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Exploring Nature's Arsenal: Natural Bioactive Compounds for Antiplatelet and Thrombolytic Activity

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Abstract:Thrombotic events, which are primarily instigated by the activation and aggregation of platelets, can result in severe medical conditions. Given the widespread occurrence of thrombotic diseases, it is imperative to develop innovative antiplatelet medications that effectively prevent and treat arterial thrombosis while minimizing adverse side effects. Natural bioactives, sourced from a variety of origins, have a rich history of use in addressing human health issues. These bioactive compounds, extracted from natural sources, have been meticulously identified and refined through numerous pharmacological approaches, rendering them both clinically beneficial and safe for use. The inherent complementarity among natural bioactives positions them as promising candidates for inclusion in pharmacotherapy strategies. However, it is important to acknowledge that the functional efficacy of natural bioactives is not without its limitations. Therefore, conducting a comprehensive investigation into the intricate mechanisms governing the antiplatelet properties of natural bioactives and their capacity to counteract thrombotic events within platelet function is of paramount importance. This review aims to provide an in-depth exploration of our current understanding concerning the regulatory mechanisms by which natural bioactives influence antiplatelet activity. Additionally, it examines their potential as alternative therapeutic agents in the context of managing thrombotic diseases.

Keywords*: Platelet aggregation, natural bioactives, thrombosis, antiplatelet.*

1. Introduction

Thrombosis is a key factor in cardiovascular disease morbidity and mortality. Thrombus formation begins with platelet attachment to injured vessel walls (Benjamin et al., 2018). Vaso-occlusive events are major contributors to mortality due to severe vascular conditions. Platelet activation, leading to adhesion, morphological changes, and thromboxane A2 synthesis, is crucial (Reed et al., 2000). Hemostasis controls blood flow and clotting in vessels. Imbalances in this process, from genetic or acquired causes, result in hypercoagulability (Wolberg et al., 2015). Factors for this include endothelial damage, reduced blood flow, and altered blood composition (Esmon, 2009). The role of the von Willebrand factor (VWF) is central in primary hemostasis where it mediates platelet adhesion to damaged vascular sub-endothelium and subsequently platelet aggregation. Blood coagulation factor Xa sits at a pivotal point in the coagulation cascade and has a role in each of the three major pathways (intrinsic, extrinsic, and the common pathway). Due to this central position, it is an attractive therapeutic target to either enhance or dampen thrombin generation (Brown et al. 2013). Genetic factors include Factor V Leiden, prothrombin gene mutations, and deficiencies in antithrombin, protein C, and protein S. Acquired factors are

elevated homocysteine, fibrinogen, and others (Rabieian et al., 2016). Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), under Venous Thromboembolism (VTE) disorders, have a significant health impact and are treated primarily with low molecular weight heparin (LMWH) and Vitamin K Antagonists (VKAs) (Lyman et al., 2013; Kumar et al., 2023).

However, it is important to note that treatment with LMWH and VKAs, while effective, comes with potential complications, including the risk of bleeding. Therefore, close monitoring is essential to determine the most appropriate drug dosage for individual patients (Benjamin et al., 2018). To address the challenges associated with LMWH and VKAs, oral anticoagulants known as Direct Oral Anticoagulants (DOACs) have gained prominence in clinical practice. These medications offer the dual benefits of easy oral administration and the advantage of not necessitating routine laboratory monitoring (Libby et al., 2002; Kumaret al., 2016). Furthermore, oral anticoagulant drugs have been shown to offer numerous advantages over VKAs when it comes to preventing stroke in individuals with nonvalvular atrial fibrillation. While DOACs offer several advantages over LMWH and VKAs for the treatment of thrombotic disorders, it is crucial that ongoing research in the development of new anticoagulant drugs prioritizes patient safety and aims to minimize potential complications (Golebiewska et al., 2015).

In this context, exploring the extensive therapeutic potential of bioactive natural compounds extracted from plants with antiplatelet and anticoagulant properties holds promise. These compounds may offer safer and more effective alternatives in the development of anticoagulant drugs (Vallet and Wiel, 2001). Plants are rich sources of bioactive secondary compounds with potent antioxidant and anti-inflammatory properties. These substances could block various enzymes, such as plasma serine proteases, suggesting their potential to act as anticoagulants and antiplatelet agents (Seca et al., 2018; Khalid et al., 2021). These natural compounds offer considerable potential as alternative or supplementary treatments for haemostasis-related illnesses. Their natural source, safety record, and cost-effectiveness when compared to synthetic drugs make them noteworthy contenders in the field of hemostasis treatment (Esmon, 2009; Hussain et al., 2022).

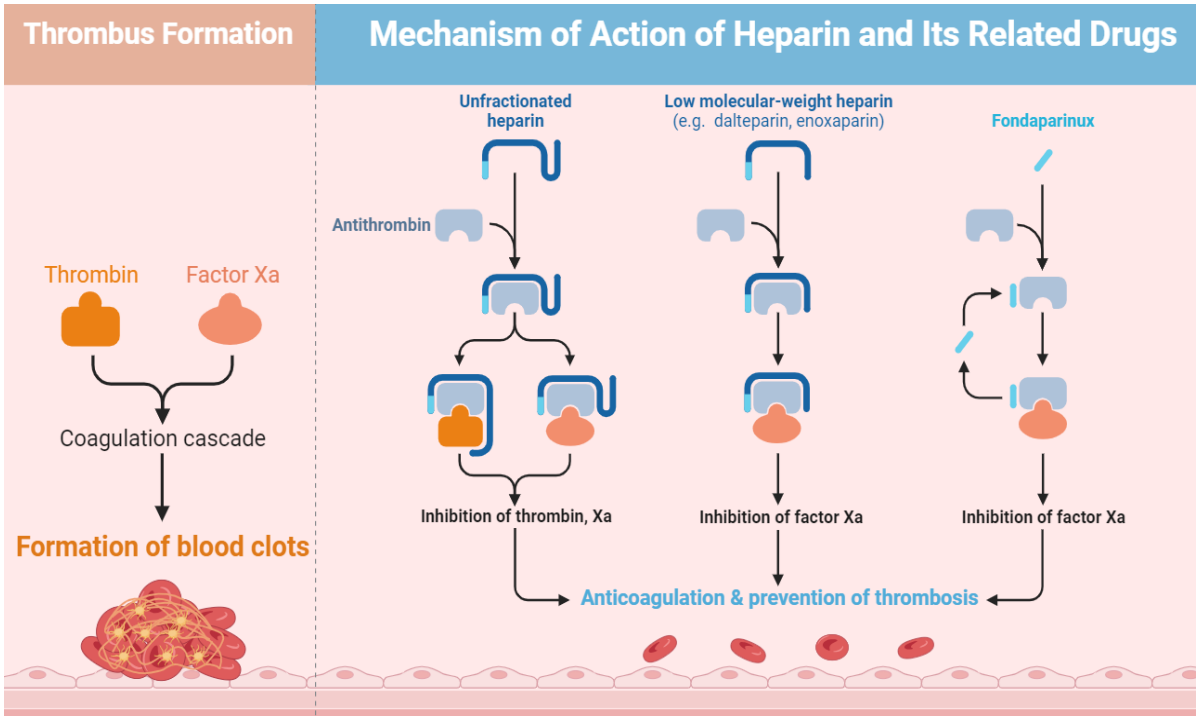


Figure 1. Anticoagulants and their targets within the coagulation cascade. Anticoagulants used target primarily coagulation factors (Xa) pathway and thrombin. VKA, and LMWH have multiple targets within the coagulation cascade.

Plants have historically been used for healing and prevention of different kinds of diseases. Modern interest is growing in plant-derived bioactive compounds for therapeutic uses (Nyakudya et al., 2020). The efficacy of plant extracts depends on their chemical composition. Plants produce primary and secondary metabolites (Erb and Kliebenstein, 2020). Primary metabolites, vital for plant growth and development, lack pharmacological effects and are divided into essential metabolites and metabolic end products. Secondary metabolites, differing among plant species, play roles in plant protection and interspecies interactions. These include bioactive compounds like terpenoids, phenolic compounds, and alkaloids, among others (Zaynab et al., 2018;Hussain et al., 2020). Phenolic compounds, especially polyphenols and flavonoids, are abundant in plants, showcasing antioxidant, anti-inflammatory, antiplatelet, and anticoagulant properties making them promising for preventing thromboembolic complications (Bijak et al., 2016; Abbas et al., 2017;Kumar et al., 2023).

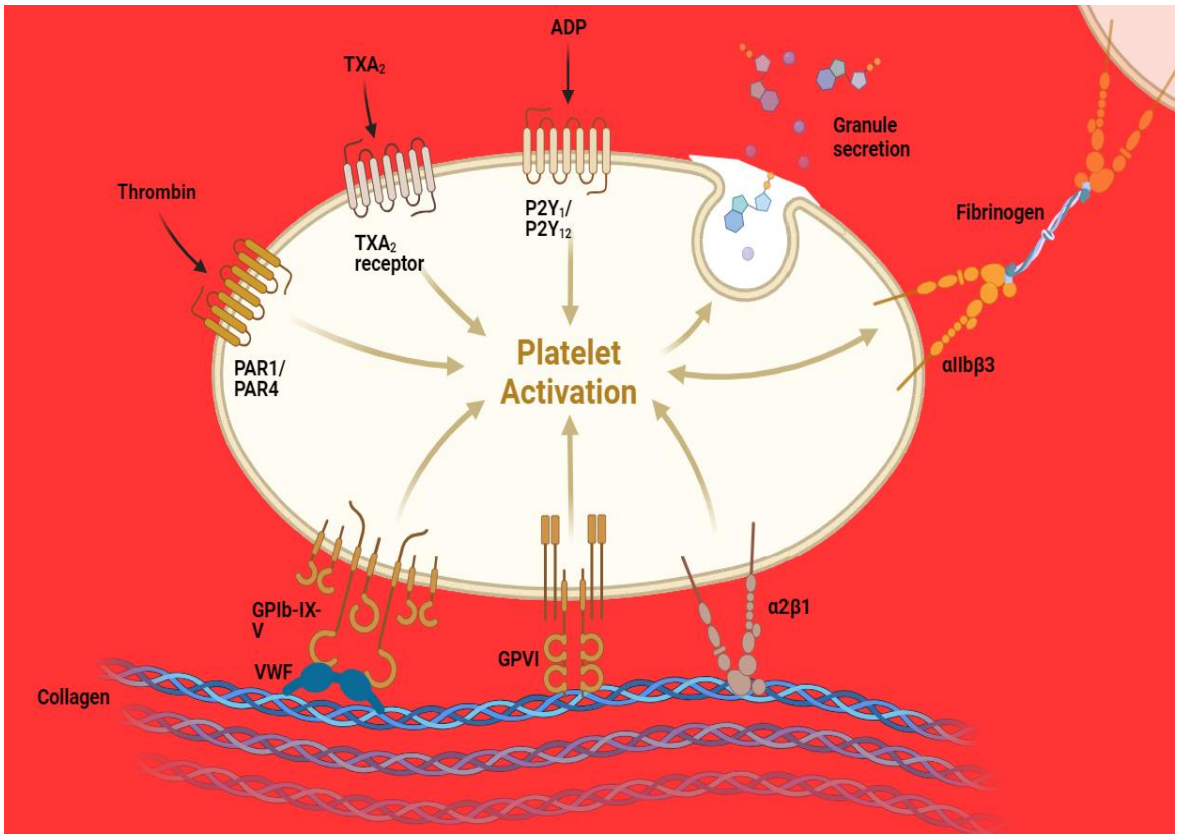


Figure 2. Schematic diagram of platelet activation and aggregation. In the resting conditions platelets, maintain their discoid form and flow in circulation. Upon injury, platelets become exposed to sub-endothelial collagen and von Willebrand Factor (VWF) and stick adhered to it. This is followed by activation and shape changes. The next phase is granules release and secondary phase aggregation and lastly the stable platelet plaque forms.

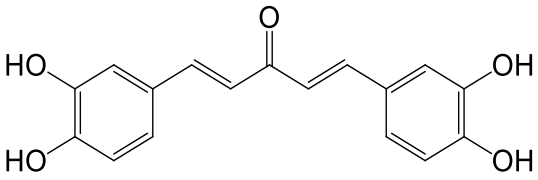
2. Antiplatelet activity of natural bioactive compounds of various investigated plants

The antiplatelet and anticoagulant properties of certain plant and herb extracts have been established. Moreover, the isolated compounds from these plants and herbs have also been studied to establish a connection between the phytochemical composition of the extract and its impact on hemostasis.

2.1. *Rhus Verniciflua*

Rhus verniciflua, previously identified as Toxicodendron vernicifluum, is a deciduous tree belonging to the Anacardiaceae family. It is commonly grown in Korea, China, and Japan. Rhus verniciflua has been employed in herbal medicine since the 15th century AD for various purposes, including treating stomach ailments,

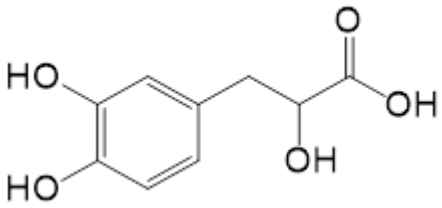
promoting liver detoxification, enhancing blood circulation, and alleviating blood stasis (Kim et al., 2014). While scientific evidence supporting the health benefits of *R. verniciflua* may be limited, recent in vitro studies have demonstrated its potential for various therapeutic activities, including antithrombotic, antioxidant, anti-obesity, anti-inflammatory, antimutagenic, and anticancer properties (Lee et al., 2003). Specifically, extracts from *R. verniciflua* demonstrate a strong antithrombotic effect on human platelets. Research has revealed that eight urushiol-type compounds derived from *R. verniciflua* effectively inhibit human platelet aggregation induced by Adenosine di-phosphate (ADP) or arachidonic acid (AA) in a dose-dependent manner, with IC50 values ranging from approximately 5 to 15 μmol/L (Jeon et al., 2006).



3-(8′R,9′R-Dihydorxypentadecyl)-Phenol

2.2 *Salvia miltiorrhiza* (Asian Red Sage)

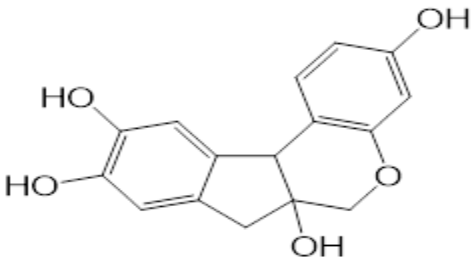
S. miltiorrhiza, or Asian red sage, is a traditional herb used in Korea, China, and Japan for circulatory health (Chen et al., 2014). It's been used to treat symptoms related to cardiovascular and cerebrovascular diseases. The herb has shown benefits against cellular damage from ischemia and reduced blood flow. It also decreased inflammatory markers IL-6 and IL-8 in human vein endothelial cells, emphasizing its anti-inflammatory properties (Song et al., 2008). The bioactive compounds in *S. miltiorrhiza*, including 15,16-dihydrotanshinone I, tanshinone IIA, and others, exhibit cardioprotective qualities against conditions like thrombosis and myocardial infarction. These extracts also have potent antiplatelet effects, inhibiting platelet aggregation and promoting fibrinolysis (Park et al., 2008). It aids in preventing blood stasis and enhancing blood flow in cerebral incidents. With a history of use in Asia, *S. miltiorrhiza* is considered safe, with minimal side effects reported (Cheng 2007).



15,16-dihydrotanshinone I

2.3 *Caesalpinia Sappan* (Brazilin)

Caesalpinia sappan, known as Brazilin or Sappan wood, is a medicinal plant from the Leguminosae family with a rich history in traditional medicine. It offers a variety of health benefits, such as analgesic, antibacterial, and blood circulation-enhancing effects (Toegel et al., 2012).

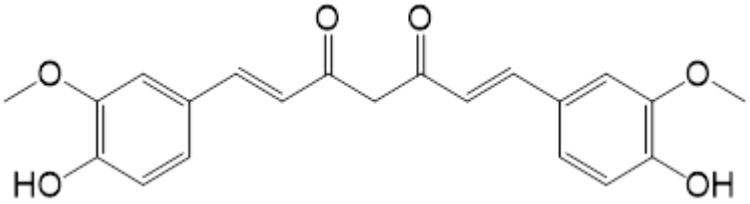


Brazilin

The main active compound in C. sappan is brazilin, which boasts a spectrum of biological activities like hypoglycaemic and anticancer properties (Kim et al., 2012). Brazilin, in concentrations between 0.1 to 1 mM, notably inhibits rat platelet aggregation caused by thrombin and other agents, likely due to its regulation of calcium ion mobilization and phospholipase activity. This indicates brazilin's potential in thrombosis drug development (Hwang et al., 1998).

2.4. *Curcuma zedoaria* and *Curcuma aromatic* (Turmeric)

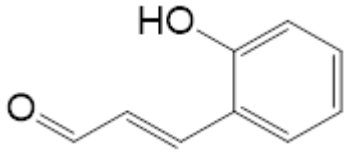
Curcuma zedoaria (white turmeric) and Curcuma aromatic (wild turmeric) are perennial herbs from the Zingiberaceae family with a deep-rooted medicinal history in Asia. These Curcuma species display various pharmacological properties like anti-tumor and anti-inflammatory effects (Khar et al., 1999). Traditionally, they have been used to treat circulatory issues. Curcumin, a key component in Curcuma, has multiple cardiovascular benefits due to its antioxidant and anti-inflammatory activities (Ghandadi and Sahebkar, 2017). Notably, curcumin is deemed safe, with doses up to 8 grams daily showing no adverse effects in certain patients (Cheng et al., 2001). In vitro studies have further revealed curcumin's ability to inhibit platelet aggregation prompted by various inducers suggesting its potential to manage platelet activation and aggregation (Shah et al., 1999).



Curcumin

2.5. *Cinnamomum cassia* (Cinnamon)

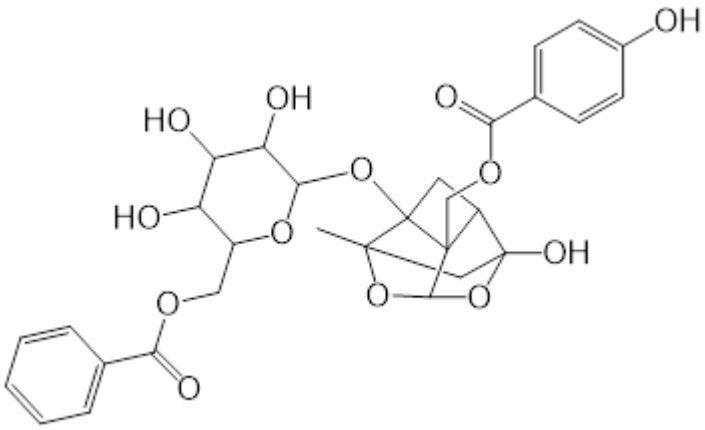
Cinnamomum cassia, or cinnamon, is an evergreen tree from the Lauraceae family, predominantly found in Asia. Traditionally, its extract has been used for various ailments including fever, inflammation, and to enhance blood circulation (Ho et al., 2013). Key components of cinnamon include cinnamaldehyde, trans-cinnamaldehyde, and other derivatives contributing to its aroma and multiple biological activities like antioxidant and antimicrobial properties (Ngoc et al., 2009). Extracts from C. cassia have shown effectiveness in inhibiting platelet activation. Specifically, compounds like eugenol, cinnamic alcohol, and others exhibited substantial inhibitory activity on platelet aggregation, rivaling acetylsalicylic acid (ASA) (Kim et al., 2010).



2-Hydroxycinnamaldehyde

2.6. *Paeonia lactiflora* (Peony)

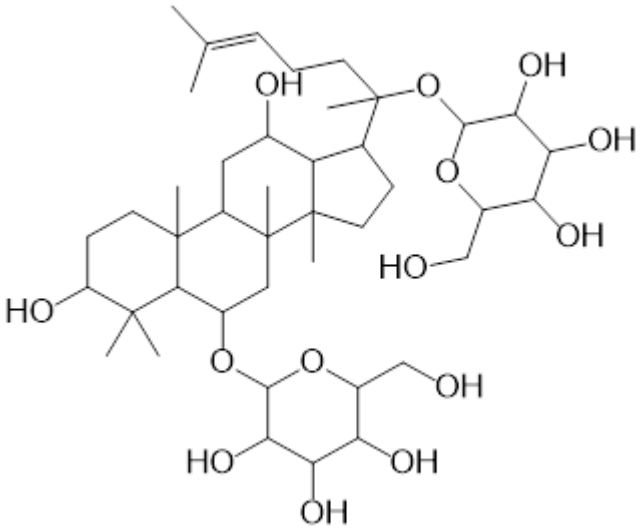
Paeonia lactiflora, or garden peony, is an herbaceous plant native to parts of Asia and is part of the Paeoniaceae family. Its roots, referred to as Paeoniae Radix, have been traditionally used in Korea, China, and Japan for their antipyretic, anti-inflammatory, and analgesic properties (Chou et al., 2003). Notably, these extracts have been employed to treat cardiovascular issues, particularly to enhance blood circulation. Paeonol, a primary component, has been found to inhibit platelet aggregation by reducing the production of thromboxane A2 (TxA2) and prostaglandin D2 (PGD2) (Hirai et al., 1983). Furthermore, various compounds within Paeoniae Radix extract, such as paeoniforin and benzoylpaeoniforin, have been shown to promote blood circulation by inhibiting platelet aggregation and blood coagulation (Koo et al., 2010).



Benzoyloxypaeoniforin

2.7. *Panax ginseng* (Ginseng)

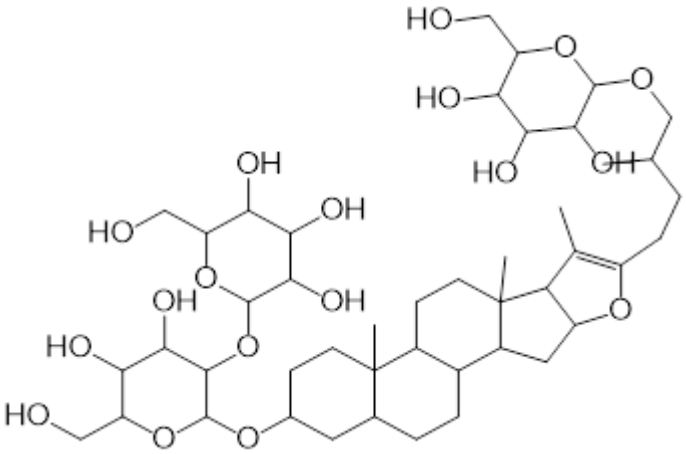
Ginseng, sourced from the Panax genus, encompasses species like *Panax ginseng* and *Panax quinquefolius.* Historically valued in traditional medicine for treating various conditions and bolstering immunity, its broad claims have seen limited clinical validation (McEwen et al., 2015). Recent research has highlighted ginseng's potential vasorelaxant, antioxidant, and anti-inflammatory effects, among others (Samukawa et al., 2008). For instance, oral administration of P. ginseng extract led to significant inhibition of platelet aggregation in rat platelets, and *P. notoginseng* extract inhibited collagen-induced platelet aggregation by 60% at certain concentrations (Lau et al., 2009). Ginseng is rich in constituents like ginsenosides and polysaccharides. Specific ginsenosides, such as Rg1 and Rg3, have shown promise in inhibiting platelet aggregation by influencing the PI3K/Akt signaling pathway (Jeong et al., 2017).



Ginsenoside

2.8. *Anemarrhenaasphodeloides*

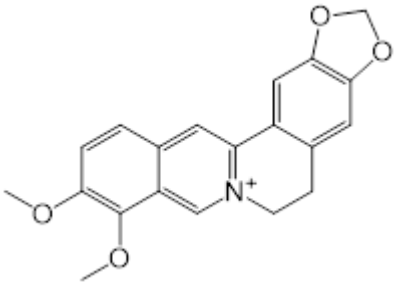
Anemarrhenaasphodeloides, native to Korea, China, and Mongolia, is part of the Asparagaceae family. It has been traditionally used for its therapeutic properties, including antidiabetic, antiplatelet, and diuretic effects (Takahashi et al., 1985). The plant also demonstrates positive impacts on the central nervous system, gastric cancer, and inflammation (Takeda et al., 2001). Key compounds in A. asphodeloides include xanthones, steroidal saponins, and flavonoids. Specifically, steroidal saponins like timosaponin A-III have shown to inhibit ADP-induced platelet aggregation (Zhang et al., 1999).



Anemarsaponin

2.9. *Coptis chinensis* (Goldthread)

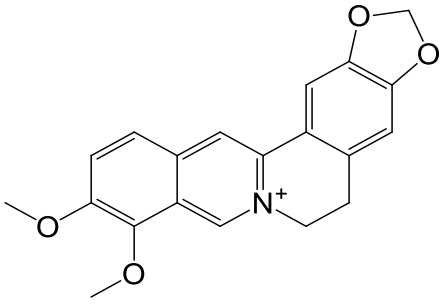
Coptis chinensis, native to regions in Korea, China, and Japan, belongs to the Ranunculaceae family. Its rhizome has been traditionally used for liver and cardiovascular ailments (Ikram 1975). Recent pharmacological research highlights its potential in treating bacterial infections, cancer, and inflammation (Kettmann et al., 2004). The primary compound in C. chinensis is berberine (BBR), known for its benefits on metabolism, inflammation, and cardiovascular health (Kong et al., 2004). BBR showcases antiplatelet activity by regulating AA metabolism and calcium. Specifically, BBR inhibits TxA2 synthesis in rabbit platelets and directly interacts with thrombin, inhibiting thrombin-induced platelet aggregation (Huang et al., 1991).



Berberine

2.10. *Carthamus tinctorius* (Safflower)

Carthamus tinctorius, or safflower, is an annual plant in the Compositae family. Historically, its extracts and oil have been used in traditional medicine for various purposes, including as analgesics and antipyretics (Asgarpanah and Kazemivash, 2013). In Korea, known as Honghwain, it's utilized for conditions like osteoporosis and menstrual issues. Clinical studies have delved into its therapeutic potentials. Extracts from *C. tinctorius* inhibit platelet aggregation induced by ADP and PAF and demonstrate antithrombotic activity in animals (Qu C et al., 2017).



Hydroxysaforyellow

Table 1. List of plants and their phytoconstituents used for Antiplatelet and Thrombolytic activity

Scientific name	Active compound	Findings
Rhus verniciflua	3-(8′R,9′R-dihydorxypentadecyl)-Phenol, 1-[3,4-dihydroxy-5-(12′Z)-12-heptadecen-1-ylphenyl]-Ethenone, Isomaltol Pentagalloyl glucose	ADP and AA-induced inhibition of platelet aggregation. inhibition of platelet aggregation driven on by collagen, AA, and ADP (Jeon *et al.*, 2006).
Salvia miltiorrhiza	15,16-dihydrotanshinone I, Cryptotanshinone, Danshensu, Salvianolic acid B, Tanshinone I, Tanshinone IIA.	Through Ca^{2+}mobilization and Thromaboxane A2 (TxA2) production, inhibited platelet aggregation brought on by collagen, and inhibited AA metabolism (Zhou *et al.*, 2005).
Caesalpinia sappan	Brazilin	Inhibited the thrombin, collagen, and ADP-induced platelet aggregation activities (Lobo *et al.*, 2009).
Curcuma zedoaria& Curcuma aromatic	Curcumin	ADP, AA, collagen, and platelet activation factor inhibition (Srivastava *et al.*, 1995).
Cinnamomum cassia	2-Hydroxycinnamaldehyde, 2-Methoxycinnamaldehyde, Amygdalactone, Cinnamic alcohol, Coniferaldehyde, Eugenol.	Aggregation of platelets caused by Platelet activating factor (PAF). Inhibition of platelet activation and aggregation brought on by ADP, collagen, and AA. TxA2 formation and Ca^{2+} mobilisation is inhibited (Chen *et al.*, 1996).
Paeonia lactiflora	Benzoyloxypaeoniforin, Benzoylpaeoniforin, Catechin, Daucosterol, Galloylpaeoniforin, Methyl gallate, Paeoniforigenone, Paeoniforin and Paeonol	Platelet aggregation caused by ADP, AA, and collagen was prevented by blocking the production of TxA2 and PGD2. Blood coagulation and anti-platelet aggregation are used to improve blood circulation (Yasuda *et al.*, 1999).
Panax ginseng	Ginsenoside Rg1 Ginsenoside Rg3 Ginsenoside Rp4	Inhibition of thrombin, ADP, collagen, and U46619-induced platelet activation and aggregation (Wang *et al.*, 2014).
Anemarrhena asphodeloides	Anemarsaponin B Timosaponin A-III Timosaponin B-II	Substantially delayed thromboplastin time and reduced ADP-induced platelet aggregation (Iida *et al.*, 1999).
Coptis chinensis	Berberine	ADP, collagen, AA-induced platelet aggregation, and TxA2 production were all inhibited (Zhou *et al.*, 2014).
Carthamus tinctorius	Hydroxysafor yellow A	Platelet aggregation caused by ADP and PAF was inhibited, and Prothrombin Time (PT), Thrombin Time (TT), and Activated Partial Thromboplastin Time (APTT) were delayed (Li *et al.*, 2010).

3. Conclusion

The medical field has long acknowledged the significance of platelets in the development of vascular diseases, as their aggregation and activation play a substantial role in cardiovascular conditions. Current medications designed to inhibit platelet activation often carry adverse effects, prompting the investigation of natural bioactive substances as potential alternative treatments. Phyto-bioactives from natural sources have a historical record of use in managing cardiovascular diseases, particularly those involving blood clot formation and coagulation. This review provides a concise summary of existing platelet receptor antagonists while highlighting their primary drawbacks. Additionally, it explores the potential of natural bioactive compounds in preventing blood clot formation. It's worth noting that there is currently limited preliminary evidence regarding the effectiveness of these natural compounds in this context. Therefore, further research is necessary to assess the availability and therapeutic efficacy of natural bioactives in comparison to platelet receptor antagonists approved by the U.S. Food and Drug Administration (FDA). A more in-depth exploration of the factors affecting the accessibility of these natural compounds may reveal new therapeutic opportunities for preventing and treating diseases related to blood clot formation.

Declaration of competing interest:
All the authors declare they have no conflict of interest.

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