Natural Products for Antithrombosis

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1. Introduction

The hemostatic system, which comprises platelet aggregation, coagulation, and fibrinolysis, is a host defense mechanism that preserves the integrity of the high pressure closed circulatory system in mammals after vascular damages [1]. Under normal physiological conditions, the thrombi formation, controlled by the regulatory system, is temporary and spatial [2–5]. However, when pathological processes overwhelm the regulatory system of hemostasis or a shift in the hemostatic balance towards the procoagulant side, thrombosis is initiated [6]. Under this hypercoagulable state, excessive quantities of thrombi will be formed, which will ultimately lead to parts or total blockage of blood vessels [7, 8]. The development of clots in the artery, vein as well as microvascular circulation is the most frequent cause of morbidity and mortality worldwide [9, 10]. The formation of thrombi in the arterial circulation usually occurs in individuals at high risk of cardiovascular diseases [11] and coronary myocardial infarction and ischemic stroke are the main results of atherosclerosis and thrombosis in the coronary arteries [12]. Furthermore, peripheral arterial diseases including mesenteric artery embolism and limb arterial thrombosis are also closely related to the arterial thrombosis. Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE), is a relatively common condition that associated with serious symptoms [13, 14]. In reality, venous thrombosis is the second leading cause of death in patients with cancer. In addition, disseminated intravascular coagulation and microangiopathy hemolytic anemia (thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)) are associated with microvascular thrombotic disorders [6]. Therefore, more and more studies have been focused on preventing thrombosis for the treatment of those thrombotic diseases.

In recent years, antithrombotic drugs, which can be classified into three major categories including anticoagulation, antiplatelet aggregation, and fibrinolysis, have been intensively studied and developed as potential therapeutic approaches for arterial and venous thrombosis [15, 16]. Among these clinical used drugs, heparin [17], warfarin [18], and their derivates are mainly applied in inhibition of the blood coagulation factors, while plenty of antiplatelet drugs such as aspirin (ASP), clopidogrel, and abciximab have been...
used in reducing the risk of cardiovascular diseases [19–22]. Furthermore, fibrinolytic agents, such as streptokinase, tissue plasminogen activator (t-PA), and reteplase, are engaged to remove and dissolve the formed blood clots [23, 24]. Despite intense investigation over the last 40 years into the discovery and development of more effective antithrombotic drugs, the effect of these therapies on mortality rates still remained small [25]. And this situation will probably become more challenging in the future as the incidences of obesity, diabetes, and the metabolic syndromes rapidly increase. The reasons of low cure rates of these drugs mainly lie in drug resistance, limited efficacy in some patients, and side effects such as higher bleeding risk and gastrointestinal dysfunctions [26]. A study in United Kingdom, researchers indicated that the responsible drug for over 60% of the deaths caused by adverse drug reactions is ASP [27]. The side effects of ASP include bleeding, gastrointestinal toxicity, and thrombocytopenia. Cilostazol, a potent inhibitor of cyclic adenosine monophosphate-(cAMP-) phosphodiesterase 3 (PDE3), has serious side effects such as headache and palpitation [28]. Apixaban is an oral selective direct factor Xa (FXa) inhibitor and its most common adverse event is bleeding [29], and other adverse events reported are hypersensitivity reactions, syncope, nausea, dizziness, and so forth. Therefore, there is a rising urgent need for novel therapeutic approach to reduce current adverse effects of antithrombotic drugs without impairing their efficacy.

Nowadays, much effort has been focused on the discovering of natural products as effective supplements or even substitutes to those currently used antithrombotic drugs [30]. These natural products, composing of natural plants [31–33], traditional Chinese medicines (TCMs) [34, 35], and functional foods [36–38] as well as some special animal materials [39], have been found to possess remarkable antithrombotic property both in experimental and clinical stages. It is known to all that TCMs have a long history for treating many kinds of human diseases including thrombotic diseases and blood stasis syndromes. In reality, in Shennong’s Classic of Materia Medica (Shennong Bencao Jing in Chinese) [40], 83 of 365 TCMs were recorded with the function of “HuoXueHuaYu,” which means to promote blood circulation for removing blood stasis. Nowadays, there are some natural products that have been used in clinic for the treatment of thrombotic diseases. For example, Shimotsu-To, which is a combined prescription of four herbal extracts, Paeonia lactiflora, Rehmania glutinosa, Angelica sinensis, and Ligusticum chuanxiong, has been used in clinic for improving abnormal blood coagulation, fibrinolysis, and atherosclerosis [41]. Kang naoxueshuan (in Chinese) tablet, which consists of Flos Carthami, Radix Angelicae Sinensis, Hirudo, and so forth, can protect cerebral ischemia through antiplatelet aggregation and reduction of blood viscosity [42]. Besides, Ginkgo biloba leaves tablets are widely used in treating ischemic cerebrovascular diseases [43]. The main reasons for applying natural products to the treatment of thrombotic diseases are that they comprise multiple constituents and each constituent may have multiple targets; they may exert pleiotropic and synergistic effects that have positive functions for increasing the therapeutic efficacy. Besides, the constituents of natural products usually have less side effects on the gastrointestinal system [44].

This review will provide an overview on the formation mechanisms of thrombosis and the antithrombotic properties exerted by natural products and describe the pathways by which their activities may contribute to reduce thrombotic risks.

2. The Formation of Thrombosis

Thrombus can be classified into four groups based on different positions and constituents [45]: (1) pale thrombus, mainly occurs in fast-flowing blood with numerous platelets; (2) red thrombus, constituting of fibrin and erythrocyte in slow-flowing blood; (3) mixed thrombus, a continuous process of thrombus formation; (4) hyaline thrombus (also called microthrombus), the formation of cellulose in microcirculation small vessels. On the other hand, venous thrombosis, arterial thrombosis, and microvascular thrombosis are more likely to be distinguished depending on different blood vascular systems [46].

Thrombus formation, including platelet adhesion, activation, secretion, and aggregation as well as tissue factor (TF) initiating thrombin generation and fibrin formation, is highly complex [1]. When the vessel wall is breached or the endothelium is disrupted, collagen, and TF become exposed to the flowing blood, thereby initiating formation of a thrombus. Exposed collagen triggers the accumulation and activation of platelets, whereas exposed TF initiates the generation of thrombin, which not only converts fibrinogen to fibrin but also further activates platelets [8]. In this paper, the formation of thrombi is described in brief on three aspects, including coagulation system, platelet activation, and aggregation, and the change of blood flow conditions.

2.1. Coagulation System

Blood coagulation and platelet adhesion and activation are critical for cessation of blood loss at sites of vascular injury in the high-pressure closed circulatory system [47]. Upon vessel injury, coagulation system can be activated via either the contact activation (or intrinsic) pathway or by the TF (or extrinsic) pathway and converge on a common (intrinsic + extrinsic) pathway, which starts at the level of factor X (FX) to lead to thrombin and fibrin formation [48]. The extrinsic pathway is initiated by excessive exposure of TF which is a 263-residue membrane-bound glycoprotein [49] and as receptor and cofactor for factor VII (FVII) and its active form VIIa (FVIIa) [3, 50, 51]. On binding of FVIIa to TF, complex (TF-FVIIa) acquires catalytic activity and converts factors IX (FIX) and X (FX) to their active derivatives factors IXa (FIXa) and Xa (FXa), respectively [52]. Simultaneously, the intrinsic pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen, prekallikrein, and FXII. FXII firstly becomes FXIIa; and FXIIa converts FXI to FXIa (FIXa) and Xa (FXa), respectively [53]. Simultaneously, the intrinsic pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen, prekallikrein, and FXII. FXII firstly becomes FXIIa; and FXIIa converts FXI to FXIa. FXIa activates FIX, which with its cofactor FVIIa forms the tenase complex and then activates FX to Fxa [53]. In the common pathway, Fxa derived from both intrinsic and extrinsic processes with FVIIa on membrane surface in complex with prothrombinase complex activates thrombin.
formation which finally converts fibrinogen to fibrin polymers [54, 55] (Figure 1).

2.2. Platelet Activation and Aggregation. The intact vascular endothelium is a semipermeable barrier that controls the diffusion of plasma molecules, regulates vascular tone and inflammatory, and releases gaseous signal molecule including nitric oxide (NO) and prostacyclin (PGI₂) as well as endothelial CD₃₉ to prevent platelet aggregation or dilate blood vessels under physiological conditions. However, dysfunctional or impaired endothelium is characterized by the loss of such antiplatelet properties and tends to mediate and accelerate thrombosis. The exposure binding sites of collagen and von Willebrand factor (vWF), a multimeric plasma glycoprotein, allow the platelet membrane glycoprotein (GPIb-IX-V or GPVI) to adhere on it in the first place. After the initial adhesion of platelets to the extracellular matrix, platelets undergo shape change and the activation process requires a rapid response to autocrine and paracrine mediators, including adenosine diphosphate (ADP), thrombin (THR), epinephrine, and thromboxane A₂ (TXA₂) [56]. Furthermore, platelet granule secretions lead to the local release of ADP/adenosine triphosphate (ATP), 5-hydroxytryptamine (5-HT), Ca²⁺, adhesion proteins (e.g., fibrinogen, fibronectin, thrombospondin, vitronectin, P-selectin, and GPIIb/IIIa), and coagulation factors (factor V, factor XI, plasminogen activator inhibitor type 1, plasminogen, and protein S), all of which contribute to perpetuate and amplify the thrombogenic response [57]. These platelet agonists binding to specific membrane receptors (e.g., collagen binds to GPVI or α₃β₁, THR interacts with protease activated receptors, and ADP binds at least two ADP receptors on platelets) [58–60] activate phospholipase Cβ (PLCβ), resulting in the production of diacylglycerol (DAG) and inositol trisphosphate (IP₃). DAG and IP₃ activate protein kinase C (PKC) and mobilize cytoplasmic Ca²⁺, respectively. Then TXA₂ is produced as a consequence of increased cytoplasm Ca²⁺-levels and the high concentration of Ca²⁺ is necessary for the activation of PLA₂ through phosphorylation by p-38-mitogen-activated protein kinase (MAPK) [61]. Platelet aggregation is regulated in the final part of the pathway by activation of the platelet heterodimer GPIIb/IIIa receptor, the most abundant proteins on the platelet surfaces. Fibrinogen, the main ligand for the GPIIb/IIIa receptor, binding to GPIIb/IIIa also triggers an “inside out” signaling, causing amplification of the initial signal and further platelet activation. In the final phase of thrombus formation, fibrinogen is converted to fibrin by thrombin, leading to the stabilization of the platelet aggregates with more platelets and blood cells (leukocytes and red blood cells), thus getting trapped and contributing to growth of thrombus [62].

2.3. Change of Blood Flow Conditions. Physiologically, plasma separates blood vessel from the tangible components such as erythrocyte, leukocyte, and platelet in blood. Once the blood flow slows down, platelet will move to the edge of blood
vessel as well as adhere to the impaired endometrial, coagulator factors will be activated, and thrombin accumulates and amounts to a high concentration to facilitate thrombus formation. Furthermore, the blood viscosity [63], which will result in a lower erythrocytic deformability and a stronger platelet aggregation, will increase under slow blood flow condition. This cycling process between increasing erythrocytic deformability and slowing down blood flow finally promotes the adherence and aggregation of platelet. As a result, it is easy to form thrombus in vein with slow blood flow, where the concentration of coagulation factors and thrombin are very high locally [64, 65]. On the contrary, in artery where coagulation factors and thrombin can be scattered by fleet blood flow and it is less likely to achieve effective concentrations, so the thrombus formation in artery mainly relies on the adherence, activation, and aggregation of platelet rather than the impacts of coagulation factors and thrombin [66].

3. Antithrombotic Effects of Natural Products

Studies have demonstrated that natural products become increasingly crucial in reducing the thrombotic risks and treating various cardiovascular diseases. As previously mentioned, drugs for treating thrombosis can be divided into three categories: (1) anticoagulants, which prevent the coagulation system and interfere with further plaque expansion; (2) antiplatelet agents, which decrease platelet aggregation and inhibit thrombus formation; (3) fibrinolytic drugs, which dissolve the formed thrombus directly [67].

3.1. Anticoagulation. The extrinsic and intrinsic coagulation systems are initiated after vascular disruption via TF and collagen, respectively [8]. In clinical treatment, inhibition of coagulation system is an effective way to prevent the pathological thrombus formation.

3.1.1. Inhibition of Tissue Factors. TF as a membrane protein and the main initiator of the coagulation cascade is essential for thrombus formation [68]. TF expression in endothelial cells is induced by different inflammatory mediators including tumor necrosis factor- (TNF-) α [69], interleukin- (IL-) 1β [70], or histamine [71]. In reality, reducing TF expression significantly impairs thrombus formation, and agents focused on inhibition of TF activation become increasingly used effective clinical methods to treat coagulation diseases.

It has been reported that Chaenomeles sinensis has antithrombotic and antiplatelet aggregation activities [72]. Thirteen components were isolated and purified from the fruits of C. sinensis and five of them including hovertrichoside C (IC_{50} = 14.0 μg), luteolin-7-O-β-D-glucuronide (IC_{50} = 31.9 μg), hyperin (IC_{50} = 20.8 μg), avicularin (IC_{50} = 54.8 μg) and quercitrin (IC_{50} = 135.7 μg) can inhibit the TF expression of rat plasma after the addition of CaCl₂ in vitro. Furthermore, the TF inhibitory activity of the C-ring pentacyclic flavonol was evidently stronger than that of C-ring hexacyclic flavonol [73]. Rhizoma Ligustici Chuanxiong (with the main active component ligustrazine) is widely used in treating cardiovascular diseases, pulmonary hypertension, chronic renal failure and liver cirrhosis [74]. Shang et al. reported the inhibitory effects of ligustrazine on the expression of TF and vWF in human blood induced by THR in vitro. The result showed that ligustrazine suppressed TF expression not only in quiescent condition but after being induced by THR, and also decreased vWF formation after being induced by THR. These results provide a scientific basis for Rhizoma Ligustici Chuanxiong to be used as an antithrombotic agent [75]. In addition, a sesquiterpene glycoside (3-O-α-L-rhamnopyranosyl-(→4)-α-L-rhamnopyranosyl-(1→2)-α-L-(4-trans-feruloyl)-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl) isolated from the leaves of Eriobotrya japonica Lindley (Rosaceae) showed a strong TF inhibitory activity (IC_{50} = 2 μM) in vitro and another component ferulic acid illustrated a weak inhibitory activity (IC_{50} = 369 μM). This active sesquiterpene glycoside was composed of three parts including nerolidol, carbohydrate and feruloyl moieties, and the nerolidol moiety was mainly responsible for the inhibitory effect against TF [76].

In addition, estrogen replacement therapy could protect cardiovascular system and decrease the incidence of related diseases [77]. α-Zearalanol (ZAL), which is one of the natural phytoestrogens usually found in beans and grain, could decrease the contents of TF and its expression on vascular endothelium in rat plasma ex vivo with similar to or better than that of positive drug 17β-estradiol [78].

3.1.2. Inhibition of the Coagulation Pathways. The pathways of the coagulation system mainly consist of two distinct cascades (intrinsic and extrinsic coagulation pathways) ultimately contributes to the formation of the key protease thrombin which in turn converts fibrinogen into fibrin to stabilize the formed platelet-rich plug. In experiment models, activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) are tested to indicate the activation of intrinsic, extrinsic and their common (intrinsic + extrinsic) pathway, respectively [79]. The anticoagulation effects by inhibition of the coagulation pathways of natural products are summarized in Table 1.

The green algae Monostroma arcticum (MA), with polysaccharide as its important bioactive substance, is widely distributed in China. A polysaccharide HAF0 (average molecular weight of 9.36 kDa) isolated from MA showed the inhibition effect on the intrinsic and/or common coagulation pathway with prolonging APTT and TT [80]. Polygala falax (MA), with polysaccharide as its important bioactive substance, is widely distributed in China. A polysaccharide HAF0 (average molecular weight of 9.36 kDa) isolated from MA showed the inhibition effect on the intrinsic and/or common coagulation pathway with prolonging APTT and TT [80]. Polygala falax (MA), with polysaccharide as its important bioactive substance, is widely distributed in China. A polysaccharide HAF0 (average molecular weight of 9.36 kDa) isolated from MA showed the inhibition effect on the intrinsic and/or common coagulation pathway with prolonging APTT and TT [80]. Polysaccharide from Umbilicaria esculenta inhibited the thrombus formation
Table 1: Inhibition on the coagulation pathways of natural products.

| Natural products                                      | Experimental models | Pathways | Effects                                                                 | Reference |
|-------------------------------------------------------|---------------------|----------|-------------------------------------------------------------------------|-----------|
| Polysaccharide HAF0 of Monostroma arcticum            | Human blood (in vitro) | IN & CO  | Prolonging APTT and TT, but without PT                                  | [80]      |
| Total saponin of Polygala fallax Hesml.               | Rabbit blood (in vitro) | IN       | Prolonging APTT and RT and fibrinogen clotting time, but without PT    | [81]      |
| Borneol                                               | Rat blood (ex vivo)  | EX & CO  | Prolonging PT and TT and inhibition of arteriovenous shunt as well as venous thrombosis | [97]      |
| Withaferin A of Withania somnifera                    | Human blood (ex vivo) | IN & CO  | Prolonging APTT and PT and inhibition of thrombin, FXa formation, and TNF-α induced PAI-1 production as well as extending in vivo and ex vivo bleeding time | [86]      |
| Saline extract of Hirudinaria manillensis             | Rat blood (ex vivo)  | IN, EX & CO | Prolonging APTT, PT, and TT                                             | [98]      |
| Total glycosides of paeony                            | Rabbit blood (in vitro) | IN, EX & CO | Prolonging APTT, TT, and PT                                              | [90]      |
| 95% ethanol extract of Ferula lehmannii Boiss.        | Rat blood (in vitro) | IN, EX & CO | Prolonging APTT, TT, and PT                                              | [99]      |
| Dilinoleic acid, safflower yellow, and compatibility preparation | Rat blood (ex vivo)  | IN & EX  | Prolonging APTT, TT, CT, and BT                                         | [100]     |
| Aqueous extract of Whitmania pigra Whitman            | Rat blood (in vitro) | IN & EX  | Prolonging APTT as well as TT and suppression of fibrinogen formation | [101]     |
| Phlorotannins STP-1 and STP-2 of Sargassum thunbergii Kuntze | Rabbit blood (in vitro) | IN, EX & CO | Prolonging APTT, TT, PT, CT, and BT                                     | [102]     |
| Sulfated polysaccharides of Hizikia fusiformis        | Rat/Rabbit blood (in vivo/in vitro) | IN | Prolonging rats BT, CT in vivo, and rabbits APTT in vitro              | [103]     |
| Hyperoside of Rhododendron brachycarpum               | Rat blood (ex vivo)  | IN & EX  | Prolonging APTT and PT                                                  | [82]      |
| Polysaccharide of Umbilicaria esculenta               | Rat blood (in vitro) | IN, EX & CO | Prolonging APTT, PT, and TT                                              | [83]      |
| Sulfated (1→3)-β-L-arabinan of Codium vermilare       | Human blood (in vitro) | IN, EX & CO | Prolonging APTT, PT, and TT                                              | [104]     |
| Wogonin and wogonoside of Scutellaria baicalensis Georgi | Human blood (in vitro) | IN & EX  | Prolonging APTT and PT and inhibition of the activities and production of THR and FXa | [88]      |
| Crude extracts of Erigeron canadensis L.              | Human blood (in vitro) | IN & EX  | Prolonging APTT and PT                                                  | [89]      |

IN, EX, and CO represent for intrinsic, extrinsic, and common coagulation pathways, respectively; APTT: activated partial thromboplastin time; TT: thrombin time; PT: prothrombin time; RT: recalcification time; CT: coagulative time; BT: bleeding time.

Those results indicated that WFA possessed antithrombotic activities and might be developed as a new anticoagulant agent [86]. Wogonin (WGN) as well as its metabolite wogonoside (WGSN) is the flavonoids from Scutellaria baicalensis Georgi [87]. Treatment with WGN and WGSN resulted in prolonging APTT and PT as well as inhibition of the activities and production of THR and FXa in tumor necrosis factor-α activated human umbilical vein endothelial cells [88]. Pawlaczyn et al. studied the anticoagulant and antiplatelet activities of different fractions of Erigeron canadensis L. The mixture parts of polysaccharide-polyphenolic macromolecules inhibited both intrinsic and extrinsic coagulation pathways, as well as platelet aggregation.
induced by collagen in vitro. While in the carbohydrate part, only glucuronic acid and galacturonic acid showed weak anticoagulant activity [89]. In addition, the anticoagulant effect of total glycosides of paeony included prolonging APTT, PT, and TT in vitro confirmed that intrinsic, extrinsic, and common coagulation pathways were all inhibited [90].

3.2 Anti-Platelet Aggregation. The inhibition of platelet function has been widely studied for a long time in an effort to prevent and treat thrombosis, especially in antiplatelet aggregation. Andrographolide, the active component of Andrographis paniculata, could inhibit PAF-induced human blood platelet aggregation in a dose-dependent manner (IC$_{50}$ = 2 µM) [91]. Bupleurum from the aerial parts of Bupleurum falcatum showed an 8-fold potent inhibitory effect (IC$_{50}$ = 47.5 µM) compared to that of ASP (IC$_{50}$ = 420 µM) on collagen-induced platelet aggregation, and comparable inhibitory effects as ASP on AA-induced platelet aggregation [92]. In Maione's study, Tanshione IIA (TIIA) selectively inhibited rat platelet aggregation induced by reversible ADP stimuli (3 µM) in a concentration-dependent manner (0.5–5 µM). Nevertheless, TIIA was less active against the aggregation induced by irreversible ADP (10 µM) and collagen (10 µg/mL) stimuli [93]. Apart from single bioactive component, studies have also provided evidences for antiplatelet aggregation effects of crude extracts of natural products. The 80% aqueous-ethanol extract of Abies webbiana was found to inhibit both ADP- and epinephrine-induced human platelets aggregation, thereby suggesting therapeutic potential of this plant against thromboembolic conditions [94]. In Gadi’s study, crude aqueous extract (CAE) of parsley was evaluated for its antiplatelet aggregation activity in rats in vitro and ex vivo. CAE dose-dependently inhibited platelet aggregation in vitro induced by THR, ADP, collagen and epinephrine. The oral administration of CAE (3 g/kg) significantly (P < 0.001) inhibited platelet aggregation ex vivo and prolonged bleeding time (P < 0.001) without changes of the platelet amount [95]. In terms of the mechanisms for antiplatelet therapies, they are mainly composed of platelet membrane protein inhibitors, impacting nucleotide and arachidonic acid system as well as inhibition of platelet granules secretion.

3.2.1 Inhibition of Platelet Membrane Receptors. Development of definite platelet receptor inhibitors contributed to clinical treatment of antiplatelet aggregation, for example, ADP P2Y$_{12}$ receptor antagonists include ticlopidine and clopidogrel; GPIIb/IIIa antagonists include abciximab, tirofiban, and eptifibatide [96]. Based on the variety of protein structures, functions and ligand properties, platelet receptors can be classified into three groups include integrin, adhesion and agonist receptors. A large number of natural products and their constituents are reported as platelet receptors antagonists (Table 2).

GPIIb/IIIa, a heterodimeric receptor of the integrin family expressed at high density (50000–80000 copies/cell) on the platelet membrane, determines the final process during platelet aggregation. So many new antiplatelet aggregation drugs mainly focus on inhibition of this dominant receptor [151]. Spatholobus suberectus is a widely used TCM to promote blood circulation for the treatment of diseases related to the blood stasis syndromes [152]. It has been demonstrated that 95% ethanol extract of S. suberectus significantly inhibited ADP- and collagen-induced platelet aggregation in human platelet by inhibiting fibrinogen binding to the GPIIb/IIIa receptor and further suppressing the formation of TXA$_2$ [106]. Garlic is a common used spicy food all over the world, and a garlic preparation aged garlic extract (AGE) is reported to have inhibition effect of platelet aggregation [153]. Allison et al. [113] investigated the antiplatelet aggregation mechanism of AGE by testing their adhesion to fibrinogen using Rose Bengal and 51Cr uptake, fluorescence activated cell sorting (FACS) analysis and measurement of intracellular cAMP contents in human platelet after induced by ADP. The results showed that AGE at concentrations of 3.12% to 12.5% (v/v) can inhibit the binding of platelets to fibrinogen by approximately 40% in the Rose Bengal assay (P < 0.05) as well as 61.5%~72% in the 51Cr experiments (P < 0.05), and significantly decrease the amount of PAC-1 binding to GPIIb/IIIa by approximately 72% in the FACS analysis with increasing platelet cAMP (P < 0.01) level. These findings suggested that AGE inhibits platelet aggregation via inhibition of the GPIIb/IIIa receptor and an increase of cAMP level. In Jeon’s study, two bioactive compounds isomaltol and pentagalloyl glucose were separated from bark of Rhus verniciflua Stokes, and their antiplatelet mechanism were evaluated using receptor expression on platelet membranes, including GPIIb/IIIa (CD41), GPIIb/IIIa-like expression (PAC-1) and P-selectin (CD62), and intracellular calcium mobilization responses. The results indicated that pentagalloyl glucose had a significant inhibitory effect on the expression of P-selectin, but isomaltol had no such effect. Furthermore, isomaltol and pentagalloyl glucose decreased the expression of GPIIb/IIIa, which appeared to have anti-GPIIb/IIIa activity [118].

Adhesion receptors, which mainly refer to collagen receptors, mediate the platelet binding to injury endothelium including α2β1 (GPIa/IIa) and GPVI. Glaucocalyxin A (GLA) is a biosynthetically active ent-kauanoid diterpenoid isolated from Rubdosa japonica var. glaucocalyx, a traditional Chinese medicinal herb. GLA can significantly inhibit platelet aggregation in response to most of the platelet agonists including collagen, THR and ADP [154]. The inhibitory effect of GLA on collagen-stimulated platelet aggregation was notably potent, even occurred at as low as 0.01 µg/mL. GLA inhibited platelet aggregation induced by collagen-related peptide (CRP), a GPVI specific agonist in a dose-dependent manner and reduced collagen-induced phosphorylation of three major molecules, tyrosine kinase Syk, LAT, and phospholipase Cγ2 in GPVI signaling pathway. Therefore, GLA can be developed and used as a collagen receptor antagonist for antiplatelet aggregation [108]. Salvianolic acid B (SB) is an active component isolated from Danshen (Salvia miltiorrhiza), a TCM widely used for the treatment of cardiovascular disorders. Ma et al. demonstrated that α2β1 might be one of the direct target proteins of SB on platelets, and the signal cascade network of SB after binding with integrin α2β1 might include regulation of intracellular Ca$^{2+}$ level, cytoskeleton-related proteins such as coronin-1B and
| Natural products                                                                 | Experimental models                        | Possible mechanisms                                                                 | Reference |
|--------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------|-----------|
| 2,3,5,4'-Tetrahydroxystilbene-2-O-β-β-D-glucoside of Polygonum multiflorum     | Human blood (in vitro); agonist: collagen  | Inhibition of FcγRIIa, Akt (Ser473), and GSK3β (Ser9) phosphorylation               | [105]     |
| 95% ethanol extract of Spatholobus suberectus                                  | Human blood (in vitro); agonist: collagen  | Blockage of fibrinogen binding to the GP IIb/IIa; suppression of TXA₂ formation     | [106]     |
| A new tripeptide (AAP) of Agkistrodon acutus Venom                            | Rabbit blood (in vitro); agonist: ADP, PAF-acheter, collagen and THR | Inhibition of fibrinogen binding to GP IIb/IIa                                      | [107]     |
| Glaucocalyxin A of Rabdosia japonica (Burm. f.) var. glaucocalyx (Maxim.) Hara | Human blood (in vitro); agonist: collagen  | Inhibition of tyrosine phosphorylation of Syk, LAT, phospholipase Cγ₂, and P-selectin secretion | [108]     |
| Salvanolic acid B of Salvia miltiorrhiza                                       | Rat blood (in vitro and ex vivo); agonist: collagen | Exerting binding affinity to α₂β₁, decreasing of intracellular Ca²⁺, and impacting on cytoskeleton-related proteins level | [109]     |
| Indole-3-carbinol of cruciferous vegetables                                    | Human blood (in vitro); agonist: collagen  | Inhibition of fibrinogen binding to GP IIb/IIa and decreasing the levels of TXB₂, prostaglandin E₂ | [110]     |
| II-3,1-5,II-7,II-4',II-4'-Hexahydroxy-(I-3,II-8)-flavonylflavanonol and acacetin of Garcinia nervosa var. pubescens King | Rabbit blood (in vitro); agonist: PAF | Possessing strong PAF antagonistic activity                                           | [111]     |
| Essential oils of five Goniothalamus species                                   | Human blood (in vitro); agonist: ADP, AA, and collagen | Possessing strong PAF antagonistic activity                                           | [112]     |
| 15–20% ethanol extract of aged garlic                                          | Human blood (in vitro); agonist: ADP       | Inhibition of fibrinogen binding to GP IIb/IIa and increasing the level of cAMP       | [113]     |
| Tetramethylpyrazine of Ligusticum wallichii Franch                             | Human blood (in vitro); agonist: ADP, collagen, and U-46619 | Inhibition of fibrinogen binding to GP IIb/IIa and the levels of intracellular Ca²⁺ as well as TXB₂ | [114]     |
| Aqueous extract of Agrimonia pilosa                                            | Human blood (in vitro); agonist: ADP       | Inhibition of fibrinogen binding to GP IIb/IIa and decreasing the level of P-selectin | [115]     |
| N-butanol extract of Toona sinensis Seed                                        | Human blood (in vitro); agonist: THR       | Inhibition of fibrinogen binding to GP IIb/IIa and decreasing the level of intracellular Ca²⁺ | [116]     |
| Eryloside F of Erylus formosus                                                | Human blood (in vitro); agonist: ADP, THR, SFLLRN, and U-46619 | Possessing strong THR antagonistic activity                                           | [117]     |
| Isomaltol and pentagalloyl glucose of Rhus verniciflua Stokes                  | Human blood (in vitro); agonist: ADP, AA, and collagen | Decreasing the expression of GPⅡb/Ⅲa                                               | [118]     |
| Piperlongumine of Piper longum L.                                               | Rabbit blood (in vitro); agonist: U4619 and THR | Inhibition of U46619-induced phosphatidylinositol hydrolysis as well as the binding of (³H)SQ29548 to TXA₂ receptor | [119]     |
| Hot-water extract of modified Je-Ho-Tang (Mume Fructus, Amomi Tsao Fructus, Santali Albi Lignum, and Amomi Fructus) | Human blood (in vitro); agonist: collagen | Inhibiting adhesion and decreasing the activation of GPⅡb/Ⅲa-like expression and P-selectin monoclonal, Ca²⁺ mobilization | [120]     |
| Pomolic acid of Licaria pittieri                                                | Human blood (in vitro); agonist: ADP       | Competitive antagonism of ADP-induced platelet aggregation                            | [121]     |

ADP: adenosine diphosphat; PAF: platelet activating factor; THR: thrombin; AA: arachidonic acid; SFLLRN: thrombin receptor activating peptide; GP IIb/IIa: Glycoprotein IIb/IIa; TXA₂: thromboxane A₂; TXB₂: thromboxane B₂; cAMP: cyclic adenosine monophosphate; (³H)SQ29548: TXA₂ receptor antagonist.
cytoskeleton structure of platelets [109]. A traditional Korean
formula called modified Je-Ho-Tang (MJHT), which is com-
posed of Mume Fructus, Amomi TsaoKo Fructus, Santalii
Albi Lignum and Amomi Fructus, could promote blood flow
and eliminate blood stasis. The hot-water extract of MJHT
dose-dependently inhibited collagen-induced whole blood
aggregation and adhesion by shear stress in flow conditions.
Besides, the extract significantly inhibited the conformational
change of GPIIb/IIIa (PAC-1), the activation of P-selectin
and mobilization of platelet Ca\(^{2+}\) [120].

Once adhere to the sites of vascular injury, platelets are
involved in the process of activation and aggregation by
releasing of agonists such as ADP, 5-HT, TXB\(_2\) to amplify
the thrombus. Therefore, inhibition of the agonist’ receptor
can attenuate the formation of thrombus. Two active com-
ponents, acacetin and II-3,1-5,II-5,II-7,II-4',II-4'-hexahydroxy-
(1-3,II-8)-flavonolflavanol from the leaves of Garcinia nervosa var. pubescens King, showed strong inhibitory effects on
platelet-activating factor (PAF) receptor [111]. Another ago-
nist receptor of THR could be strongly inhibited by Eryloside
F, a novel steroidal disaccharide metabolite of Erylus formosus,
and finally led to inhibit human platelet aggregation in vitro [117]. Piper longum L. has been used as a crude drug
to improve intestinal disorder as well as the activity of peripher-
ally poor blood circulation in Asia [155]. Piperlongumine, a
constituent of P. longum, could concentration-dependently
inhibited platelet aggregation induced by TXA\(_2\) receptor agonist U46619, but slightly inhibited THR-induced aggregation.
Piperlongumine also inhibited U46619-induced phosphatidylinositol hydrolysis and the binding of \(^{(3)}\)HSO29548
(TXA\(_2\) receptor antagonist) to TXA\(_2\) receptor, so it is
assumed that piperlongumine act as a TXA\(_2\) receptor antag-
onist to inhibit platelet aggregation [119]. Pomolic acid (PA),
triterpenoid isolated from Licania pittieri, has shown a potent
ability to inhibit ADP- and epinephrine-induced human platelet aggregation. According to the mechanism study, PA
could be a potent competitive antagonist of P2Y\(_{12}\) receptor
[121].

3.2.2. Impacting on Nucleotide System. cAMP plays a mod-
ulatory role in PLC-mediatedsecretion and aggregation of
human platelets. The levels of cAMP are tightly controlled
and dependent on both its synthesis rate by adenylate
cyclase (AC) and its hydrolysis rate by PDE [156]. In
addition, cAMP levels may be increased by peroxisome
proliferator-activated receptors (PPARs) activation [157].
Intracellular cyclic guanosine monophosphate (cGMP) levels
are rapidly increased by soluble guanylyl cyclase (sGC), which
modulates multiple signaling pathways, including cGMP-
derpendent receptor proteins, cGMP-regulated PDE and
cGMP-dependent protein kinases. The increasing in cGMP
levels is accompanied by a decrease in intracellular Ca\(^{2+}\)
mobilization while the decrease in Ca\(^{2+}\) levels inhibits the
conformation change of GPIIb/IIIa into its active form and
thus decreases platelet binding to fibrinogen [158]. In a word,
the increasing in cAMP and cGMP levels may exert a strong
platelet inhibitory effect by decrease of intracellular Ca\(^{2+}\)
levels.

Cordycepin (3’-deoxyadenosine), the major active com-
ponent in Cordyceps militaris, had significant inhibition effect
on human platelet aggregation. Cordycepin may increase
cAMP and cGMP levels and subsequently inhibit the intra-
cellular Ca\(^{2+}\) as well as TXA\(_2\) but without affecting on
PLC-γ2 or IP3 [159]. In another study, cordycepin-enriched-
(CE-) WIB801C from Cordyceps militaris dose-dependently
inhibited ADP-induced platelet aggregation with IC\(_{50}\) of
18.5 μg/mL. The possible inhibition mechanism was that CE-
WIB801C elevated cAMP involved in IP3 or IP2 [156]
phosphorylation to inhibit Ca\(^{2+}\) mobilization and VASP (Ser\(^{157}\))
phosphorylation to inhibit \(\alpha_{\text{IIb}}/\beta_3\) activation [160]. The
ancient plant Ginkgo biloba possesses many biological activi-
ties such as radical scavenging, blood flow improvement and
vasoprotection. Ginkgolide C, one of the active components
in G. biloba, can significantly increase the formation of cAMP
and cGMP as well as suppressing the level of intracellular
Ca\(^{2+}\) and TXA\(_2\). In addition, zymographic analysis confirmed
that pro-matrix metalloproteinase-9 (pro-MMP-9, 92-kDa)
released from human platelets can be activated by Ginkgolide
C to form an activated MMP-9 (86-kDa), which can sig-
ificantly inhibit platelet aggregation stimulated by collagen
[161]. Furthermore, another active component of G. biloba,
quercetin prevented platelet aggregation by inhibition of
PDE\(_{12}\) [162]. It should be mentioned that PDEs can limit
the intracellular levels of cyclic nucleotides by catalyzing
the hydrolysis of cAMP and cGMP, thus regulating platelet
function. The inhibition of PDEs may therefore exert a strong
platelet inhibitory effect [163]. Oligoporin A from Oligoporus
tephroleucus, an edible mushroom cultivated in Korea, inhib-
ited collagen-induced platelet aggregation in a concentration-
dependent manner, but not affecting ADP- and THR-induced
platelet aggregation. Further study revealed that oligoporin
A can induce the dynamic increase of cAMP and cGMP in
platelet. Rat blood in vitro pretreatment with oligoporin A
significantly blocked collagen-induced ERK2 phosphoryla-
tion as well as diminished the binding of fibrinogen to its
cognate receptor, integrin \(\alpha_{\text{IIb}}/\beta_3\) [164].

3.2.2.3. Inhibition of Platelet Granules Secretion. Platelet gran-
ules mainly consist of \(\alpha\)-granules, dense granules and lys-
osomes which serve an essential role in promoting platelet
aggregation by releasing numerous activated factors such as
Ca\(^{2+}\), 5-HT, ATP, ADP, P-selectin, and so forth [165]. In-
hibitions of platelet granules secretion by natural products are
summarized in Table 3.

The concentration of cytosolic Ca\(^{2+}\) plays a fundamental
role in mediating dense granule release and platelet aggrega-
tion. Crocetin, a major ingredient of saffron, against platelet
aggregation were mainly contributed to inhibiting Ca\(^{2+}\)
mobilization via reducing both intracellular Ca\(^{2+}\) release and
extracellular Ca\(^{2+}\) influx, as well as inhibiting secretion of
5-HT, an independent risk factor for platelet aggregation and
for thrombus formation [122]. Geiji-Bokryung-Hwan
(GBH), Korean traditional formulation, consisting of Cin-
amomum Ramulus, Poria Cocos, Mountain Cortex Radicis,
Paoniae Radix and Persiae Semen. GBH potently inhibited
thrombin, CRP, U46619 (a TXA\(_2\) mimic), ADP, or SFLRN
Table 3: Inhibition of the platelet granules secretion of natural products.

| Natural products | Experimental models | Possible mechanisms | Reference |
|------------------|---------------------|---------------------|-----------|
| Crocetin of Saffron | Rat blood (ex vivo); agonist: ADP | Inhibition of Ca$^{2+}$ mobilization via reducing both intracellular Ca$^{2+}$ release and extracellular Ca$^{2+}$ influx as well as 5-HT secretion | [122] |
| Aqueous extract of Soshiho-tang | Rat blood (in vitro); agonist: collagen, THR and AA | Inhibition of 5-HT and TXA$_2$ formation | [123] |
| Geiji-Bokryung-Hwan (Cinnamomi Ramulus, Poria Cocos, Mountain Cortex Radicis, Paeoniae Radix, and Persicae Semen) | Human blood (in vitro); agonist: THR and CRP | Inhibition of IP3-mediated Ca$^{2+}$ mobilization | [124] |
| 20% ethanol extract of black soybean | Human blood (in vitro); agonist: collagen | Attenuating 5-HT secretion and P-selectin expression, and inhibiting TXA$_2$ formation | [125] |
| Magnolol of magnolia bark | Rabbit blood (in vitro); agonist: collagen | Inhibition of 5-HT secretion | [126] |
| Ligustrazine ferulate of Rhizoma Ligustici Chuanxiong | Rat blood (ex vivo); agonist: THR | Reduction of the expression of platelet P-selectin as well as suppression of platelet adhesion to neutrophil | [127] |
| Dihydroxybenzyl alcohol of Gastrodia elata Blume. | Rabbit blood (in vitro); agonist: AA | Inhibition of Ca$^{2+}$ mobilization via reducing both intracellular Ca$^{2+}$ release and extracellular Ca$^{2+}$ influx | [128] |
| Rhynchophylline | Rabbit blood (in vitro); agonist: ADP and THR | Inhibition of Ca$^{2+}$ mobilization via extracellular Ca$^{2+}$ influx rather than intracellular Ca$^{2+}$ release | [129] |
| Salvianolic acid B of Salvia miltiorrhiza | Human blood (in vitro); agonist: ADP and THR | Inhibition of P-selectin and CD40L releasing | [130] |
| Guanosine of Solanum lycopersicum | Human blood (in vitro) agonist: ADP and collagen | Inhibition of CD40L and ATP secretion | [131] |
| Curdione of Rhizoma Curcumae | Human blood (in vitro) agonist: THR, PAF, ADP and AA | Inhibition of P-selectin expression, intracellular Ca$^{2+}$ mobilization and increasing the cAMP levels in PAF-activated platelets | [132] |

ADP: adenosine diphosphate; THR: thrombin; AA: arachidonic acid; CRP: collagen-related peptide; 5-HT: 5-hydroxytryptamine; IP3: inositol-1,4,5-trisphosphate; TXA$_2$: thromboxane A$_2$.

(a thrombin receptor agonist peptide) induced platelet aggregation by acting on a certain step of the signal transduction pathway. Park et al. confirmed that GBH inhibited IP3-mediated Ca$^{2+}$ mobilization without altering tyrosine phosphorylation of PLC-$\gamma$2 [124]. Magnolol was isolated from Magnolia bark for the treatment of anxiety, neural and cardiovascular disorders [166], the antiplatelet aggregation mechanism of magnolol contribute to an inhibitory effect on 5-HT releasing [126]. Curdione, one of the major sesquiterpene compounds from Rhizoma Curcumae, had a potent protective effect on acute liver injury in mice and potentially to be an active constituent for strengthening the anti-inflammatory or cancer chemo-preventive capacity [167]. In the antiplatelet aggregation test, curdione preferentially inhibited PAF- and THR-induced platelet aggregation in a concentration-dependent manner ($IC_{50} = 60–80 \mu M$). Curdione can inhibit P-selectin expression, intracellular Ca$^{2+}$ mobilization as well as causing an increase of cAMP levels in PAF-activated platelets [132].

P-selectin, shows a crucial function in mediating platelet adhesion to the damage vessels, is localized in the $\alpha$-granules and released when activation of platelet. Black soybean (BB) significantly inhibited collagen-induced platelet aggregation by attenuating 5-HT secretion and P-selectin expression, as well as inhibiting TXA$_2$ formation in vitro [125]. Ligustrazine ferulate, the main active component of Rhizoma Ligustici Chuanxiong had distinct antithrombotic effect. Ligustrazine ferulate reduced the expression of platelet P-selectin as well as suppression of platelet adhesion to neutrophil [127]. Soshiho-tang (SH), which consists of seven herbal drugs, had antithrombotic and antiplatelet activities. Lee et al. reported that SH significantly inhibited various agonist-induced platelet aggregations and completely inhibited 5-HT secretion and TXA$_2$ formation. Furthermore, SH presented antithrombotic activity by prolonging the occlusion time of thrombus formation when applied in a FeCl$_3$-induced thrombus formation model [123]. Fuentes et al. demonstrated for the first time that guanosine from Solanum lycopersicum
possessed antiplatelet (secretion, spreading, adhesion and aggregation) activity induced by ADP as well as collagen in vitro and inhibited platelet inflammatory mediator of atherosclerosis (sCD40L), while depression of CD40L expression can prevent thromboembolic-related disorders [131].

3.2.4. Impacting on Arachidonic Acid System. TXA₂, intensely induces platelet activation and vasoconstriction, is generated from arachidonic acid (AA) which released when membrane phospholipids are broken down by diverse agonists such as collagen, thrombin and ADP. The enzymes related to TXA₂ production are cyclooxygenase (COX-1) and thromboxane synthase (TXAS), which are located at microsomes. COX-1 produces prostaglandin (PGG₂) from substrate AA, TXAS produces TXA₂ from PGG₂ that oxidized from PGG₂ by endoperoxidase. Therefore, inhibition of COX-1 or TXAS is a very useful marker to evaluate the antiplatelet effect of compound. For instance, COX-1 inhibitor aspirin and TXAS inhibitor ozagrel are being used as antiplatelet agents [168].

Another metabolic pathway of AA is the lipoxygenase (LOX) pathway that forms hydroxyeicosatetraenoic acids (HETE) and leukotrienes. TXB₂ and 6-keto-PGF₁₀ are the stable metabolites of TXA₂ and PGL₂, respectively. When the ratio of TXA₂/PGL₂ is above normal conditions, thrombus formation will occur. On the other hand, when the ratio of TXA₂/PGL₂ is lower than normal conditions, the processes of platelet aggregation or thrombus formation will be self-limited and a bleeding tendency may occur. A variety of natural products (Table 4) including berberine [138], hesperetin [139] and ethyl acetate extract of Caesalpinia sappan L. [145] inhibited platelet aggregation by keeping balance of TXA₂ and PGL₂.

As mentioned above, interference of the activation of the associated enzymes such as COX-1, COX-2, TXAS and LOX during arachidonic acid pathway is regarded as an effective way to inhibit platelet aggregation. Obovatol, a major biphenolic component of Magnolia obovata leaves, presented antiplatelet activity by inhibiting COX-1 and LOX activities to suppress production of TXB₂, PGD₂ and 12-HETE [136]. Morroniside, extracted and purified from Cornus officinalis Sieb.et Zucc., significantly inhibited the activation of COX as well as TXB₂ generation, and had a selective antiplatelet effect on ADP-induced aggregation [146, 147]. Coy et al. isolated 26 neolignans (14 bicyclooctane-type and 12 benzofuran-type) from three Lauraceae species (Pleuraythrum cinereum, Ocotea macrophylla, and Nectandra amazonum) and evaluated their antiplatelet aggregation property in vitro through inhibition of COX-1, COX-2, 5-LOX and agonist-induced aggregation of rabbit platelets. The results showed that benzofuran neolignans were found to be the COX-2 selective inhibitors, whereas bicyclooctane neolignans selectively inhibited the PAF-action as well as COX-1 and 5-LOX. The neolignan 9-nor-7, 8-dehydro-isolocarin B, and cinerin C were found to be the most potent COX-2 inhibitor and PAF-antagonist, respectively. In addition, nectamazin C (bicyclooctane-type neolignan) exhibited dual 5-LOX/COX-2 inhibition [148]. Abe et al. screened for inhibitors of human platelet aggregation and human 5-LOX from the Myoga (Zingiber mioga Roscoe) extracts. Experimental results indicated that miogatrial, miogadial, sesquiterpene and polygnal were potent inhibitors of human platelet aggregation and human 5-LOX, and their 3-formyl-3-butenal structure was essential for the activities [149]. In addition, Ginsenoside Rk₁ from white ginseng decreased the 12-HETE level involved in AA pathway, which is related to 12-LOX translocation resulting from the decreased of Ca²⁺ levels [150].

3.3. Fibrinolysis. The conversion of fibrinogen to fibrin and the consequent formation of a stable fibrin clot are the ultimate events in the coagulation and thrombotic cascades [169]. The agents available for clinical treatment on fibrinolysis can be classified into two groups: plasmin-like proteases which can directly hydrolyse fibrin, for example, nattokinase and lumbrokinase; and plasminogen activators, for example, tissue type plasminogen activator (t-PA) and streptokinase [170]. In recent years, some effective thrombolytic agents have been purified and characterized from foods or animal materials such as Japanese natto, douche (a traditional Chinese soybean food) [171] and earthworm [172].

In 1983, a high fibrinolytic active enzyme named lumbrokinase was firstly separated from artificial breeding earthworm in Japan [173]. This fibrinolytic enzyme had a dual function included dissolving fibrin directly and activate plasminogen. Furthermore, Mihara et al. [172] isolated a strong fibrinolytic enzyme from Lumbricus rubellus which contained abundant asparagine and aspartic acid with little proline or lysine. In addition, Xiong et al. separated and purified a fibrinolytic enzyme (33 kDa) with strong fibrinolysis effects and proteolytical activity from Eisenia fetida [174].

Nattokinase (27.3 kDa to 35 kDa) is a kind of serine proteases which is produced in the fermentation process of Bscillus natto or Bacillus subtilis var. natto. Nattokinase possesses a significant fibrinolytic property and the main mechanisms were to dissolving fibrin directly as well as activating plasminogen to increase the intrinsic plasmin formation. In the expectation to be developed as a new generation of fibrinolytic agents and health food, nattokinase has lots of advantages such as high safety, low cost and fast acting [175, 176]. Another serine protease (31 kDa with a single polypeptide chain) with fibrinolytic activity named CSP was purified from the culture supernatant of the fungus Cordyceps sinensis. CSP was found to be a plasmin-like protease, but not a plasminogen activator through preferentially cleaving the Aα chain of fibrinogen and the α chain of fibrin [170].

Pinus densiflora, an evergreen needle-leafed tree indigenous to Asia Pacific, has been used for the treatment of multiple ailments such as cardiovascular disease, cancer, diabetes and antihypertension. It was reported that pine needle extract would facilitate fibrinolysis, decrease the blood plasma cholesterol and triglyceride in cholesterol fed rat, and it’s helpful in removing blood clots [177]. On the other hand, Huang et al. screened for the fibrinolytic activities of 6 kinds of authentic medicinal materials from Guangxi (China) by fibrin plate method in vitro. As a result, Pueraria lobata, Trichosanthes kirilowii, Lonicera japonica, and Desmodium styracifolium showed fibrinolytic activity, and in particular the fibrinolytic activity of D. styracifolium
### Table 4: Impacting on the arachidonic acid system of natural products.

| Natural products | Experimental models | Possible mechanisms | Reference |
|------------------|---------------------|---------------------|-----------|
| Epigallocatechin-3-gallate of green tea leaves | Rat blood (in vitro); agonist: collagen | Inhibiting the activation of COX-1 and TXAS, with a stronger selectivity in COX-1 inhibition than TXAS inhibition | [133] |
| Jujuboside B of seeds of *Ziziphus jujuba* | Rat blood (in vitro); agonist: collagen | Inhibition of TXA₂ production | [134] |
| Alditol and monosaccharide of sorghum vinegar | Human blood (in vitro); agonist: AA, collagen, ADP, and THR | Inhibition of COX-1 and TXAS and attenuating TXA₂ production | [135] |
| Diacetylated obovatol of *Magnolia obovata* leaves | Rabbit blood (in vitro); agonist: collagen and AA | Inhibition of COX-1 and LOX activities and decreasing in cytosolic Ca²⁺ mobilization and 5-HT secretion | [136] |
| Ethanol extract, eupatilin, and jaceosidin of *Artemisia princeps* Pampanini | Human blood (in vitro); agonist: AA | Inhibition the generation of 5-HT and TXA₂ | [137] |
| Berberine of berberine sulfate injection | Rabbit blood (ex vivo); agonist: ADP, AA, and collagen | Suppressing of TXA₂ | [138] |
| Hesperetin of grapefruits and oranges | Rabbit blood (in vitro); agonist: AA and collagen | Inhibition of PLC-γ₂ phosphorylation, COX-1 activity, and decreasing of Ca²⁺ as well as TXA₂ | [139] |
| Green tea catechins of *Camellia sinensis* | Rabbit blood (in vitro); agonist: AA, collagen, and U-46619 | Inhibition of AA liberation, TXA₂ synthesis, PGD₂, and ATP formation | [140] |
| Hydroxychavicol of betel quid | Rat blood (in vitro); agonist: AA, collagen, and THR | Inhibition of COX-1/COX-2 enzyme activity and decreasing TXA₂ and ROS production as well as Ca²⁺ mobilization | [141] |
| Tetrandrine and fangchinoline of *Radix Stephaniae Tetrandrae* | Human blood (in vitro); agonist: PAF, THR and AA | Suppression of TXA₂ formation, but without inhibiting the binding of PAF to PAF-receptor | [142] |
| Isorhynchophylline of *Uncaria sinensis* (Oliv.) Havil. | Rabbit blood (in vitro); agonist: collagen | Inhibition of TXA₂ formation | [143] |
| Genistein | Rabbit blood (in vitro); agonist: PAF | Inhibition of TXA₂ formation and increasing PGI₂ generation | [144] |
| Ethyl acetate extract of *Cacalpinia sappan* L. | Rat blood (ex vivo); agonist: ADP | Inhibition of TXA₂ formation and increasing PGI₂ generation | [145] |
| Morroniside of *Cornus officinalis* Sieb.et Zucc | Rabbit blood (in vitro); agonist: ADP | Inhibition of COX activation and decreasing TXB₂ generation | [146, 147] |
| Neolignans of three Lauraceae species (*Pleurothyrium cinereum*, *Ocotea macrophylla*, and *Nectandra amazonum*) | Rabbit blood (in vitro) agonist: PAF, ADP and AA | Inhibition of COX-2 by Benzoafuran neolignans; inhibition of PAF-action, COX-1, 5-LOX by bicyclooctane; inhibition of COX-2, PAF-action by neolignan 9-nor-7,8-dehydro-isolicarin B and cinerin C; inhibition of 5-LOX/COX-2 by Nectamazin C | [148] |
| Extracts of *Myoga* (*Zingiber mioga* Roscoe) | Human blood (in vitro) agonist: ADP and AA | Inhibition of 5-LOX by miogatial, miogadial, sesquiterpene and polygalidial | [149] |
| Ginsenoside Rk1 of white ginseng | Rat blood (in vitro) agonist: AA | Decreasing of 12-HETE, 12-LOX, and Ca²⁺ levels | [150] |

AA: arachidonic acid; ADP: adenosine diphosphate; THR: thrombin; PAF: platelet activating factor; COX-1: cyclooxygenase-1; COX-2: cyclooxygenase-2; TXAS: thromboxane synthase; LOX: lipooxygenase; TXA₂: thromboxane A₂; TXB₂: thromboxane B₂; 5-HT: 5-hydroxytryptamine; PLC-γ₂: phospholipase C-γ₂; PGD₂: prostaglandin D₂; ATP: adenosine triphosphate; ROS: reactive oxygen species; PGI₂: prostacycline 2; 12-HETE: 12-hydroxy-5,8,10,14-eicosatetraenoic acid.
was similar to that of positive drug urokinase [178]. In addition, two components (1-palmitoyl-2-oleoyl-3-\(\alpha\)-D-glucopyranosylglycerol and 1-myristoyl-2-oleoyl-3-\(\alpha\)-D-glucopyranosylglycerol) were purified from Sargassum fulvellum and the fibrinolytic effect was identified in vitro [179].

4. Conclusion

Thrombosis remains a final pathway to disease and death in some of our most common diseases such as myocardial infarction and stroke. Although substantial progress has been made in understanding the biology of thrombus formation and the pathophysiology of thrombosis, all the pharmacological agents available for prevention or treatment have been in use for decades or have been replaced with newer variants that offer a modest incremental improvement. Natural products have been reported with apparent inhibitory activity on thrombotic diseases both in experimental and clinical stages, which provide a useful preventive approach or an adjunct to current pharmacological treatments for thrombotic diseases. Advances in the knowledge of both the mechanisms of thrombus formation and of the biological functions of natural products will provide new insights to promote human health.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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