i>Olibanum</i> (7.5g) | Hwa-Je-Gug-Bang |
| Saeng-Hwa-Tang | Korean angelica (18.7g), <i>Cnidium</i> (7.5g), Peach kernel (10g), <i>Rehmania</i> (11.25g), <i>Jujube</i> (2g), licorice (1.87g), <i>Zingiberis Rhizoma</i> (1.12g) | Gyeong-Ag-Jeon-Seo |

TABLE 4: The antiplatelet activity of Korean medicine prescriptions.

| Sample | The inhibition of rat platelet aggregation following collagen stimulation |
|--------------------------|---|
| Do-Haeg-Seung-Gi-Tang | 65.9 ± 3.8 |
| Bo-Yang-Hwan-O-Tang | 54.6 ± 6.43 |
| On-Gyeong-Tang | 4.7 ± 0.2 |
| Byeol-Gab-Jeon-Hwan | 1.5 ± 6.9 |
| Tong-Gyu-Hwal-Hyeol-Tang | 13.6 ± 6.43 |
| Tal-Hwa-Jeon | 8.9 ± 6.5 |
| So-Pung-Hwal-Hyeol-Tang | 13.6 |
| Saeng-Hwa-Tang | 17.1 ± 10.8 |

All samples were prepared as described in Table 3. Washed platelets in HEPES-Tyrode buffer were preincubated with 0.01% DMSO or 100 µg/ml of samples for 10 minutes at 37°C and then stimulated with collagen (1 µg/ml). Platelet aggregation was monitored in a platelet aggregometer (Chronolog Corp., Havertown, PA) at 37°C with stirring (1,000 rpm).

Among these, we have found the twenty-six prescriptions of KTM based on the Dong-Eu-Bo-Gam (by Hur Joon, AD1713), Je-Jung-Sin-Pyeon (by Kang Myeonggil, AD1799), Gyeong-Ag-Jeon-Seo (by Jang Gaebin, BC 1624), Hwa-Je-Gug-Bang (by Jin samun AD1078), Geum-Gwe-Yo-Lag (by Jang Jungkyung, BC 250), and Ui-Lim-Gae-Chag (by Wang cheongim BC1830), which had a significant efficacy of blood circulation and stasis (Table 3). Further, we found that eight prescriptions of KTM (unpublished data), including Do-Haeg-Seung-Gi-Tang, Bo-Yang-Hwan-O-Tang, On-Gyeong-Tang, Byeol-Gab-Jeon-Hwan, Tong-Gyu-Hwal-Hyeol-Tang, Tal-Hwa-Jeon, So-Pung-Hwal-Hyeol-Tang, and Saeng-Hwa-Tang, had a significant inhibitory effect on platelet aggregation following collagen stimulation (Table 4). These findings might provide the standardization, regulation, and quality control of KTM in the future antithrombotic studies.

5. Concluding Remarks

The pathophysiological role of platelet during vascular disease has long been considered to be important. Platelet aggregation and activation are a major cause of cardiovascular disease. Because of the side effects of current antiplatelet agents, TMHs have been mentioned as alternative therapeutic agents. TMHs have been traditionally used in the management of cardiovascular diseases and its progression, particularly, in thrombosis and coagulation. In this review, we give a brief overview of some current platelet receptor antagonists and their main disadvantages. Further, we focused on the bioavailability of TMHs that possess antithrombotic properties. However, only preliminary evidence of the usefulness of TMHs is currently available. Therefore, further studies are required to assess the bioavailability of TMHs and to compare their therapeutic efficacy against the currently FDA-approved platelet receptor antagonists. A better understanding of the

mechanisms mediating the bioavailability of TMHs could lead to the identification of a novel therapeutic target for the prevention and treatment of thrombotic diseases.

Conflicts of Interest

All authors declare no competing financial interests.

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