A RECENT UPDATE ON ANTIPLATELET POTENTIAL OF HERBAL PLANTS

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ABSTRACT
Antiplatelet has found use clinically in the management of coagulation disorders. Blood platelets play an essential role in the hemostasis and wound-healing processes. However, platelet hyperactivity is associated to the development and the complications of several cardiovascular diseases. Various herbal plants have been investigated for their antiplatelet potential to treat different types of blood disorder. Numerous herbal plants and formulations are effective in treatment of blood disorder. This systemic review mainly is focused on herbal plants as antiplatelet in various traditional medicines and explores the herbal plant, isolated active constituent and formulation with antiplatelet activity.

KEYWORDS: platelets, medicinal plants, Coagulation factors, antiplatelet, platelet aggregation.

INTRODUCTION
Platelets are the smallest, unnuclated morphotic elements of blood that play a key role in maintaining hemostasis, i.e. the physiological balance between the processes of pro- and anti-coagulants. The biological activity of platelets, both in physiological processes and under pathological condition, is dependent on the degree of their activation. Platelet activation, despite the absence of the nucleus, is very complex. It is associated with signal transduction through a number of surface receptors in the cell membrane of platelets, combined with elements of enzymatic signal transduction chains. Because of a large number of specific membrane receptors, blood platelets are high reactivity cells, readily activated by many physiological and unphysiological agonists.¹

The activation of blood platelets is a multi-step process, where various responses occur, i.e. shape change and adherence to the vessel wall, secretion of biological active compounds from cell granules, aggregation, expression of P-selectin, phosphorylation of specific proteins, exposure of the anionic phospholipids on the extracellular surface of the platelet membrane, and release of micro particles rich in pro-coagulant activity. The morphological changes are accompanied by biochemical pathways: the enzymatic cascade of arachidonic acid, change in the concentration of
cAMP and cGMP, activation of kinases and phosphorylation of proteins, formation of reactive oxygen species (ROS), and the transformation of phosphatidylinositols. [2]

**Role of platelets in thrombus formation** [3]

Platelets, cytoplasmic fragments (2–5 μm) originated from bone marrow megakaryocytes; circulate within the vascular tree without significant interaction with the vessel wall. The endothelium inhibits platelet reactivity by producing several local active substances, including nitric oxide (NO) and prostacyclin as well as by the presence on its surface of an ectoADPase and thrombomodulin. The endothelium also blocks the activation of the coagulation cascade by expressing tissue factor pathway inhibitor and enhances fibrinolysis via activation of tissue plasminogen activator. The clustering of cardiovascular risk factors, among which high-LDL levels play a critical role, results in the aforementioned endothelial dysfunction, characterized by a decrease in NO bioavailability. NO is produced through the conversion of L-arginine to L-citrulline by the enzyme endothelial NO synthase (eNOS). NO then diffuses to the underlying vascular smooth muscle cells or circulating platelets to stimulate the production of cyclic guanosine monophosphate through the activation of the enzyme guanylate cyclase.

GC activation ultimately induces the activation of cGMP and/or cAMP-related kinases and the subsequent vasodilation and/or inhibition of platelet aggregation. Enhanced cAMP has shown to induce VASP-phosphorylation and subsequent platelet inactivation. Hence, the reduction in endothelial-related antithrombotic properties in concurrence with high reactive oxygen species generated by atherosclerotic risk factors and the local increase in pro-thrombotic and pro-inflammatory mediators seem to contribute to platelet activation in the onset of atherosclerosis. In advanced disrupted plaques, platelet adhesion varies according to the shear rate. Under low shear rate conditions platelet attachment mainly occurs through the collagen receptor that directly binds to the platelet receptor GPIa/IIa. To a lesser extent, fibronectin, laminin, vitronectin and thrombospondin also contribute to platelet adhesion by binding to GPIc-IIa, GPIc-IIa, vitronectin receptors, and to GPIV. Thereafter, the binding of platelet GPVI receptor to collagen promotes firm platelet adhesion and mediates platelet activation and aggregation.
## Drugs available in market and their sideeffects

<table>
<thead>
<tr>
<th>S.no</th>
<th>Available drugs</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>1</td>
<td>Aspirin</td>
<td>Major bleeding, Gastrointestinal- Nausea, Stomach pain, heart burn, Nausea, Consipation, hematemesis, and melena&lt;sup&gt;[4]&lt;/sup&gt;</td>
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<td>3</td>
<td>Coumarins</td>
<td>Coumarin is a vascular purpura that causes skin necrosis. This is associated with protein C deficiency and malignancy. Coumarins cross the placenta and cause spontaneous abortion and specific embryoabnormalities if administered in the first trimester of pregnancy&lt;sup&gt;[6]&lt;/sup&gt;</td>
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<td>4</td>
<td>Urokinase</td>
<td>Most Common- Severe bleeding. (Haemorrhage) Heart - Heart attack, pulmonary embolism. Blood- Decreased red blood cells and platelets. Miscellaneous- Excess sweating&lt;sup&gt;[7]&lt;/sup&gt;</td>
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<td>5</td>
<td>Warfarin</td>
<td>Tingling sensation, headache, chest, abdomen, joint, muscle pain, dizziness, shortness of breath, difficulty in breathing and swallowing, weakness, low Blood pressure and shock. Severe active bleeding during pregnancy; documented hypersensitivity - fever, rash and Hair loss. Gastrointestinal - Nausea, vomiting, diarrhea and abdominal Pain. Central Nervous System - Fatigue, tiredness, uneasiness, weakness, headache, dizziness, loss of consciousness, fainting, coma and taste perversion&lt;sup&gt;[8]&lt;/sup&gt;</td>
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Plants Acting as Antiplatelet agent

Plants may serve as the best alternative sources for the development of new antiplatelet agents due to their biological activities. Phytochemicals present in plants with having antiplatelet properties can ultimately reduce or eliminate the risk of thromboembolic diseases.

### Showing the plant and its mode of action as antiplatelet

<table>
<thead>
<tr>
<th>No.</th>
<th>Plant Name</th>
<th>Family</th>
<th>Plant Part</th>
<th>Mode of Action</th>
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<tbody>
<tr>
<td>1</td>
<td><em>Brassica oleracea</em></td>
<td>Brassicaceae</td>
<td>Flower extract</td>
<td>The methanol extract of crude extract of <em>B. oleracea</em> flower indicates qualitative presence of Alkaloid, saponins, steroids, flavonoids, tannins and Reducing sugar. The plant extract showed moderate clot lysis activity (42.75±3.72%) as compared to standard streptokinase’s clot lysis (67.32±5.25%) activity.</td>
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<td>2</td>
<td><em>Aegle marmelos</em></td>
<td>Rutaceae</td>
<td>Leaves extract</td>
<td>Concentrations of leaf ethanolic extract enhanced the percentage of clot lysis in dose-dependent manner. However, streptokinase a reference standard and water were used as a positive and negative control showed clot lysis maximum 89% and 2% in 90 mins of incubation respectively.</td>
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<tr>
<td>3</td>
<td><em>Saraca indica</em></td>
<td>Caesalpinaceae</td>
<td>Leaves extract</td>
<td>Hexane, chloroform and methanolic crude extract fractions were tested for their ability to inhibit calcium chloride induced platelet aggregation in-vitro. The presence of tannins, flavanoids, and triterpenes. The anti-platelet aggregation activity of the leaf extracts of <em>Saraca indica</em> were assessed by the presence of aggregation free platelets, when extracts were incubated with calcium chloride aggregation induced platelets. The scanning electron microscope images showed that the various leaf extracts of <em>Saraca indica</em> were effective against platelet aggregation.</td>
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</table>
4. *Carica papaya*, papaya, Caricaceae  
**Plant part used**: latex of unripe fruit extract  
**Mode of Action**: Saponins, tannins, glycosides, terpenoids, flavonoids, and alkaloids were present in CPUFL. Treatment with CPUFL increased both PT and aPTT. There was also a significant increase in clotting time of whole blood. CPUFL treatment showed a dose-dependent increase in bleeding time. Effect between CPUFL, heparin, and aspirin treatment were not significantly different.\(^{[12]}\)

5. *Careya arborea*, White Teak., Lecythidaceae,  
**Plant part used**: Bark extract  
**Mode of Action**: The methanolic bark extract of Careya arborea exhibited anticoagulant activities when compared with the standard warfarin. Prolongation in PT and prolongation of aPTT may be due to decrease in coagulation factors like V, VII and X involved in extrinsic pathway, and there is also decrease in coagulation factors such as VIII, IX, XI, XII.\(^{[13]}\)

6. *Artocarpus Heterophyllus*, jackfruit  
**Plant part used**: seed extract  
**Mode of Action**: Aqueous Extract specifically prolonged the clot formation process of only APTT but not PT, revealing the anticoagulation triggered by the extract could be due to its interference in an intrinsic pathway of the blood coagulation cascade.\(^{[14]}\)

7. *Allium sativum*, Garlic, Lilliaceae  
**Plant part used**: Whole fresh bulb, dried bulb.  
**Mode of Action**: Bulbs that have been dried and re-moistened ferment into various types of oils. Oils that are act as clot preventing agents. At the high dose of garlic and decrease of TXB 2 levels in the serum of the rats was observed. Boiled garlic and at high concentration had very little effect on TXB2 synthesis. A high dose of garlic and onion produces toxicity in the rats. These results show that garlic can be taken frequently in low doses without any side effects, and can still produce a significant antithrombotic effect.\(^{[15]}\)
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| 8| *Allium cepa*, L., Red onion, Amaryllidaceae | The aqueous extract of red onion was found to inhibit coagulation process in vitro and significantly prolonged prothrombin time in a dose-dependent manner. The prothrombin time test (also known as the pro test or PT test) is a useful screening procedure for the extrinsic coagulation mechanism including the common pathway. It detects deficiencies in factor II, V, VII, and X. Prolongation indicate a deficiency in one or more of II, V, VII, and X factors.  

Curcuma longa, Turmeric, Zingiberaceae | Turmeric suppresses the ability of platelets to stick together to form clots, which may help to boost circulation. Curcumin prolonged aPTT and PT significantly and inhibited thrombin and FXa activities.  

| 10| *Melastoma malabathricum*, Sendudok, Melastomataceae | The aqueous extract of leaves prolonged aPTT and thrombin time (TT). Further investigations evaluated the bioactive compound(s) responsible for the anticoagulant activity as well as the determination of the coagulation factor affected.  

| 11| *Terminalia belerica*, Bahera, Combretaceae | Terminalia belerica fruits possess thrombolytic and antithrombotic activity in vitro; however in vivo clot-dissolving properties and active component of *Terminalia belerica* for clot lysis are yet to be discovered. In case of antithrombotic experiment, the clot was formed in normal time or slight delay when NS was added to the control. Whereas tube to which SK was added, the clot was not formed and in case of extract solutions; significant delay in clot formation time is noted. |
| 12 | *Cyperus rotundus*, motha, Cyperaceae  
**Plant part used:** Rhizomes extract  
**Mode of Action:** *Cyperus rotundus* EtOH extract (CRE) and its constituent compounds. During the in vitro platelet aggregation study, CRE showed significant and concentration, (+)-nootkatone was found to have the most potent inhibitory effect on collagen-, thrombin-, and AA-induced platelet aggregation. In addition, CRE- and (+)-nootkatone-treated mice exhibited significantly prolonged bleeding times. Furthermore, (+)-nootkatone had a significant inhibitory effect on rat platelet aggregation ex vivo. \[19\] |
| 13 | *Porana volubilis* (Horse-Tail Creeper) Convolvulaceae.  
**Plant part used:** Flowers and leaves extract  
**Mode of Action:** Its anticoagulant activity is mediated by the enhancement of thrombin inhibition that in turn is mediated by heparin cofactor II but not by antithrombin. Anticoagulant activity is mediated by the enhancement of thrombin inhibition that in turn is mediated by heparin cofactor II. \[20\] |
| 14 | *Ocimum basilicum* and *Mentha spicata*,  
**Plant part used:** leaves extract  
**Mode of Action:** The in vitro antiplatelet activity was determined by platelet aggregation assay using platelet rich plasma (PRP) in the methanol extracts of the investigated plants. The percentage inhibition of platelet aggregation was found to be 63.79 ± 1.2 and 73.2 ± 0.6 for *Ocimum basilicum* and *Mentha spicata* respectively. The IC50 values for inhibition of platelet aggregation were found to be 8.433 and 8.586 mg/ml for *Ocimum basilicum* and *Mentha spicata*. The presence of the bio-active compounds especially, polyphenols in the crude extracts of the investigated plants may be responsible for the platelet inhibitory function. \[21\] |
| 15 | *Eichhornia crassipe*, water-hyacinth, Pontederiaceae  
**Plant part used:** Leaves extract  
**Mode of Action:** Anticoagulant activity by acting on the intrinsic pathway of the coagulation cascade \[22\] |
16  *Codium fragil* & *Sargassum horeri*, Marine Algae, Gracilariaceae  
**Plant part used:** Algae  
**Mode of Action:** Algal anticoagulant polysaccharides exert their anticoagulant activity through potentiating antithrombin III (ATIII) and/or heparin cofactor II (HC II) that are important endogenous inhibitors, called SERPIN. The anticoagulant mechanism is the one by which heparin; heparin sulfate and dermatan sulfate exert their activity. On the other hand, some algal anticoagulant polysaccharides exert anticoagulant activity through directly inhibiting fibrin polymerization and/or thrombin activity without potentiating AT III and HC II. Recent studies conducted on marine algal biologically active compounds have shown antiplatelet and anticoagulant proteins and fibrinolytic enzymes.[23]

17  *Glycyrrhiza Glabra*, liquorice, leguminosae.  
**Plant part used:** root extract  
**Mode of Action:** 3-aryl comarin derivative, GU-7 isolated from Liquorice possesses antiplatelet activity. It inhibits platelet aggregation by increasing intraplatelet cyclic AMP concentration. Here we report the in-vivo effects of extract of Glycyrrhiza glabra and also the combined effect with Vitamin K and Heparin. Extract of Glycyrrhiza glabra increased the bleeding time when given in the dose. Blood loss was evaluated 60 minute later as a function of absorbance at 540 nm due to hemoglobin content in water solution.[24]

18  *Molineria recurpata*, Palm Grass, Hypoxidaceae  
**Plant part used:** Leaf extract  
**Mode of Action:** anticoagulant activity of *Molineria recurpata* leaf extract (Methanol) on fresh human blood. Both the extracts were found to have sufficient anticoagulant activity. But the concentration of 2g/ml methanolic leaf extract showed the maximum effect with respect to others. It detects deficiencies in factor and X. Thus prolongation indicates a deficiency in one or more of these factors II, V, VII, & X.[25]

19  *Phyllanthus niruri*, Euphorbiaceae  
**Plant part used:** extract  
**Mode of Action:** In PT activity was observed maximum in aqueous extracts of aerial parts at 1000 gmL-1, which was 28 times higher than the standard value. Among the plant parts, aerial parts gave better activity than roots. APTT activity was higher in aqueous extract of roots at 750 gmL-1 and aerial parts at 1000 gmL-1 that was 10.75 and 9 times
| 20 | *Nigella sativa* | Plant part used: seed extract  
Mode of Action: Collagen was used as platelet aggregation inducer. 0.4 ml of 0.9mg/dl aspirin solution was used as standard dose. The final working concentration of aspirin and collagen was 18 g/ml and 2 g/ml respectively. The aqueous extract was found to have antiplatelet activity. The 5.0 g/ml of seed extract was found 67% active against 18 g/ml of aspirin.\(^{[27]}\) |
| 22 | *Ficus carica*, Fig, Moraceae | Plant part used: Dried ripe fruit extract  
Mode of Action: Cromakalim inhibited the contractions induced by low K+, but not of high K+, while verapamil equally inhibited the contractions of K+ at both concentrations. Fc.Cr inhibited the adenosine 5'-diphosphate and adrenaline-induced human platelet aggregation. Possibly mediated through the activation of K+ATP channels along with antiplatelet activity which provides sound pharmacological basis for its medicinal use in the gut motility and inflammatory disorders.\(^{[29]}\) |
| 23 | *Hemidesmus indicus*, Asclepiadaceae | Plant part used: root extract  
Mode of Action: The methanolic extract of Hemidesmus indicus roots was found to inhibit lipid peroxidation and scavenge hydroxyl and superoxide radicals in vitro. The amount required for 50% inhibition of lipid peroxide formation was 217.5 g/ml. The concentrations needed to scavenge hydroxyl and superoxide radicals were 73.5 and 287.5 g/ml, respectively. delayed the plasma recalcification time and enhanced the release of lipoprotein lipase enzymes significantly.\(^{[30]}\) |
CONCLUSION

These plant products are safe and cost effective. Despite their wide spread usage traditional medicines have not been evaluated scientifically with regard to their safety and efficacy and has many limitations. The review explored invitroand invivo activity of various plant extracts. The plant medicine requires exploitation up to desired level to reach some conclusion regarding their use in pharmacopeia.

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