



## Plant products as an alternative phytotherapeutics to regulate thrombosis – A review

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Thrombosis, a life-threatening disease causes thrombus formation within blood vessels to obstruct the flow of blood through vascular system. The disease causes morbidity and mortality of arterial and venous thrombosis which can result in acute infarction and deep vein thrombosis. Majority of clotting factors are serine proteases and are present as precursors of proteolytic enzymes known as zymogens that circulate in inactivated forms but get activated in response to injury in blood vessels. The serine proteases are involved in coagulation, anticoagulation, and fibrinolysis. Thrombin and fibrin are the main key therapeutic target for the treatment of thrombosis. Commercially available antithrombotic and thrombolytic drugs are known to be associated with serious side effects like bleeding, hypertension, and haemorrhage therefore natural products have been suggested as best replacement of synthetic antithrombotic and thrombolytic drugs with less side effects for human health. Plants have been suggested as potential source of anticoagulants against thrombosis with fewer or no side effects.

**Keywords:** Alternative therapeutics, Anticoagulant, Plant products, Thrombin, Thrombosis.

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### Introduction

Thrombosis is a life-threatening disease which occurs due to excessive blood clots formation inside the blood vessel and blocks blood circulation. The blood clot formed by this phenomenon of thrombosis is known as a “thrombus” and more than one thrombus formation is called as “thrombi” formation<sup>1</sup>.

Thrombosis is majorly categorized into arterial and venous thrombosis<sup>2</sup>. Arterial thrombosis is caused by thrombus formation within arteries<sup>3</sup>. Thrombus formation leads to cause pulmonary embolism, stroke and heart attack. The clots formed in arteries lead to cause transient ischemic attack or strokes<sup>4</sup>. Venous thrombosis is caused by thrombus formation within the veins<sup>5</sup>. It is known to be the third most common disease after heart diseases<sup>6</sup>. As per study conducted by global burden of disease (2010) venous thrombosis accounts for 1 death out of 4 deaths all over the world. The occurrence of venous thrombosis has been reported up to 2 cases per 1000 individuals which increases with age. This disease results in major complication to human health by causing cardiovascular disorders which is the main reason of death and disability in the world<sup>7-9</sup>.

Imbalance between procoagulant and anticoagulant factors is responsible for thrombus

formation. The two main risk factors for thromboembolic diseases are acquired factors and genetic factors. The acquired factors are age, trauma, obesity, cardiac diseases, malignancy, neurological disorders, and oral contraceptive use<sup>10</sup>. Genetic factors of venous thrombosis are elevated levels of blood clotting factors (X, VIII, XI, VII, IX and II), dysfibrinogenemia, antithrombin protein C deficiency, and dysplasminogenemia<sup>11</sup>. The risk factors responsible for myocardial and cerebral infarction appear to overlap, even though risk factors are more evident for myocardial infarction (e.g. male sex, hypercholesterolemia) as compared to cerebral infarction. Thrombus is formed due to coagulation of the blood due to endothelial cell damage, stasis and changes in blood compositions.

### Majority of clotting factors are serine proteases

The blood clotting is key defence mechanism against bleeding<sup>12</sup>. The blood coagulation pathway involves fibrin formation through intrinsic (contact activation) and extrinsic (tissue factor) pathways<sup>12</sup>. Extrinsic pathway initiated by a plasma membrane anchored glycoprotein called tissue factor which is found on variety of cells like platelets, epithelial cells, fibroblasts etc. Intrinsic pathway is activated by internal injury where collagen fibres come in contact with broken walls of blood vessels that are in direct contact with flowing blood<sup>13</sup>.

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The intrinsic pathway plays an important role in activation of clotting factors. The intrinsic blood coagulation pathways gets activated by activation of blood protease factors FXII with sequential proteolytic activation of FXI and FIX<sup>14</sup>, finally leading to formation of prothrombin activator which causes conversion of prothrombin into thrombin<sup>12</sup>. The thrombin is essential for conversion of fibrinogen to fibrin (Fig. 1) which is the end product of blood clot formation<sup>15</sup>. The imbalance between pro-coagulant and anticoagulant system due to alterations in genetic and acquired factors cause thrombosis to occur<sup>12</sup>.

Majority of clotting factors belong to class of serine proteases and are present as zymogen that circulate in an inactivated form but get activated in response to injury in blood vessels<sup>16</sup>. The serine proteases have been recognised for activation of anticoagulant and fibrinolytic responses towards vascular damage. The serine proteases involved in coagulation, anticoagulation and fibrinolysis have been suggested as developed from a common trypsin like ancestral proteases<sup>17,18</sup>. They are characterized by the existence of highly conserved modular protein domains which have related functions in different proteins<sup>19</sup>. The clotting factors are essential for retaining the fluidity of flowing blood as well as important for normal haemostasis<sup>19</sup>.

Thrombin, a serine protease is one of the most important factors involved in blood coagulation and is

responsible for conversion of fibrinogen to fibrin, which by further reaction helps in stabilization of clot<sup>20</sup>. Thrombin is formed by proteolytic digestion of prothrombin by factor Xa. Thrombin catalysed the cleavage of fibrinogen into active fibrin and has been identified as the target to control thrombosis. Many thrombin inhibitory drugs have been suggested acting via direct or indirect binding to different sites of thrombin<sup>21</sup>. Other factors that are involved in the process of blood clotting include: Factor XII, is a single chain glycoprotein containing 596 amino acids (human) and 16.8% carbohydrate with molecular weight of 76-80 kDa and belongs to clan PA of family S1 serine protease<sup>22</sup>. Factor XIa is formed from its zymogen FXI by proteolytic cleavage by Factor XIIa<sup>23</sup>. Another factor FIX is a vitamin K dependent glycoprotein with molecular weight 57 kDa in humans<sup>24</sup>. The factor IXa belongs to clan PA of family S1 serine protease<sup>25</sup>. Factor XIa causes proteolytic cleavage to convert FIX into its activated form FIXa<sup>24</sup>. Fibrinogen is an important glycoprotein, a precursor of fibrin with three polypeptide chains connected by disulphide bridges. The thrombin cleaves fibrinogen to generate fibrin monomer. Fibrin is formed at the end of blood coagulation and is clotted form of blood<sup>26</sup>. Therefore FXa, thrombin and fibrin have been suggested key therapeutic target for treatment of thrombosis<sup>20,27</sup>.

### Current antithrombotic therapy

Currently, antithrombotic drugs are categorised into three major categories; anticoagulants, antiplatelet and thrombolytic drugs<sup>28</sup>. The anticoagulant and antiplatelet agents play a role in the prevention of excessive blood clot formation thereby controlling heart attacks and strokes. These drugs are also known as blood thinners. Anticoagulant agents help in dissolving the venous clots by disrupting the development of fibrin protein and are helpful in dissolution of artery clots already formed in the body<sup>29</sup>. Anticoagulant agents help to prevent fibrin formation and can be divided into direct acting drugs (heparin) and indirect acting drugs (coumarin derivatives).

Heparin (direct acting drug) is naturally present in mast cells, liver and lung cells<sup>30</sup>. Binding of heparin to antithrombin III increases its activity by changing its conformation<sup>31,32</sup>. This causes inhibition of factor Xa, IIa, IXa, and XIa. Coumarin derivatives (indirect acting drug) are lactones joined by a benzene ring fused to pyrone ring<sup>33</sup>. These are natural compounds

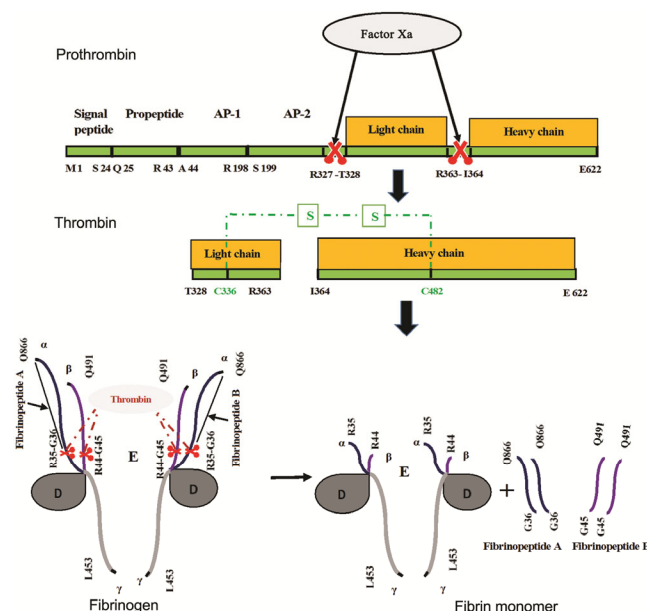


Fig. 1 — Thrombin and fibrin are therapeutic targets for treatments of thrombosis.

generally present in roots, leaves, fruits, and integument of seeds. They belong to the type of vitamin K antagonists e.g. warfarin, dicoumarol etc<sup>34</sup>.

Antiplatelet agents help to prevent platelet aggregation and are known as platelet agglutinator inhibitor. These drugs are used to reduce the risk of blood clots formation or prevent existing clot to become larger in body e.g. aspirin, clopidogrel, prasugrel, dipyridmalole and triflusal etc<sup>29</sup>.

Thrombolytic agents help to induce fibrin degradation by dissolution of blood clot and are known as plasminogen activators. These activators convert plasminogen into plasmin and helps in fibrin degradation<sup>35</sup> e.g. streptokinase, tissue plasminogen activator and urokinase etc.

Streptokinase is a best known protein plasminogen activator with molecular size of 47 kDa. It binds non-covalently to plasminogen to generate plasmin. Recently an important form of streptokinase was developed that is anisoylated plasminogen streptokinase activator complex (APSAC)<sup>36</sup>. This hybrid molecule is inactive and is produced by acylation of active centre of plasminogen and gets activated by deacylation to act on plasminogen. Urokinase, a serine protease of 54kDa isolated from human urine has been reported to cleave inactive plasminogen to active plasmin by catalysing the cleavage of Arg-Val bonds in plasminogen. The active plasmin help in breakdown of fibrin polymers<sup>35,37</sup>.

Various chemical and synthetic drugs are being used as a thrombosis therapy. ASH (American society of haematology) has recommended direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban for the treatment of venous thromboembolism. Among these, use of heparin is considered to be the best therapeutic to prevent thrombosis<sup>38</sup>. The direct oral anticoagulants are also recommended for cancer patients associated with VTE are rivaroxaban, edoxaban, and apixaban<sup>39</sup>. The direct oral anticoagulants are also recommended for the treatment of cerebral venous thrombosis<sup>40</sup>. The deep vein thrombosis and pulmonary embolism in hospitalized patients are treated with unfractionated heparin or low molecular weight heparins<sup>38</sup>. These antithrombotic and thrombolytic drugs are known to be associated with severe and serious side effects like bleeding, hypertension, oedema, chest pain, haemorrhage etc<sup>41</sup>.

Recently nanotechnology based approach have been developed to increase specificity of drug with improved management for target delivery of

anticoagulants<sup>42</sup>. Some of the nanoparticles used for the management of VTE are: argatroban-loaded poly vanillyl alcohol-co-oxalate nanoparticle (H<sub>2</sub>O<sub>2</sub> responsive platelets membrane coated nanoparticles) and fibrin-targeted imaging and anti-thrombotic nanoparticles (FTIAN) (local fibrin targeting)<sup>43</sup>. However, nanoparticle mediated treatment is inconsistent between animal models and human patients and could gather in various organs, leading to unwanted side effects<sup>43,44</sup>.

Due to high cost, side effects, and long time required for the development of these drugs, natural products have been suggested as the best replacement of synthetic antithrombotic and thrombolytic drugs with minimized side effects for human health<sup>45</sup>. The best reasons for using natural products in the treatment of thromboembolic diseases are presence of multiple bioactive ingredients. Bioactive ingredients have multiple targets which may exert synergistic effects to increase therapeutic efficacy. Besides, natural products show fewer side effects on the digestive system<sup>46</sup>. Experimental and clinical evidences have suggested the inhibitory action of natural compounds on thromboembolic diseases and can serve as beneficial preventive measure for pharmacological treatments for thromboembolic diseases<sup>47</sup>. Currently lots of attention has been given to natural anticoagulant therapy due to their biological origin and minimum side effects. These natural medicines may provide an alternative to chemical and synthetic anticoagulants<sup>48</sup>.

### **Plant products as effective therapeutics against thrombosis**

Attention has been directed towards discovering more specific and effective natural products as an alternative to chemical and synthetic antithrombotic drugs<sup>49</sup>. Plants have been used as a remedial therapy and as an alternative antithrombotic therapy amongst blood related disorders<sup>50</sup>. According to the WHO, 80% of population uses traditional plants in treatment of blood disorders<sup>51</sup>. Thus in many developing countries, medicinal plants are considered as the best option for the production of natural drugs to be used being more cost effective with fewer complications to treat blood related disorders<sup>52</sup>. Traditionally, plants are reported to possess anticoagulant properties<sup>53</sup> and have been used as blood tonic for the treatment of blood related disorders to prevent excessive bleeding in the treatment of hemorrhoids. Evidences also support that

consumption of plants as dietary supplements help in reducing the risk of thromboembolic disorders<sup>54</sup>. Various plants have been documented for their role in anticoagulation<sup>51,55,56</sup>. All these studies indicate that plants can be the best source for alternative anticoagulants and natural drugs for the treatment of thrombosis<sup>53,57</sup>.

### Plants exhibiting anticoagulant activity

The bulbs extract of *Allium sativum* (Amarillidaceae), commonly known as garlic showed anticoagulant and fibrinolytic activity by prolonging the time required for blood to clot in the coagulation pathway<sup>58</sup>. The leaves aqueous extract of *Bauhinia forficata* (Leguminosae) commonly known as brazilian orchid tree have anticoagulant and anti-fibrinogenolytic properties. It is used as antidote for blood coagulation caused by snake venom<sup>59</sup>. Berberine compound isolated from Chinese herbs has been suggested as potential candidate for the development of thrombin drug<sup>60</sup>. Seeds of the *Brassica spp.* (Brassicaceae), commonly known as cabbage, contains tight-binding inhibitor of trypsin with activity towards thrombin has been reported<sup>61</sup>. *Brownea grandiceps* (Fabaceae) commonly known as scarlet flame bean contain an active compound brownplaminin which has antifibrinolytic activity. It inhibits specifically plasmin activity without affecting the activity of other serine proteases like trypsin, tissue plasminogen activator or urokinase plasminogen activator<sup>62</sup>. The methanolic bark extract of *Careya arborea* (Icycythidaceae), commonly known as wild guava showed prolonged blood clotting time and has been compared with standard anticoagulant drug warfarin<sup>63</sup>.

The anticoagulant effect of *Cinnamomum cassia* (Lauraceae), commonly known as cassia has also been reported. It is known to improve blood circulation and effectively inhibits platelets in blood coagulation. The major chemical components present are coumarin, N-acetyl-L-cysteine, cinnamyl acetate, cinnamaldehyde and hydroxycinnamaldehyde. *C. cassia* compounds showed both platelet anti-aggregation and blood anticoagulation effects in preliminary tests<sup>64</sup>. The antiplatelet activity has been reported in the aqueous extracts of *Cucurbita maxima* (Cucurbitaceae) seeds. The aqueous seed extracts has been known to play role in the prevention of thromboembolic diseases. A squash protease inhibitor has been reported from this plant and its inhibitory

activity has been checked on thrombin, factor Xa, and factor XIIIa<sup>65</sup>. *Cyamopsis tetragonoloba* (Fabaceae) commonly known as cluster bean is an annual legume grown in India as a vegetable, fodder or green manure crop. Galactomanna a low molecular weight compound from seeds has been shown to possess anticoagulant activity under *in vitro* and *in vivo* experiment. Ethanolic leaves extract of *C. tetragonoloba* has wound healing (90%) effect on swiss albino mice<sup>66</sup>. It has been advised to avoid its use in patients on anticoagulant therapy because it can enhance anticoagulation potential<sup>67</sup>. The methanolic extract of *Eichhornia crassipes* (Pontederiaceae), commonly known as water hyacinth has shown antiplatelet and anticoagulant activity<sup>68</sup>.

*Erigeron canadensis* (Asteraceae) commonly known as horseweed. Polyphenolic-polysaccharides isolated from flowering parts have been suggested for anticoagulant therapy<sup>69</sup>. The leaves of *Ferula communis* (Apiaceae), commonly known as giant fennel have potential to act against cardiovascular disorders<sup>70</sup>. The leaves, roots and flowers of *Filipendula ulmaria* (Rosaceae), commonly known as meadowsweet, contain heparin like compounds responsible for anticoagulant and antifibrinolytic activity<sup>71</sup>.

The leaf extracts of *Gloriosa superba* (Lilaceae) commonly known as glory lily have shown anticoagulant effects by reducing thrombin-induced clotting with an IC<sub>50</sub> value of 2.97 mg/mL<sup>72</sup>. *Glycyrrhiza glabra* (Leguminosae) commonly known as sweet wood is recognized as a thrombin inhibitor with prolonged thrombin, fibrinogen and plasma recalcification clotting time<sup>73</sup>. The plant *Jatropha curcas* (Euphorbiaceae) is commonly known as purging nut. The traditional use of its leaves and latex showed wound healing property. The latex possesses both procoagulant and anticoagulant activities. The latex anticoagulant inhibits clotting factors in the intrinsic pathway of blood coagulation<sup>74</sup>.

The plant *Lythrum salicaria* (Lythraceae) commonly known as loosestrife has a role in bleeding control. The flowers of *L. salicaria* contain glycoconjugates that have shown procoagulant properties under *in vivo* by reducing the blood clotting time in rats<sup>75</sup>. The aqueous extract of the leaves of *Melastoma malabathricum* (Melastomataceae), commonly known as Indian rhododendron possess anticoagulant property by inhibiting thrombin induce blood clotting<sup>76</sup>.

*Myristica fragrans* (Myristicaceae) commonly known as nutmeg. Three compounds belonging to lignan and phenol, isolated from episperms showed inhibition of fibrinolytic pathway activated by urokinase. It is also reported that this plant helps in promoting blood coagulation via APTT, PT and TT assays<sup>77</sup>. In a study, *in vitro* clot lysis experiments showed thrombolytic potential of *Ocimum sanctum* as 30.01±6.168%, *Azadirachita indica* as 32.94±3.663%, and *Curcuma longa* as 27.47±6.943%<sup>78</sup>.

Fruits and roots extract of *Paeonia anomala* (Paeoniaceae) commonly known as herbaceous peony has been shown to possess antithrombotic, thrombolytic and anticoagulant property<sup>48</sup>. Plant roots of *Panax notoginseng* (Araliaceae) commonly known as sanchi ginseng has been used in the treatment of bleeding<sup>48</sup>. The crushed leaves of *Pelargonium zonale* (Geraniaceae) which is commonly known as zonal geranium have wound healing property. It also helps in decreasing 50-80% bleeding time<sup>48</sup>.

The crude aqueous extract of *Petroselinum crispum* (Apiaceae) which is commonly known as parsley has been shown to prolong the bleeding periods in rats and inhibits platelet aggregation both *in vitro* and *ex vivo* experiments. *Ex vivo* trial showed bleeding time increased when the medication was given at a dose of 3 g/kg, although platelet count remain unaffected. This study validates its use in cardiovascular diseases as anticoagulant agent<sup>79</sup>.

*Porana volubilis* (Convolvulaceae) which is commonly known as horse-tail creeper contains polysaccharides (galactose, galacturonic acid, and mannose) with high anticoagulant activity<sup>48</sup>. The major reported chemical components in *Pulmonaria officinalis* (Boraginaceae), commonly known as lungwort are flavonoids, nickel, copper, vitamin C, B complex and manganese. Anticoagulant glycopeptides reported from *P. officinalis* are shown to lower the mortality rate of animals by preventing platelets from coagulation<sup>48</sup>. *In vitro* study showed *Terminalia bellerica* (Combretaceae) commonly known as baheda (in Hindi) has thrombolytic potential in clot lysis (32.95%) experiments. This plant may act as a new thrombolytic agent in development of natural drug<sup>80</sup>. The anticoagulant activity evaluated using the APTT assay (Activated Partial Thromboplastin Time Assay) for *Tridax procumbens* (Asteraceae) which is commonly known as coatbuttons was found to be comparable to heparin<sup>81</sup>.

## Discussion

Thrombosis is a life threatening disease. Despite significant understanding of physiology and biology of thrombosis, current treatments involving synthetic and chemical drugs have serious side-effects. Therefore, it is important to overcome these side-effects by developing more advanced or alternate therapy. Recently nanotechnology based approach has been developed for target specific delivery of drugs. Another alternative approach which is currently been suggested is the use of natural products as drugs. There are various reports available for antithrombotic activity possessed by different plants. More plants and their products are required to be screened for their efficiency as antithrombotic agents either alone or in combination with other natural molecules for the development of efficient therapeutic. This review highlights the potential of various plants for their antithrombotic role which may be further exploited for the development of phytotherapeutics.

## Conclusion

Thrombosis is a serious disease for which currently various chemical and synthetic drugs are being used as a therapy. Use of these drugs is associated with various side effects. Therefore attention has been diverted towards more specific and effective natural products as substitute to currently in use chemical and synthetic antithrombotic drugs for thromboembolic diseases. Plants products have been suggested as good source of anticoagulants that can substitute the chemical and synthetic drugs presently used for the treatment of thrombosis. Traditionally, various plants are already being used for the treatment of blood related disorders, remedial therapy and as an alternative antithrombotic therapy amongst blood related disorders. It has been shown that consumption of plants with anticoagulant properties as dietary supplements helps in reducing the risk of thromboembolic disorders to occur. There is a need of screening of more plants for their anticoagulant properties and understanding the mode of action of these phytotherapeutics in the regulation of thrombosis.

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**Conflict of interest**

The authors have no conflict of interest.

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