**A review on Natural products as Anti-thrombotic agents**

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**Abstract**

Thrombosis is identified to be related with a few illnesses like atherosclerosis, ischemic coronary illness and stroke, etc along with rheumatoid joint pain, hyperuricemia, and different inflammatory conditions. An ever-increasing number of studies have been engaged on understanding the process relating molecular and cellular premise of thrombosis for rectification of disease caused. With the advent of increasing need of thrombotic agents, there is impressive interest in the part of naturally occurring items and their bioactive elements to prevent and treat of thrombotic disorders. This chapter briefly explains the mechanism of clots development on three perspectives, including coagulation framework, platelet actuation, conglomeration, and change of blood stream conditions. Furthermore, role of natural products used thus far for antithrombosis by anticoagulation, antiplatelet conglomeration, and fibrinolysis were summed up, individually.

**Keywords**: Thrombosis, coagulation, fibrinolysis, deep vein thrombosis (DVT),Coagulation Pathways

**Introduction**

The hemostatic system, which includes platelet aggregation, coagulation, and fibrinolysis, is a host defensive measure in mammals that helps to ensure the integrity of the closed circulatory system after vascular damage. The formation of thrombi, which is regulated by the regulatory system, is reversible and spatial under normal physiological conditions. Thrombosis occurs when pathological mechanisms overwhelm the hemostasis control system or when the hemostatic equilibrium shifts to the prothrombotic side ([Furie and Furie, 2008](#_ENREF_11)). Excessive amounts of thrombi can accumulate in this hypercoagulable state, eventually leading to partial or complete blockage of blood vessels. Atherosclerosis and thrombosis of the coronary arteries are the biggest factors of coronary myocardial infarction and ischemic stroke in people who are at high risk of cardiovascular disease. Deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE), are 2 types of venous thromboembolism (VTE) ([Bahl and Alsbrooks, 2023](#_ENREF_3)). Venous thromboembolism (VTE), which includes DVT and its complication, pulmonary embolism (PE), is a relatively common disorder that can cause severe symptoms ([Horne, 2005](#_ENREF_12)). In fact, venous thrombosis is perhaps the second most common cause of death among cancer patients. Antithrombotic drugs, which are classified into three parts: anticoagulation, antiplatelet aggregation, and fibrinolysis, have been extensively researched and introduced as alternative treatments for arterial and venous thrombosis in recent years. Heparin, warfarin, and their derivatives are the most commonly used clinical treatments for impeding blood coagulation factors. Antiplatelet drugs like aspirin (ASP), clopidogrel, and abciximab have all been shown to reduce the risk of cardiovascular disease. To extract and dissolve the developed blood clots, fibrinolytic agents such as streptokinase, tissue plasminogen activator (t-PA), and reteplase are used. Despite extensive research into the discovery and development of more successful antithrombotic drugs over the last 40 years, the effect of these therapies on mortality rates has remained limited ([Jackson and Schoenwaelder, 2003](#_ENREF_15)). And as the prevalence of obesity, diabetes, and metabolic syndromes grows, this problem will probably become more difficult in the future. Currently, much work is being put into developing natural products that can be used as viable options to the antithrombotic medications which are presently in use.

Natural products are diverse molecules that are flavonoids, alkaloids, terpenoids, and phytosterols. The natural products possess many beneficial effects including antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, antibacterial and anticancer ([da Silva et al., 2023](#_ENREF_8); [Senes-Lopes and Luz, 2023](#_ENREF_27); [Venkatesan et al., 2021](#_ENREF_33)). These natural products, which include natural herbs, conventional Chinese drugs, functional foods, and some unique animal materials, have been discovered to have remarkable antithrombotic properties for both experimental and clinical levels. Some herbal products are also being used in clinics to treat thrombotic diseases. Shimotsu-To, for example, has been used in clinic to improve pathological blood coagulation, fibrinolysis, and atherosclerosis by combining four herbal extracts: Paeonia lactiflora, Rehmannia glutinosa, Angelica sinensis, and Ligusticum chuanxiong. The key reasons for using natural products to treat thrombotic diseases are that they include several components, each of which may have multiple targets; they may have pleiotropic and synergistic effects that have positive functions for increasing clinical efficiency; and they may induce pleiotropic and synergistic effects that have positive functions for increasing therapeutic efficacy. Furthermore, the constituents of natural products typically have less gastrointestinal side effects ([Islam et al., 2016](#_ENREF_14)).

This chapter will provide an overview of thrombosis formation mechanisms and natural products' antithrombotic properties, as well as the pathways through which their activities can help to reduce thrombotic risks.

**Formation**

Platelet adhesion, activation, secretion, and aggregation, as well as tissue factor (TF) initiating thrombin production and fibrin formation, all play a role in thrombus formation ([Furie and Furie, 2007](#_ENREF_10)). Collagen and TF are exposed to the circulating blood when the vessel wall is broken or the endothelium is disrupted, resulting in the development of a thrombus. Exposed collagen causes platelets to accumulate and activate, while exposed TF causes thrombin to be produced, which not only transforms fibrinogen to fibrin but also activates platelets. The development of thrombi is presented in this paper from three perspectives: the coagulation mechanism, platelet activation and aggregation, and changes in the blood flow conditions ([Choi et al., 2014](#_ENREF_6)).

1.Thrombosis by coagulation

In the high-pressure closed bloodstream, blood coagulation and platelet adhesion and stimulation are important for preventing loss of blood at vascular injury sites. When a vessel is injured, the coagulation mechanism can indeed be activated through the touch stimulation (or intrinsic) pathway or the TF (or extrinsic) pathway, all of which converge on a common (intrinsic + extrinsic) pathway that begins at the level of factor X (FX) and leads to formation of thrombin and fibrin. The popular pathway stimulates thrombin production by combining FXa derived from both intrinsic and extrinsic processes with FVa on the surface of the membrane in complex with prothrombinase complex, which then converts fibrinogen to fibrin polymers ([Aird, 2007](#_ENREF_1)).

2. Aggregation and activation of platelets

Under physiological conditions, the intact vascular endothelium is a semipermeable membrane that governs plasma molecular diffusion, regulates vascular tone and inflammation, and produces gaseous signal molecules such as nitric oxide (NO) prostacyclin (PGI2), and also endothelial CD39, to avoid platelet aggregation and dilate blood vessels. The loss of antiplatelet properties in defective or damaged endothelium, on the other hand, appears to mediate and intensify thrombosis. Collagen and von Willebr factor (vWF), a multimeric plasma glycoprotein, have exposure ligands that enable the platelet membrane glycoprotein (GPIb-IX-V or GPVI) to attach to this in the first case ([Reininger, 2008](#_ENREF_26)). Platelets undergo shape shift after adhesion to the extracellular matrix, and the activation phase necessitates a rapid response to autocrine and paracrine mediators. Adenosine diphosphate (ADP), thrombin (THR), epinephrine, and thromboxane A2 are a few examples (TXA2). Platelet aggregation is regulated at the end of the pathway by the platelet heterodimer GPIIb/IIIa receptor, which is one of the Ia and causes “inside out” signalling, which causes amplification of the initial signal and further platelet activation. Thrombin converts fibrinogen to fibrin in the final step of thrombus formation, resulting in the stabilization of platelet aggregates with more platelets and blood cells (leukocytes and red blood cells), trapping them and contributing to thrombus development.

3. Blood flow condition change

Plasma physically distinguishes blood vessels from the visible components of blood, such as erythrocytes, leukocytes, and platelets. Platelets will migrate to the edge of the blood vessel as well as stick to the affected endometrial, coagulator factors will be stimulated, and thrombin will accumulate and amount to a high concentration to promote thrombus formation until blood flow slows down. Furthermore, under sluggish blood flow conditions, blood viscosity increases, resulting in lower erythrocytic deformability and greater platelet aggregation. This cycle of increasing erythrocytic deformability and decreasing blood flow eventually promotes platelet adhesion and aggregation. As a result, thrombus can easily form in a vein with sluggish blood flow, where coagulation factors and thrombin concentrations are very high locally. On the other hand, in an artery, where coagulation factors and thrombin can be scattered by fleet blood flow, effective concentrations are less achievable. As a result, platelet adherence, activation, and aggregation, rather than coagulation factors and thrombin, play a major role in thrombus formation in arteries ([Cohen and Efthymiou, 2021](#_ENREF_7)).

**Natural products and their anti-thrombotic effects**

Natural products are becoming increasingly important in reducing thrombotic risks and treating various cardiovascular diseases, according to studies. Anticoagulants, which stop the coagulation system from working and preventing further plaque development; antiplatelet drugs, which stop the platelet system from working and preventing further plaque expansion; and antiplatelet drugs, which stop the platelet system from working and preventing further plaque expansion. Antiplatelet drugs prevent thrombus formation by reducing platelet aggregation; fibrinolytic drugs remove the thrombus as it forms ([Belizna, 2015](#_ENREF_4); [Wang and Ng, 1999](#_ENREF_34)). Table 1-4 depicts the various natural products against thrombotic activity.

Rugosin E, a material contained in *rosa rogusa*, aids in the formation of clots. If you've ever had a deep vein thrombosis (DVT), pulmonary embolism, or any blood clot-related illness, you can stop rosehip. Rose hip can also reduce the effectiveness of blood thinners such as warfarin, that were used to prevent or treat cardiovascular disease.

1. Anticoagulation

Anticoagulation is a term that refers to the process of preventing blood from clotting. After vascular disruption, the extrinsic and intrinsic coagulation systems are activated via TF and collagen, respectively. In clinical practice, inhibiting the coagulation mechanism is an efficient way to avoid the development of pathological thrombus ([Beretz and Cazenave, 1991](#_ENREF_5)).

*Table 1. Inhibition of the mechanisms of coagulation of natural products.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Natural products**  | **Experimental****models** | **Pathways** | **Effects** | **References** |
| Polysaccharide HAF0 of*Monostroma arcticum* | Human blood | IN & CO | Prolonging APTT & TT |  ([Li et al., 2015](#_ENREF_22)) |
| Total saponin of *Polygala fallax* Hesml. | Rabbit blood | IN | Prolonging APTT, RT and fibrinogen clotting time, but without PT | ([Lichota and Szewczyk, 2020](#_ENREF_23)) |
| Borneol | Rat blood | EX&CO | Prolonging PT & TT & inhibition of arteriovenous shunt as well as venous thrombosis | ([Ku et al., 2014](#_ENREF_19)) |
| *Rhododendron**Brachycarpum’s hyperoside* | Rat blood  | N&EX | Prolonging APTT & PT | ([Ku et al., 2014](#_ENREF_19)) |

1. Inhibition of tissue factors

Tissue factor (TF) is needed for thrombus formation because it is a membrane protein and the key initiator of the coagulation cascade. Different inflammatory mediators, such as tumour necrosis factor (TNF-α), interleukin-1 (IL-1), or histamine, cause TF expression in endothelial cells. In fact, reducing TF expression greatly reduces thrombus formation, and drugs that inhibit TF activation are becoming more widely used as effective clinical remedies for coagulation disorders. Rhizoma Ligustici Chuanxiong (which contains the active ingredient ligustrazine) is commonly used to treat cardiovascular disorders, pulmonary hypertension, chronic renal failure, and cirrhosis of the liver. Estrogen replacement therapy has been shown to protect the cardiovascular system and reduce the prevalence of diseases associated with it. Zearalanol (ZAL), a natural phytoestrogen typically found in beans and grains, has been shown to minimise the contents of TF and its expression on vascular endothelium in rat plasma *ex vivo* in a way that is comparable to or better than positive medicines ([Wang et al., 2004](#_ENREF_35)).

Table 2: Inhibition of platelet membrane receptors for natural products.

|  |  |  |  |
| --- | --- | --- | --- |
| **Natural products** | **Experimental models** | **Possible mechanisms** | **Reference** |
| 95% of the Extract of Ethanol From *Spatholobus Suberectus* | Human blood (*in vitro*);agonist: collagen | Blocking of fibrinogen binding to GP IIb/IIIa, suppression of TXA2 | ([Lee et al., 2011](#_ENREF_20)) |
| *Salvia Miltiorrhiza’s Salvianolic Aci- B* | Rat blood (*in vitro & ex**vivo*);agonist: collagen | Exerting binding affinity to 𝛼2𝛽1, decreasing of intracellular Ca2+, and impacting on cytoskeleton-related proteins level | ([Ma et al., 2011](#_ENREF_24)) |
| Essential Oils of Five Species of Goniothalamus | Human blood (*in vitr*o);agonist: ADP, AA, &collagen | Possessing solid PAF antagonisticActivity | ([Moharam et al., 2010](#_ENREF_25)) |
| Isomaltol And Pentagalloyl Glucose Rhus Verniciflua Stokes | Human blood (*in vitro*);agonist: ADP, AA, &collagen | Decreasing the expression ofGPIIb/IIIa | ([Jeon et al., 2006](#_ENREF_16)) |
| Pomolic Acid of *Licania Pittieri* | Human blood (*in vitro*);agonist: ADP | Competitive antagonism ofADP-induced platelet aggregation | ([Alvarado-Castillo et al., 2012](#_ENREF_2)) |

1. *Coagulation Pathway inhibition*

Activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) are measured in experiment models to determine if the intrinsic, extrinsic, or typical (intrinsic + extrinsic) pathways are activated, respectively. Ex vivo in mice, hyperoside, isolated from the leaves of *Rhododendron brachycarpum*, was found to prolong the APTT and PT in a dose-dependent manner, as well as inhibit platelet aggregation induced by THR and collagen in vitro and ADP *in vivo*.

1. *Anti-Platelet Aggregation.*

Platelet function inhibition has been studied extensively for a long time in the hopes of preventing and treating thrombosis, especially in antiplatelet aggregation. PAF-induced human blood platelet aggregation was inhibited in a dose-dependent manner by andrographolide, the active component of *andrographis paniculata* (IC50 2 M). Tanshinone IIA (TIIA) inhibited rat platelet aggregation induced by reversible ADP stimuli (3 M) in a concentration-dependent manner (0.5– 5 M) in Maione's study. TIIA, on the other hand, was less efficient in preventing aggregation caused by irreversible ADP (10 M) and collagen (10 g/mL) stimuli. Antiplatelet therapies are primarily composed of platelet membrane protein inhibitors, which affect the nucleotide and arachidonic acid systems, as well as platelet granule secretion inhibition ([Sirikarin and Palo, 2018](#_ENREF_30)).

1. *Plateletorial Membrane Receptors’ inhibition*

The development of specific platelet receptor inhibitors has assisted in the clinical treatment of antiplatelet aggregation. ADP P2Y12 receptor antagonists include ticlopidine and clopidogrel, while GPIIb/IIIa antagonists include abciximab, tirofiban, and others. Platelet receptors are categorised into three classes based on the variety of protein structures, functions, and ligand properties, integrin, adhesion and agonist receptors.

Table 3. Inhibition of secretions of natural products through platelet granules.

|  |  |  |  |
| --- | --- | --- | --- |
| **Natural products** | **Experimental models** | **Possible mechanisms** | **ReferenceS** |
| Saffron’s Crocetin | Rat blood;agonist: ADP | Inhibition in Ca2+ mobilization by reducing the intracellular Ca2+ secretion & extracellular Ca2+ inflow along with 5-HT secretion | ([Yang et al., 2008](#_ENREF_37)) |
| Soshiho-Tang’s Extracts | Rat blood;agonist: collagen, THR & AA | Inhibition of formation of 5-HT & TXA2. | ([Lee et al., 2013](#_ENREF_21)) |
| 20 % Black Soybean Ethanol Extract | Human blood (*in vitro*);agonist: collagen | Modulating 5-HT secretion as well as P-selectin expression & impeding the development of TXA2. | ([Kim et al., 2011](#_ENREF_18)) |
| Magnolol of the Bark of Magnolia | Rabbit blood (*in vitro*);agonist: collagen | 5-HT secretion’s inhibition | ([Tsai et al., 1995](#_ENREF_32)) |
| Rhynchophylline | Rabbit blood;agonist: ADP & THR | stopping of Ca2+ movement via extracellular Ca2+ inflow rather than intracellular Ca2+ release | ([Xie et al., 2008](#_ENREF_36)) |
| *Solanum Lycopersicum’s* Guanosine | Human bloodagonist: ADP & collagen | CD40L as well as ATP secretion inhibition | ([Fuentes et al., 2013](#_ENREF_9)) |

It was reported that the antiplatelet aggregation mechanism of AGE by measuring their adhesion to fibrinogen using Rose Bengal and 51Cr uptake, fluorescence triggered cell sorting (FACS), and measurement of intracellular cAMP contents in human platelets after ADP was induced. Platelets become adherent to the sites of vascular damage after adhering to them. Release of agonists such as ADP, 5-HT, and TXB2 to amplify the activation and aggregation phase. The thrombus is a blood clot. As a consequence, blocking the agonist receptor is advantageous can help to prevent thrombus formation. Pomolic acid (PA), a triterpenoid derived from *Licania pittieri*, has been shown to have a potent inhibitory effect on ADP- and epinephrine-induced platelet aggregation in humans. PA may be a potent competitive antagonist of the P2Y12 receptor, according to the mechanism analysis ([Alvarado-Castillo et al., 2012](#_ENREF_2)).

1. *Nucleotide System’s impact*

PLC-mediated secretion and aggregation of human platelets are modulated by cAMP. The amount of cAMP released by adenylate cyclase (AC) and the rate at which it is hydrolyzed by PDE are both tightly regulated. Activation of peroxisome proliferator-activated receptors (PPARs) can also boost cAMP levels. CGMP (cyclic guanosine monophosphate) is an intracellular cyclic guanosine monophosphate (cGMP). By inhibiting PDE3, quercetin from G. biloba prevented platelet aggregation. PDEs, by catalysing the hydrolysis of cAMP and cGMP, can restrict the intracellular levels of cyclic nucleotides, thereby regulating platelet activity. As a consequence, inhibiting PDEs can have a powerful platelet inhibitory effect.

1. *Platelet Granules Secretion’s inhibition*

Platelet granules are made up primarily of -granules, dense granules, and lysosomes, which play an important role in platelet aggregation by releasing a number of activated factors such as Ca2+, 5-HT, ATP, ADP, and P-selectin. When SH was added to a FeCl3-induced thrombus formation model, it demonstrated antithrombotic activity by prolonging the occlusion time of thrombus formation. For the first time, Fuentes et al. demonstrated the guanosine from Solanum lycopersicom In vitro, it inhibited platelet inflammatory mediator of atherosclerosis (sCD40L), and it had antiplatelet (secretion, spreading, adhesion, and aggregation) activity caused by ADP as well as collagen, and it inhibited platelet inflammatory mediator of atherosclerosis (sCD40L).

Table 4. Effect on the arachidonic acid mechanism of natural products.

|  |  |  |  |
| --- | --- | --- | --- |
| **Natural products** | **Experimental models** | **Possible mechanisms** | **References** |
| Jujuboside B of Zizyphus Jujuba Seeds | Rat blood (*in vitro*);agonist: collagen | Inhibition of TXA2 production | ([Seo et al., 2013](#_ENREF_28)) |
| Berberine of Berberine Sulfate Injection | Rabbit blood (*ex vivo*);agonist: ADP, AA, &collagen | Suppressing of TXA2 | ([Huang et al., 2002](#_ENREF_13)) |
| Green Tea Catechins (*Camellia**Sinensis)* | Rabbit blood (*in vitr*o);agonist: AA, collagen, &U-46619 | Inhibition of AA liberation, TXA2 synthesis,PGD2, & ATP formation | ([Son et al., 2004](#_ENREF_31)) |
| Tetr and Rine, Radix Fangchinoline Stephaniae Tetr and Rae | Human blood (*in vitro*);agonist: PAF, THR & AA | Suppression of TXA2 formation, but withoutinhibiting the binding of PAF toPAF-receptor | ([Kim et al., 1999](#_ENREF_17)) |
| Ginsenoside Rk1 of White Ginseng | Rat blood (*in vitro*)agonist: AA | Decreasing of 12-HETE, 12-LOX, & Ca2+ levels | ([Shin et al., 2021](#_ENREF_29)) |

1. *Fibrinolysis.*

The ultimate events in the coagulation and thrombotic cascades are the conversion of fibrinogen to fibrin and the creation of a stable fibrin clot. The agents used in clinical fibrinolysis treatment can be divided into two categories: plasmin-like proteases that can hydrolyze fibrin directly, In 1983, lumbrokinase, a high fibrinolytic active enzyme, was isolated for the first time from an artificial breeding earthworm in Japan. This fibrinolytic enzyme had two functions: it disintegrated fibrin and activated plasminogen.

Isolated a powerful fibrinolytic enzyme via Lumbricus rubeulls, which had a lot of asparagine and aspartic acid but not much proline or lysine. In addition, Xiong et al. isolated and purified a fibrinolytic enzyme (33 kDa) from Eisenia foelide with good fibrinolysis and proteolytical activity. Pinus densiflora, a needle-leaved evergreen tree native to Asia - pacific Region, is being used to treat a range of ailments including cardiovascular disease, cancer, diabetes, even anti-hypertension. Pine needle extract has been shown to assist fibrinolysis, lower blood plasma cholesterol and triglycerides in cholesterol-fed rats, and aid in the removal of blood clots. Similarly, Huang et al. used the fibrin plate method in vitro to test for fibrinolytic activities of six different authentic medicinal materials from Guangxi (China). As a result, fibrinolytic activity was found in Pueraria lobata, Trichosanthes kirilowii, and Desmodium styracifolium, with D. styracifolium's fibrinolytic activity being close to that of the positive drug urokinase ([Huang et al., 2002](#_ENREF_13)).

**Conclusion**

In some of our most common illnesses, such as myocardial infarction and stroke, thrombosis remains a final pathway to illness and death. Despite significant progress in understanding the biology of thrombus formation and the pathophysiology of thrombosis, all presently offered pharmacological agents for prevention or treatment have been in use for decades or have been replaced by modern variants that provide a marginal gain. Natural goods significant inhibitory activity has been recorded on Thrombotic diseases at both experimental and clinical levels, to provide a useful preventive approach or an adjunct to this present pharmacological therapy for thrombotic diseases. Advances in the understanding of both pathways. The EEAV in rosa rogusa had important anticarcinogenic and antioxidant activity due to the existence of terpenoids and flavonoids. Further research into the various biological activities of this plant with different modes will not only validate the types of activities claimed by Ayurvedic, Siddha and traditional practitioners, but will also lead to innovation in the field of therapeutics.

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