Fibrinolysis and Thrombolytic Therapy of Medicinal Plants

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Abstract. This study aims to explore the role of herbal medicine as an alternative treatment for cardiovascular diseases. Through an in-depth review of the available literature, 31 medicinal plants from 27 families were identified as having thrombolytic properties. A systematic approach was employed to gather, compare, and analyze the results of multiple previous studies focusing on these plants and their thrombolytic effects. Diverse databases, journals, and academic sources were consulted for comprehensive coverage. The selection of these plants resulted in findings that highlight the presence of bioactive molecules, such as flavonoids, alkaloids, and phenolic compounds, with thrombotic effects. Notable plants, including Plumbago zeylanica, Withania somnifera, and Cyperus rotundus, exhibited significant potential ranging from 60% to 96% in preventing thrombosis formation in blood vessels. This effect was achieved through mechanisms involving thrombosis formation, fibrinolysis, and the thrombolytic agentsfindings of this study provide insights for exploring novel natural substances and the development of new therapeutic agents with enhanced thrombosis management properties. Moreover, these potential alternatives offer the advantage of being potentially more sedative in nature compared to conventional treatments.

Keywords : thrombosis, medicinal plants, thrombolytic activity, phenolic compounds, fibrinolysis.

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Introduction

Cardiovascular diseases (CVD) are responsible for nearly 17.9 million deaths each year and are reported to be the leading cause of death according to the World Health Organization (WHO). The failure of hemostasis and the formation of blood clots in the arteries are the primary reasons that lead to the onset of cardiovascular diseases (CVD) such as myocardial infarction and ischemic stroke, which require urgent treatment(Nawaz et al, 2022). Therefore, thrombus dissolution, known as thrombolysis, is urgently required during heart attacks and strokes. For this purpose, various synthetic thrombolytic agents are widely used to ensure immediate clearance of the blood vessels. However, these synthetic thrombolytic drugs may carry the risk of severe bleeding, anaphylactic reactions, and shock. This has prompted the search for a better alternative as a thrombolytic agent in terms of cost-effectiveness, safety, and efficacy, which are natural resources generally considered safe and may offer improved effectiveness (Kunwar et al, 2022).

Medicinal plants are widely used in traditional systems for treating various diseases, as they contain chemical compounds that act as precursors for the synthesis of useful drugs (Shahriar et al, 2015).In this regard, there is substantial evidence that many medicinal plants with thrombolytic properties can reduce the risk of cardiovascular diseases and may be used as an alternative to medications for such conditions (Al-Snafi et al, 2017 ; Uddin et al, 2021). These plants are known for their beneficial effects on blood circulation because they contain active principles that can help dissolve blood clots.

According to a report, approximately 30% of pharmaceutical products are derived from plants worldwide and are considered to be less toxic and have fewer side effects than synthetic drugs (Bhutada, 2018). Therefore, based on the results obtained from our research, it is evident that there is a need to explore drugs based on safe but potentially less or non-effective secondary plants. This is because natural products derived from superior plants may provide a new source of thrombolytic agents (Bhutada, 2018).

In this study, we conducted a literature review on several medicinal plants with thrombolytic properties, specifically their ability to lyse thrombosis formed in the blood vessels in a sedative manner. The main objective of our review is to gather as much information as possible on in vitro studies conducted by researchers to evaluate the thrombotic activity of these plants and their potential therapeutic uses.

Methodology

A comprehensive literature search was conducted to identify relevant studies investigating the thrombolytic activity of medicinal plants. The search was performed in electronic databases including Google scholar, PubMed, Scopus, and Web of Science and other database. The search strategy involved a combination of keywords related to medicinal plants and thrombolytic activity, such as "medicinal plants," "thrombolytic activity," "thrombolytic agents," "blood clot lysis," and "fibrinolysis."

The inclusion criteria for the selection of studies were as follows:

In vitro studies evaluating the thrombolytic activity of medicinal plants.

Studies reporting on the efficacy and mechanisms of action of thrombolytic agents derived from medicinal plants.

Studies investigating the active constituents or extracts of medicinal plants with demonstrated thrombolytic potential.

Studies published in peer-reviewed journals.Studies that focused on other aspects of medicinal plants unrelated to thrombolytic activity, such as their antioxidant properties or traditional uses for non-cardiovascular conditions, were excluded from the review.

Data extraction was performed by extracting relevant information from the selected studies, including the names of the medicinal plants, active constituents or extracts, thrombolytic activity results, experimental models, and any additional relevant findings.

It is important to note that this review focused solely on in vitro studies, and the findings may not directly translate to clinical efficacy. However, these studies provide valuable insights into the thrombolytic activity of medicinal plants and their potential for further investigation as therapeutic agents for cardiovascular diseases.

By following this methodology, a comprehensive selection of relevant studies was made, and the findings were synthesized to provide an overview of the thrombolytic potential of medicinal plants.

Thrombosis formation

Thrombosis is the formation of a blood clot (partial or complete blockage) in the blood vessels, whether they are veins or arteries, restricting the natural flow of blood and resulting in clinical consequences (Ashorobi et al, 2022). Thrombosis is a major contributor to cardiovascular diseases (CVD), including acute myocardial conditions such as myocardial infarction, ischemic heart disease, valvular heart disease, peripheral vascular diseases, arrhythmias, arterial hypertension, and cerebrovascular accidents. It is a leading cause of global mortality (Barzkar et al, 2022). When a blood vessel is injured, the body utilizes platelets (thrombocytes) and fibrin to form a blood clot, preventing blood loss (Labu et al, 2015). Thrombin catalyzes the conversion of fibrinogen to fibrin, which is a key component of blood clots or thrombi. Under normal physiological conditions, there is a homeostatic balance between the formation and degradation of fibrin. However, in certain pathological disorders, this balance is disrupted, resulting in excessive fibrin aggregation and thrombosis. Rapid dissolution of blood clots and restoration of blood flow are crucial for effective treatment of thrombotic diseases ((Barzkar et al, 2022).Therefore, thrombus dissolution, known as thrombolysis, is urgently required during heart attacks and strokes. For this purpose, various synthetic thrombolytic agents, such as tissue plasminogen activator (t-PA), urokinase (UK), streptokinase (SK), alteplase, etc., are widely used to ensure immediate clearance of the blood vessels (Kunwar et al, 2022).Thrombolytic medications are also known as plasminogen activators and fibrinolytic drugs. They dissolve blood clots by activating plasminogen, which converts into a cleaved product called plasmin. Plasmin is a proteolytic enzyme capable of breaking down the cross-links between fibrin molecules (Barzkar et al, 2022).There are two types of thrombosis ; Arterial thrombosis: is typically associated with the rupture of an atherosclerotic plaque. This pathological process leads to the exposure or release of subendothelial cells and procoagulant material (e.g., tissue factor, collagen) within the plaque, triggering platelet activation and aggregation (Wolberg et al, 2012). (Fig1), and Venous thrombosis/thromboembolism: It is typically associated with plasma hypercoagulability, and it is believed to be triggered by the expression of procoagulant activity on intact endothelium caused by inflammation or stasis/decreased blood flow resulting from prolonged immobility. Venous clots have regions or layers with significant red blood cell incorporation (Wolberg et al, 2012) (Fig 2).

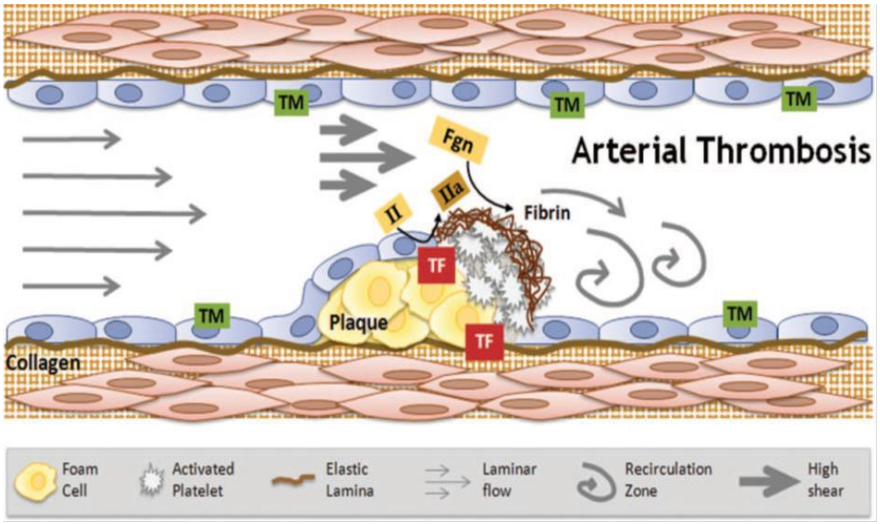

Fig. 1. Arterial thrombosis (Wolberg et al, 2012).

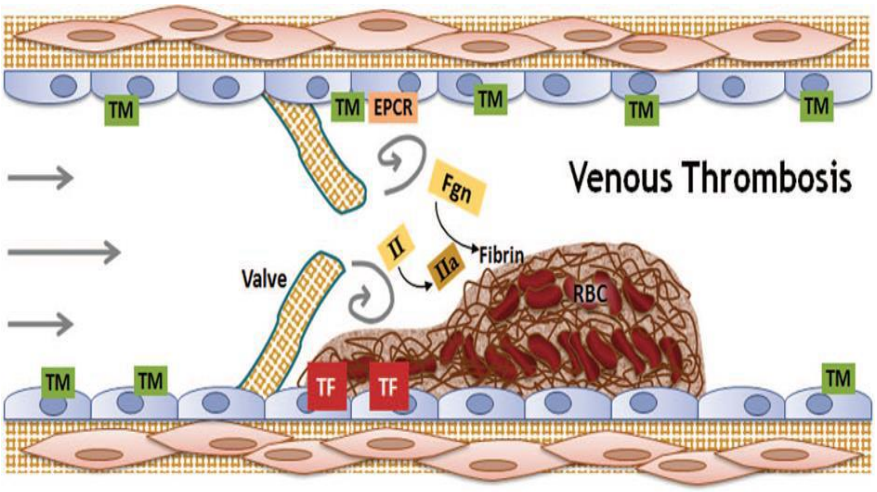

Fig. 2. Venous thrombosis (Wolberg et al, 2012).

Fibrinolysis

Fibrinolysis is a delicate and complex enzymatic process aimed at dissolving blood clots, thereby localizing and limiting clot formation (Franchini et al, 2021). Fibrinolysis is responsible for the degradation of fibrin, and it is modulated by proteases and protease inhibitors that have the opposite effect and regulate the conversion of plasminogen into plasmin (the active enzyme), which dissolves the fibrin clot into soluble fibrin degradation products (FDP) (Longstaff and Kolev, 2015). One of the main by-products of this degradation is D-dimer, which is currently used as a marker of thrombosis in COVID-19 patients (Pablo-Moreno and Juan, 2022).The fibrinolytic system includes pro-fibrinolytic components (namely tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA)) and anti-fibrinolytic components (such as α2-antiplasmin, plasminogen activator inhibitor 1 (PAI-1), and thrombin-activatable fibrinolysis inhibitor (TAFI)) (Franchini et al, 2021). (Fig 3).

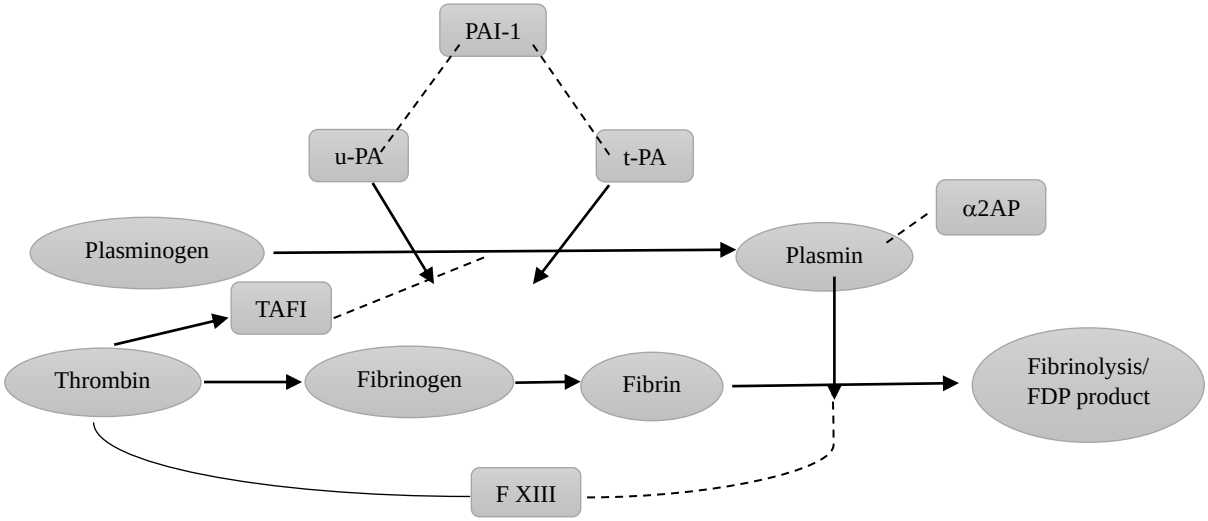

Fig 3. Fibrinolytic system.

Fibrinolytic System

The fibrinolysis system plays a crucial role in dissolving blood clots, thereby preventing vessel blockage and maintaining blood vessel openness. Plasmin, a serine protease, is the key enzyme in the fibrinolytic cascade and is generated by the proteolytic cleavage of its precursor, plasminogen. Plasminogen is synthesized by hepatic cells as a glycoprotein consisting of 810 amino acids. After cleavage of a 19-amino acid signaling peptide, plasminogen is released into the plasma, where its concentrations reach 2.4 M. Under physiological or pathological conditions, single-chain plasminogen is converted into a two-chain plasmin molecule by cleavage between Arg561 and Val562. Both plasmin and the plasminogen molecule contain five homologous kringle domains. These two molecules bind to substrates, inhibitors, and cell surface binding sites through these kringle structures, particularly to the terminal lysine residues (Syrovets et al, 2012).

The activation pathways of fibrinolysis

There are two activation pathways for fibrinolysis:

Tissue-type plasminogen activator (t-PA)

t-PA, the main activator of plasminogen in the blood, is a single-chain serine protease of 70 kDa with low proteolytic activity and a plasma concentration of (5–10 µg/L). It contains an N-terminal fibronectin type II domain, a growth factor-like domain, two kringle domains, and a C-terminal catalytic domain. Similar to u-PA, t-PA does not have any confirmed physiological substrate other than plasminogen. However, unlike u-PA, t-PA binds to fibrin through its fibronectin type II domain and these two kringle domains. Thus, t-PA specifically binds to the fibrin-plasminogen complex. t-PA converts soluble fibrinogen into insoluble fibrin, which mainly forms a thrombus. The fibrin is then degraded by plasmin, producing fibrin degradation products (FDP) (Lin et al, 2020 ; Ismail et al, 2021).

Pro-urokinase system

Single-chain urokinase-type plasminogen activator (ScuPA) is produced by fibroblasts, endothelial cells, and keratinocytes. It is synthesized as a glycoprotein with a size of 55 kDa. Its plasma concentration is (5-10 µg/L) (Ismail et al, 2021). The inactive single-chain form of

plasminogen (pro-uPA or Scu-PA) is converted into a two-chain active enzyme (tcu-PA) by plasmin and other proteases. The active tcu-PA activates both circulating plasminogen (Plg) and fibrin-bound plasminogen by cleaving the Arg561-Val562 bond at a similar rate (Ye et al, 2017). u-PA consists of an N-terminal growth factor-like domain, a kringle domain, and a C-terminal serine protease domain (Weisel et al, 2014).

Fibrinolysis inhibitors

Alpha-2-antiplasmin

Alpha-2-antiplasmin, a single-chain glycoprotein of 70 kDa synthesized by the liver, is the primary physiological inhibitor of plasmin. Alpha-2-antiplasmin inhibits fibrinolysis by forming a stable inactive complex with plasmin. It binds to the lysine binding site of plasminogen, completely inhibiting the binding of plasminogen to fibrin. Additionally, itcovalently binds to fibrin through activated Factor XIII (FXIIIa), thereby preventing fibrinolysis by plasmin (Franchini et al, 2021).

Inhibitors of plasminogen activator type 1 and 2 (PAI-1, PAI-2)

PAI-1 is the primary inhibitor of tPA in the plasma. It is a single-chain glycoprotein composed of 379 or 381 amino acids (N-terminal heterogeneity). It belongs to the serine protease inhibitor family and has a molecular weight of approximately 45 kDa. There are three different forms of PAI-1: the active form, the inactive form, and the substrate form. The active form can inhibit tPA or uPA by forming a stoichiometric 1:1 complex with each enzyme, while the inactive form does not react with the target protease. PAI-2 consists of two molecular forms: the low molecular weight (LMW) form with 43-48 kDa is intracellular and non-glycosylated, while the high molecular weight (HMW) form with 60 kDa is secreted and glycosylated (Ye et al, 2017).

Thrombin-activatable fibrinolysis inhibitor (TAFI)

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a 60 kDa pro-carboxypeptidase that, in its active form (TAFIa), becomes an efficient regulator of fibrinolysis by removing exposed C-terminal lysine residues on the surface of degraded fibrin, which prevents the binding of plasminogen (Plg) and t-PA. Additionally, TAFIa eliminates binding sites for Plg, shortens its half-life, and slows down the conversion of Glu-Plg to Lys-Plg by plasmin. Thrombin is a relatively weak activator of TAFI, but in the presence of thrombomodulin, activation by thrombin is increased by over 1000-fold (Weisel and Litvinov, 2014 ; Sillen and Declerck, 2021).

The process of fibrinolysis

Once the fibrin clot is formed, activated platelets position themselves to contract their intracellular actin or myosin cytoskeleton, contributing to clot retraction. To promote clot dissolution, a plasminogen activator converts plasminogen into plasmin. Thrombin itself activates this process by stimulating the synthesis and release of tissue-type plasminogen activator (t-PA) by endothelial cells, as well as urokinase (u-PA), which mediates the conversion of plasminogen into plasmin. Plasminogen activator inhibitor-1 (PAI-1) is the primary antagonist of this pathway. Additionally, the conversion of plasminogen into plasmin is mediated by other

coagulation factors such as FXIa, FXIIa, and kallikrein. Apart from PAI-1, there are other molecules capable of inhibiting the conversion of plasminogen into plasmin, thereby contributing to fibrinolysis regulation. The most important among them are α2-antiplasmin, α2-antimacroglobulin, and C1 esterase inhibitor. Plasmin unravels the fibrin meshwork around the injured area, generating circulating fragments that are eliminated by other proteases. This clot resolution mechanism allows for the restoration of normal blood flow by removing obstructions in injured vessels, disrupting the binding between fibrin and platelets, thus completing the clot resolution process (Periayah et al, 2017 ; Chapin and Hajjar, 2015).

The role of thrombolytic agents

Thrombolytic agents (also known as fibrinolytics) are enzymatic activators of plasminogen that convert plasminogen into plasmin. In turn, plasmin cleaves fibrin, thereby forming progressively smaller protein fragments in the process of fibrinolysis (Sharp et al, 2022).

Thrombolytic agents are commonly used for the following indications: Venous thrombosis, pulmonary embolism, myocardial infarction, arterial thromboembolism, and acute ischemic stroke (Ali et al, 2014).

There are three generations of thrombolytics that are now used in clinical practice. First-generation thrombolytics (streptokinase, urokinase) are naturally occurring agents with negligible fibrin specificity and are significantly inhibited by PAI-1. The lack of fibrin specificity increases the risk of bleeding associated with their use. Fibrin specificity is improved with second-generation agents, particularly recombinant tissue plasminogen activator (rt-PA) (Sharp et al, 2022).Alteplase is the most widely available recombinant single-chain tPA. Third-generation products, such as reteplase and tenecteplase, have been developed to reduce PAI-1 inhibition and increase half-life while maintaining or enhancing fibrin specificity. Second and third-generation thrombolytics are products derived from recombinant DNA technology and/or chemical modification, allowing for molecular optimization of their efficiencies (Sharp et al, 2022) Fig 4.

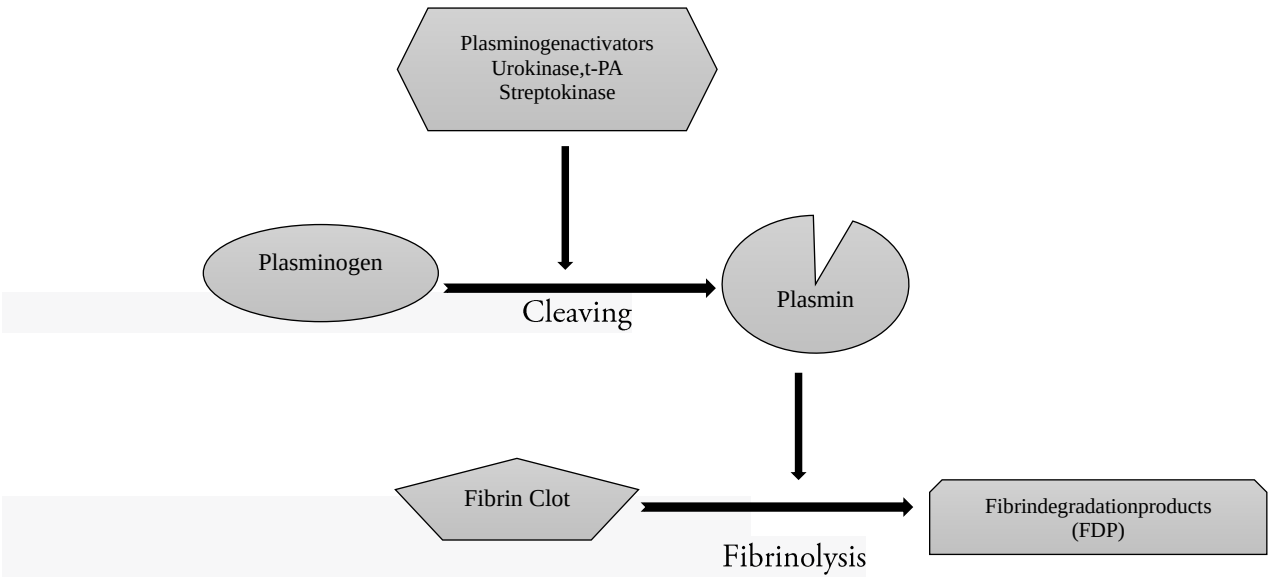

Fig 4. Mechanism of action of thrombolytic medications (Amini et al, 2022).

The fibrinolysis system plays a crucial role in dissolving blood clots, thereby preventing vessel blockage and maintaining blood vessel openness. Plasmin, the key component of this system, works to break down the fibrin mesh that forms the clot. Plasminogen, the inactive form of plasmin, binds to the fibrin mesh and is activated by two activators: tissue plasminogen activator (t-PA), primarily released by the endothelium, and urokinase-type plasminogen activator (u-PA). However, the actions of these activators are regulated and inhibited by plasminogen activator inhibitor 1 (PAI-1), which serves as the primary inhibitor of the fibrinolysis system (Quintal Martínez and Segura Campos, 2023).

Streptokinase

Streptokinase (SK) has been the first medication introduced for the treatment of acute myocardial infarction in the past 40 years (El-Dabaa et al, 2022). SK (EC 3.4.99.22) is a group of enzymatic proteins produced by various strains of hemolytic streptococci (Kunamneni and Durvasula, 2014). This protein is a single-chain polypeptide that associates with the proactivator plasminogen. This enzymatic complex leads to the conversion of inactive plasminogen into active plasmin, conferring fibrinolytic activity (Ali et al, 2014).

SK is a unique polypeptide chain consisting of 440 amino acid residues with an average molecular weight of 47 kDa. The N-terminal end of the polypeptide contains a signal peptide (26 amino acids long) that is cleaved during secretion. Mature streptokinase contains 414 amino acid residues and consists of three domains, namely α (residues 1-150), β (residues 151-287), and γ (residues 288-414) (Dey et al, 2022). Each plasminogen (PG)-binding domain is incapable of independently activating PG. Several sources of data suggest that residues 1-59 of the α domain of SK play a key role in PG activation (Kunamneni and Durvasula, 2014).

Mecanisme of action of SK

SK indirectly activates the fibrinolytic system by forming a complex with plasminogen, which then undergoes a conformational change and is converted into plasmin, leading to the degradation of the fibrin clot. The most intriguing characteristic of SK is that it lacks inherent catalytic activity until it binds to the plasminogen molecule and activates it to plasmin. Tissue plasminogen activator (tPA) shows higher affinity for a clot, but a conformational change occurs due to the binding of plasminogen and streptokinase. This newly formed complex is known as streptokinase-human plasminogen and is abbreviated as SK-HPG.This transitional complex readily converts into streptokinase-human plasmin (SK-HPN), where a peptide linking Arg 560-Val 561 is cleaved to form a new complex. After plasmin formation, streptokinase is separated from the complex, and its molecular weight decreases from 47 kDa to 36 kDa. In the overall reaction, streptokinase loses 9 kDa, but this newly formed lower molecular weight SK retains certain properties similar to the native form (Zia and Faran, 2016). (Fig 5).

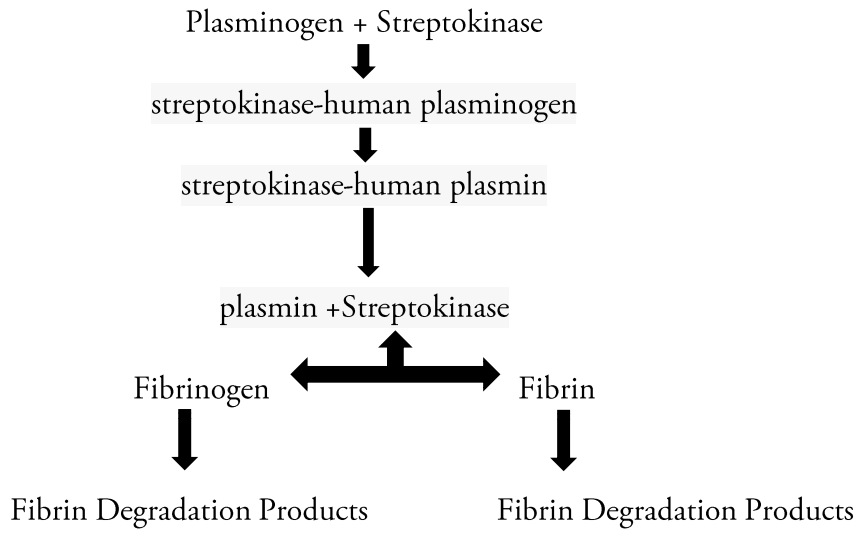

Fig5. Mode of action of SK in blood clot lysis

Tenecteplase

Tenecteplase is a third-generation thrombolytic agent produced using DNA technology as a modified form of alteplase. It undergoes structural protein alterations at three specific sites (amino acid-modified sites designated by the letters T, N, and K), which led to its alternative name, TNK. These changes prolong the half-life of tenecteplase and allow for a higher affinity binding to fibrin compared to alteplase (Mahmood and Muir, 2022). Tenecteplase is the preferred thrombolytic agent for patients with ST-segment elevation myocardial infarction and is increasingly used for the treatment of acute ischemic stroke (AIS) (Kobeissi et al, 2023).

Structurally, tenecteplase is a glycoprotein consisting of 527 amino acids, developed by modifying the complementary DNA of human tPA through the following amino acid substitutions: asparagine replaced threonine at position 103 in the kringle-1 domain; glutamine replaced asparagine at position 117 in the kringle-1 domain; and alanine replaced the amino acid occupying positions 296, 297, 298, and 299 in the protease domain (Turcasso and Nappi, 2001).

Mecanism of action

Tenecteplase is more selective for fibrin. Greater specificity towards fibrin leads to an increase in the conversion of plasminogen to plasmin compared to its conversion in the absence of fibrin. Agents that are not specific to fibrin induce systemic activation of plasminogen, depleting circulating concentrations of fibrinogen, plasminogen, and other substances necessary for hemostasis. In contrast, fibrin-specific agents activate plasminogen and induce lysis only where it is needed. It is important to note that after the administration of tenecteplase at doses of 30 to 50 mg, there are decreases in circulating concentrations of fibrinogen (5 to 10%) and plasminogen (10 to 15%) (Turcasso and Nappi, 2001).

Urokinase

UK (urokinase) is an endogenous trypsin-like hydrolase (Shen et al, 2021). This agent is physiologically secreted from renal parenchymal cells and can be obtained from human urine,

human embryos, and renal cell cultures (Ucar, 2019). UK is rapidly degraded and eliminated by the liver, with an average plasma half-life of 15 minutes. Due to its short half-life, re-embolization can occur within 15 to 30 minutes after the cessation of administration (Shen et al, 2021). UK is known as a thrombolytic agent and has been used in the treatment of pulmonary embolism, acute myocardial infarction, ocular clot formation, hemorrhage, and peripheral arterial occlusion (Massimo, 2007).

UK (urokinase) is a serine protease consisting of 411 amino acids, with the active site composed of the triad His204, Asp255, and Ser356 located in the serine protease domain (C-terminus) (Collen and Lijnen, 2005).The molecule contains an NH2-terminal growth factor domain and a kringle structure that shares homology with the kringles of plasminogen and t-PA. It also has a single N-glycosylation site at Asn302 and a fucose sugar linked to Thr18 (Massimo, 2007).

Alteplase

Alteplase is a recombinant form of tissue plasminogen activator, a protease found in endothelial cells that catalyzes the conversion of plasminogen to plasmin, which in turn breaks down the fibrin components of a thrombus (Mahmood and Muir, 2022).Alteplase has a very short circulating half-life, which requires its administration as a bolus with 10% of the dose, followed by an infusion of the remaining drug over 1 hour (Mahmood and Muir, 2022).

Alteplase is a fibrinolytic agent, also known as tissue plasminogen activator (tPA). Alteplase converts plasminogen into plasmin, a proteolytic enzyme that lyses both fibrin and fibrinogen (Fig 6).Intravenous alteplase is primarily eliminated by the liver, with an initial half-life of less than 5 minutes and a terminal half-life of 72 minutes. Then 2 mg of alteplase is instilled into occluded catheters to restore their function, it is unlikely that plasma will reach significant pharmacological concentrations of alteplase (Katsanos and Tsivgoulis, 2019 ; Knecht et al, 2018).Rt-PA is widely used for thrombosis control, especially in cases of acute ischemic strokes that need to be treated within three hours of onset (Hassanpour et al, 2020).

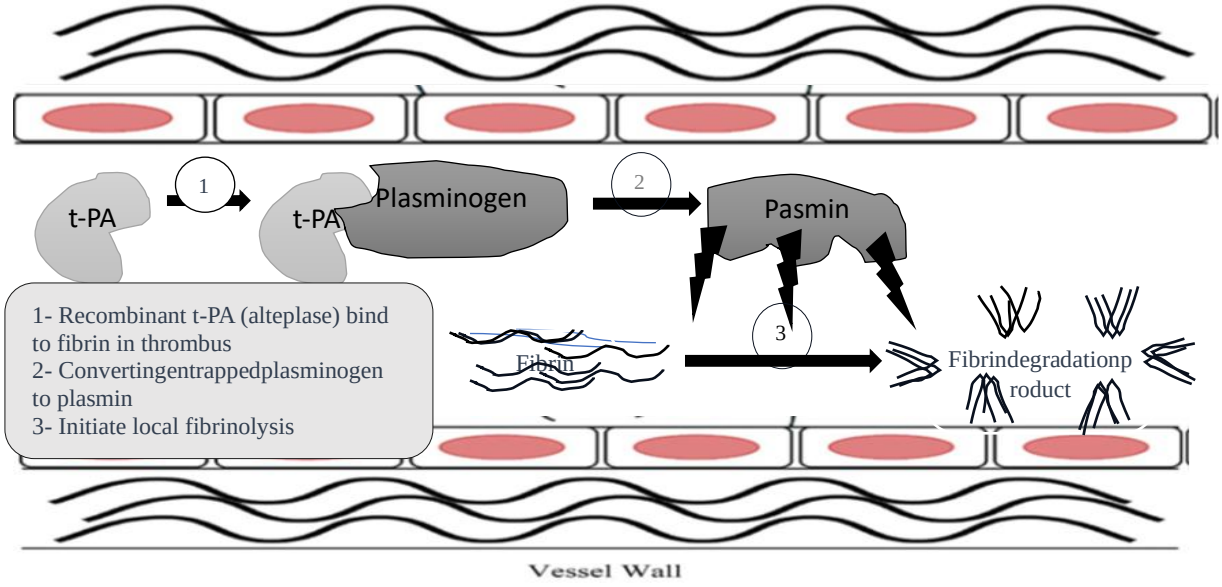

Fig 6. Mechanism of action of alteplase.

Reteplase

Reteplase is a third-generation recombinant tissue plasminogen activator that is specific to fibrin. Unlike its predecessors, it lacks the finger, epidermal growth factor, and Kringle 1 domains (Nishanth et al, 2019). The slower clearance resulting from these structural modifications allows for the administration of reteplase as a bolus without the need for weight-based dosing adjustments (Nishanth et al, 2019). Reteplase (recombinant plasminogen activator, r-PA) is a single-chain deletion mutant of alteplase expressed in Escherichia coli and, therefore, is expressed as a non-glycosylated protein (Nordt and Bode, 2003).

Reteplase consists of 355 amino acids with a total molecular weight of 39 kDa. The molecule is formed by the Kringle 2 domain and the protease domain of the alteplase molecule. Due to the deletion of the fibronectin finger region, the binding of reteplase to fibrin is significantly reduced compared to that of alteplase (Rashid et al, 2023).

The thrombolytic action of reteplase, like t-PA, catalyzes the conversion of inactive proenzyme plasminogen into active plasmin protease, which cleaves the Arg-Val bond. This action degrades the fibrin matrix of the thrombus (Mohammadi et al, 2019). In the absence of fibrin, reteplase exhibits plasminogen activation similar to t-PA. However, its binding affinity for fibrin is lower than that of t-PA, approximately 5 times less, due to the deletion of the fibronectin finger region (Mohammadi et al, 2019).In the presence of fibrin, it is known that the Kringle-2 domain enhances the protease activity, but this effect is weaker in reteplase compared to t-PA (Mohammadi et al, 2019).

In order to address the complications arising from the formation of blood clots or thrombi and restore proper function to the affected area, fibrinolytic therapy becomes necessary (Perler 2005). These agents, commonly referred to as clot busters, exhibit thrombolytic activity and offer long-term benefits to individuals, as evidenced by a low 5% mortality rate within one year for survivors (Delude et al, 2005). Fibrinolytic substances are utilized in the treatment of various conditions, including blood vessel or venous thrombosis, pulmonary embolism, myocardial infarction resulting from arterial clot formation (arterial thromboembolism), and acute ischemic stroke, among others (Thripathi, 2018).

According to the latest epidemiological data, it has been reported that 11% of individuals who received thrombolytic treatment experienced adverse effects, including hemorrhage. Among them, approximately 0.3-1.3% encountered significant adverse drug reactions such as intracranial hemorrhage. It is important to note that these drugs are contraindicated in individuals with vascular lesions, severe uncontrolled hypertension, brain tumors, peptic ulcers, and during pregnancy (Guguloth et al,2022).

The time Clot lysis measurement

To address these concerns, scientists have developed the clot lysis time (CLT) assay, a comprehensive test for plasma fibrinolysis. In this assay, plasma samples are mixed with calcium and phospholipid vesicles, forming a fibrin clot that is subsequently dissolved by the addition of exogenous tPA. Hypofibrinolysis, as determined by the CLT, has proven to be a reliable predictor of a two-fold increased risk of venous thrombosis in patients with recurrent venous thrombosis, independent of age or sex (Lisman et al, 2005). The predictive value of the CLT assay has been confirmed in larger studies like the MEGA study involving over 1000 patients

(Meltzer et al, 2008). Additionally, CLT has shown promise in predicting myocardial infarction (MI) in men under 50 with arterial thrombosis (Meltzer et al, 2009).

On the other hand, excessive fibrinolytic activity measured by the CLT assay has not demonstrated strong predictive power in bleeding disorders. For instance, hyperfibrinolysis did not correlate with bleeding scores in von Willebrand disease in a recent study (De Wee et al, 2012). There is hope that conducting further studies with the CLT assay in a larger population of individuals with bleeding disorders, especially around surgical procedures or after antifibrinolytic treatment, could yield more insightful results.

One theoretical drawback of the CLT assay is its dependence on high doses of exogenous tPA and the exclusion of other whole blood components. To address this, a whole blood global fibrinolysis assay called Global Fibrinolysis Capacity (GFC) has been developed, which includes cellular elements like red blood cells and platelets. The GFC assay has shown promise in predicting hyperfibrinolysis accurately in patients with liver disease (Rijken et al, 2012). However, its application to measure clinical bleeding and thrombotic outcomes in large populations requires further extensive validation.In summary, while the CLT assay has proved valuable in predicting thrombotic events, it still has limitations in predicting bleeding disorders. The GFC assay offers an alternative approach, but more research is needed to validate its clinical applicability.

The thrombolytic activity of plants and their bioactive compounds

Medicinal plants, also known as plants used for healthcare purposes, have the potential to offer numerous therapeutic benefits due to their rich composition of functional groups. These functional groups exhibit therapeutic activities that can address various dysfunctions in organs, tissues, or systems within the body. The utilization of plants as sources for medicinal agents in the investigation, prevention, and treatment of diseases holds great promise for the future. Herbal preparations, which encompass a diverse range of chemical constituents such as tannins, salicylates, and coumarins, have demonstrated their efficacy as clot lysis or thrombolytic agents. Consequently, the use of herbal preparations as alternatives to synthetic drugs can help avoid unwanted side effects (Guguloth et al, 2022).

Several studies have documented the thrombolytic properties of different plant parts and isolated forms of selected plants. In this review, we present the scientific data for each of the reported medicinal plants.

The subsequent plants have demonstrated extracts with thrombolytic effect. Furthermore, the relationship between the phytochemical composition of the extract and its impact on clot lysis is discussed by describing the thrombolytic properties of the individual compounds isolated from these plants.

Withania somnifera

Withania somnifera, commonly known as winter cherry (Saiyed et al, 2016).A large number of withanolides have been isolated from its roots and leaves, contributing to the medicinal properties of this plant. The plant also contains several other constituents such as withaniol, acyl-steryl-glucosides, starch, reducing sugar, hentriacontane, dulcitol, a variety of amino acids, and a significant amount of iron. Withaferin A is one of the main active withanolide compounds isolated from W. somnifera, exhibiting chemogenetic variation (Mukherjee et al, 2021).

The plant exhibits diverse medicinal activities, including cardioprotective activity (Mukherjee et al, 2021), antimicrobial activity (Mukherjee et al, 2021), anti-inflammatory activity (Singh and Singh, 2019), anticancer activity (Umadevi et al, 2012). As part of the discovery of naturally-derived cardioprotective drugs, the thrombolytic activity of extracts from Withania somnifera has been evaluated (Shahriar et al, 2014). The addition of 100 µl of Streptokinase SK (30,000 UI), the standard, showed a clot lysis of 66.77%. In this study, the methanolic extract of W. somnifera demonstrated a thrombolytic activity of 68.14%, while the ethanolic and chloroform extracts showed (21.15% and 17.46%, respectively) exhibited moderate thrombolytic activity (Shahriar et al, 2014). These findings justify the traditional uses of this plant in the treatment of cardiac patients (Shahriar et al, 2014).

Plumbago zeylanica

Plumbago zeylanica, known as Lead wort-white flowered and Ceylon lead wort in English (Sharma and Singh, 2015).Recent studies on P. zeylanica have revealed the presence of some secondary metabolites with biological activities. The stem contains plumbagin, zeylanone, isozeylanone, sitosterol, stigmasterol, campesterol, and dihydroflavinol-plumbaginol, the leaves contain plumbagin and chitanone, the flowers contain plumbagin, zeylanone, and glucose the fruit contains plumbagin, glucopyranoside, and sitosterol, the seeds contain plumbagin, and the root bark contains plumbagin (Jain et al, 2014). These secondary active metabolites exhibit diverse pharmacological activities such as activity on the central nervous system (CNS)(Roy and Bharadvaja, 2017), healing activity(Roy and Bharadvaja, 2017), cytotoxicity activity(Sharma and Singh, 2015), antifungal activity(Sharma and Kaushik, 2014)and anti-plasmodial activity (Sharma and Kaushik, 2014).

In an in vitro thrombolytic model, approximately 96.83 ± 0.657 clot lysis was achieved at a concentration of 800 µg/mL for the methanolic extract of the plant within 72 hours. On the other hand, the hydroalcoholic extract also exhibited 92.73 ± 0.768 clot lysis (Guguloth et al, 2022).

The other solvent extracts, petroleum ether extract, ethyl acetate extract, and chloroform extract, also demonstrated a moderate clot lysis effect, with values of 68.67% ± 0.974, 71.16% ± 0.235, and 73.68% ± 0.975, respectively. The standard SK exhibited clot lysis rates of 97.26% ± 0.974 , respectively (Guguloth et al, 2022).

Albizia lebbeck

Lebbeck tree or East Indian walnut (Waseem et al, 2020), is a large perennial leguminous plant with deciduous leaves and a medium-sized tree with dark gray bark, usually fissured, and young parts typically hairy(Verma et al, 2013).The stem bark produces 7 to 11% tannins; D-catechin, D-leucocyanidine, and seven compounds, including frieedlan-3-one and β-sitosterol. Three saponins have been isolated from the bark (Pal, 1995). The oil obtained from the seeds contains sterols, methyl sterols, triterpenoid alcohol, tocopherol, hydrocarbons, and carotenoids, cycloeucalenol, 24-ethylphenol, and cycloartenol. The leaves contain alkaloids, flavonoids, tannins, saponins, and carbohydrates. The seeds contain glycosides, proteins/amino acids

(arginine and lysine), resins, reducing sugars, saponins, flavonoids, and glucosides (Waseem et al, 2020).

A. lebbeck has antibacterial activity (Mishra et al, 2010), antimicrobial activity(Mishra et al, 2010). The methanol extract of A. lebbeck was subjected to a thrombolytic activity test, the addition of 100 µl of SK, a positive control (30,000 IU), to the clots,showed a clot lysis of 66.98 ± 0.15%, the crude methanol extract showed the highest percentage of clot lysis (54.13 ± 0.30%) (Sohaily et al, 2014).The results clearly demonstrate that A. lebbeck has moderate thrombolytic activity. Therefore, the plant is a promising candidate for further studies aiming to isolate the bioactive compounds responsible for this antithrombotic function, with the goal of developing new cardioprotective medications (Sohaily et al, 2014).

Pergularia daemia

P. daemia is a perennial plant characterized by paired milky sap(Ananth et al, 2021). The qualitative phytochemical analysis of the P. daemia extract reveals various groups of compounds, including alkaloids, flavonoids, terpenoids, tannins, steroids, glucosides, carbohydrates, proteins, amino acids, saponins, glycosides, fixed oils, gums, and mucilages (Ananth et al, 2021). P. daemia have revealed the presence of some secondary metabolites with biological activities such as antidiabetic, anti cancer,and antioxydant activity (Ananth et al, 2021).

The thrombolytic activity of the hexane extract from Pergularia daemia stem showed a high degree of clot dissolution, where the highest percentage of clot lysis reached 62.2% for the hexane extract, while the lowest percentage was recorded for the aqueous extract campared with the standardaspirin (1 mg/ml),which showed 67.76% of clot lysis (Sakthipriya and Vidhya, 2015). Phytochemical analysis revealed that the crude extract contains tannins, alkaloids, and saponins, which may have contributed to its clot lysis activity (Sakthipriya and Vidhya, 2015).

Centella asiatica

C. asiatica (L.), known in English as Indian pennywort (Bylka et al, 2013). The chemical components of this plant play a crucial role in these applications, and among them, triterpene saponins are considered the most biologically active. The most important biologically active components are asiatic acid, madecassic acid, asiaticoside, and madecassoside (Seevaratnam et al, 2012). In addition to terpenoids, it also contains high total phenolic contents contributed by flavonoids such as quercetin, kaempferol, catechin, rutin, apigenin, and naringin, as well as volatile oils like caryophyllene, farnesol, and elemene (Seevaratnam et al, 2012). C. asiaticapossesses several biological activities including neuroprotectrice (Prakash et al, 2017), cardioprotectrice (Seevaratnam et al, 2012), and antidepressant activity (Prakash et al, 2017).

The thrombolytic activities of different fractions of C. asiatica were analyzed by determining their ability to induce clot lysis. Streptokinase (SK) was used as a positive control, which showed a lysis of 63.34 ± 0.58%, compared to the isotonic solution with a lysis activity of 7.0 ± 0.23%. The various fractions of C. asiatica exhibited varying degrees of thrombolytic activity ranging from 17.58 ± 0.23% to 43.94 ± 0.62% (Rashid et al, 2023). The strongest clot lysis activity (43.94 ± 0.62%) was found in the chloroform-soluble fraction (Rashid et al, 2023). Further exploration of this plant could lead to the development of bioactive compounds such as

phenolics and flavonoids that might be effective in managing various chronic diseases (Rashid et al, 2023).

Capparis decidua Edgew

C. dicidua, known as Caper berry, Caper bush, Caper plant in English(Verma et al, 2011), Various biochemical compounds such as alkaloids, phenols, sterols, or glycosides present in Capparis sp. may have medical significance or nutritional value (Singh et al, 2011). These active componds are responsible for several biological activities such as: antiplatelet (Nazar et al, 2020), Antirheumatic (Nazar et al, 2020), and antibacterial activity (Singh et al, 2011).

The dried fruits of C. decidua demonstrated a significant potential for in vitro clot lysis in the present study compared to distilled water as a negative control and SK as a positive control for the first time (Kunwar et al, 2022). The preliminary evaluation of the first methanolic extract's in vitro thrombolytic activity at a concentration of 1mg showed a clot lysis activity of 23.16 ± 1.26%, and the second methanolic extract demonstrated a significant clot-dissolving activity of 32.39 ± 2.10% compared to SK, which had a clot lysis percentage of 51.60 ± 0.77 (Kunwar et al, 2022). The in vitro thrombolytic potential of C. decidua fruits may also be due to the presence of stachydrine (Kunwar et al, 2022). Stachydrine is an alkaloid isolated from the dried fruits of C. decidua and has shown a protective role against cerebral ischemia-reperfusion injury and cardiac hypertrophy by attenuating oxidative stress and inhibiting expressions of phosphorylated IκBα, NF-κB p65, JAK2, and STAT3 in isoproterenol-induced CH rats (Kunwar et al, 2022).

Protium serratum

Gutgutiya (Protium serratum) belongs to the family Burseraceae and is an evergreen perennial tree with a large spreading canopy(Hasnat and Hossain, 2018). Several phytochemicals such as polyphenols, flavonoids, tannins, sugars, alkaloids, and triterpenoids/steroids have been reported to be present in P. serratum and its various parts, including leaves, roots, fruits, seeds, and others, which are responsible for antioxidant, anti-inflammatory, larvicidal, and other medicinal properties (Mohanta et al, 2017). Species of Protium have also shown antitumor, agglutinating, and immobilizing activities (Sayeed et al, 2014). P. serratum also possesses potent antimicrobial agents (Hasnat and Hossain, 2018).

The thrombolytic activity of the methanolic extract of P. serratum (MEPS) was evaluated using an in vitro thrombolytic test with streptokinase as the standard. MEPS showed significant thrombolytic activity with 59.653 ± 8.626% clot lysis. The positive control (streptokinase) exhibited 72.835 ± 5.702% clot lysis. P. serratum demonstrated a good thrombolytic activity compared to streptokinase. Therefore, it can be inferred that these extracts may be considered as a potential source of thrombolytic agents (Sayeed et al, 2014).

Cyperus rotundus

Cyperus rotundus L., also known as edible nut grass or nut sedge, or Java grass (Kamala et al, 2018), is called "Nut grass" in English (Sharma, 2023). It belongs to the cyperaceae family (Kamala et al, 2018). Different phytochemical studies on C. rotundus have revealed the presence of alkaloids, flavonoids, tannins, starch, heterosides, furochromones, monoterpenes,

sesquiterpenes, sitosterol, fatty oil containing a neutral waxy substance, glycerol, and linolenic, myristic, and stearic acids (Kamala et al, 2018). C. rotundus possesses numerous pharmacological activities (in vitro and in vivo) such as cytotoxic, antimicrobial, anti-inflammatory, anti-allergic, anti-diarrheal, and hepatoprotective activities. Previous phytochemical studies of C. rotundus have revealed the presence of several types of secondary metabolites, including sesquiterpenes, flavonoids, iridoids, phenylpropanoids, furochromones, phenolic acids, alkaloids, steroids, and saponins (El-Wakil et al, 2023). Clinical trials and animal research support the use of the plant as an analgesic, anti-arthritic, antibacterial, anticancer, anti-candida, anticonvulsant, antidiabetic, antiemetic, antihistaminic, antimalarial, anti-obesity, antipyretic, antispasmodic, and gastroprotective agent (Al-Snafi, 2016).

A significant thrombolytic activity was observed after treating clots with the methanolic extract of Cyperus rotundus rhizome, showing 60 ± 5.18% clot lysis at 200 µg/ml, while SK (streptokinase) showed clot lysis at 70 ± 4.46%. Therefore, it can be concluded that the methanolic extract of Cyperus rotundus could be a potential candidate for future thrombolytic agents. As a result, the entire community is now engaged in the research and development of molecules that have therapeutic potential in atherosclerotic disorders such as myocardial or cerebral infarction. The phytochemical screening of the Cyperus rotundus extract was chosen due to the high concentration of phytochemical compounds. The presence of tannins, flavonoids, terpenoids, and polyphenols was also confirmed by histochemical analyses. The methanolic extract of Cyperus rotundus exhibited excellent thrombolytic activity. The presence of these phytochemical compounds was found to be responsible for the in vitro thrombolytic action (Gajendran et al, 2022).

Erythrina Variegata

Erythrina variegata, called Indian coral tree, is a fast-growing deciduous tree, reaching 50 to 60 feet in height, with spiny stems and branches. Erythrina belongs to the Fabaceae family, which comprises 290 species(Martins and Brijesh, 2022).The study of the literature has revealed that a number of compounds are available on E. variegata, such asAlkaloids, flavonoids, pterocarpans, triterpenes, steroids, alkyl trans-ferulates, proteins, and lecithin (Kumar et al, 2010).

Erythrina variegata Linn. is frequently used as an anxiolytic, vermifuge, carminative, febrifuge, diuretic, and expectorant, and for the treatment of rheumatism and skin diseases. Phytochemical screening of three extracts (petroleum ether, methanol, and aqueous) from the leaves has shown the presence of alkaloids, flavonoids, saponin glycosides, and steroidal compounds. The study of the literature has revealed that Erythrina variegata possesses scientifically justified properties such as antioxidant, anti-hyperlipidemic, anti-inflammatory, antibacterial, and osteoprotective activities (Kumara et al, 2019). However, while there are reports of anxiolytic activity in the stem bark of Erythrina variegata, there is no activity reported in the leaves of this plant (Kumara et al, 2019).

The bark extracts of Erythrina variegata were subjected to an evaluation of thrombolytic activity, which was assessed using human erythrocytes, and the results were compared with the standard SK. The methanolic extract showed 72.14 ± 3.77% clot lysis compared to 78.42 ± 1.6% lysis produced by SK. Clots treated with sterile distilled water (control) showed negligible clot lysis

(3.21%). In this study, the methanolic extract of Erythrina variegata exhibited the highest thrombolytic activity at 72.14%, while the ethanol and chloroform extracts showed moderate thrombolytic activities at 60.08% and 55.82% respectively (Shahriar et al, 2015).

Fagonia arabica

Fagonia arabica L. is a small, spiny, perennial herb, upright, and commonly found in wooded areas in the wild. The plant is distributed worldwide in Africa, Arabia, Pakistan, and India (Patel et al, 2012). It belongs to the Zygophyllaceae family (Kanwal et al, 2021), A thorough study of the literature on several reports concerning the phytochemical compounds of the genus Fagonia reveals that these species are rich in secondary metabolites. Screening of F. arabica has shown the presence of flavonoids, terpenoids, saponins, glycosides, alkaloids, and phytochemical tannins (Alamami et al, 2022). Some researchers have reported many biological activities such as Antioxidant activity (Kanwal et al, 2021), and Antibacterial activity (Gabriel et al, 2022).

The thrombolytic activity of F. arabica was tested in vitro on a clot lysis model, showing a significant percentage of clot lysis 75.6%, suggesting its potential as a medicine for patients with atherothrombotic diseases(Chaudhary et al, 2015). Another researcher also reported the thrombolytic activity of this plant through tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) induction, conducted on human umbilical cord cells (Kanwal et al, 2021).

Bougainvillea spectabilis

The bougainvillea, also known as Great Bougainvillea and Paper Flower in English, is a member of the Nyctaginaceae family, comprising 18 species of spiny trees, shrubs, and vines. (Ghogar and Jiraungkoorskul, 2017 ; Xu et al, 2009).The phytochemical analysis revealed the presence of alkaloids, flavonoids, furanoids, glycosides, phenols, phlobotannins, quinones, saponins, steroids, tannins, and terpenoids, which were extracted from the stems, flowers, and leaves of B. spectabilis. Other active constituents include bougainvinones, peltogynoids, essential oils such as methyl salicylate, terpinolene, α-(E)-ionone, pinitol, β-sitosterol, quercitrin, and quercetin-3-O-rutinoside. Furthermore, the phytochemical constituents of the leaf extract of B. spectabilis revealed the presence of tannins (27.64%), saponins (14.08%), glycosides (11.49%), flavonoids (10.05%), alkaloids (4.10%), as well as phytate (49.27%) and oxalate (27.65%) contents (Ghogar et al, 2016).

The study of the thrombolytic activity of Bougainvillea spectabilis leaf extract was conducted using a simple and rapid in vitro clot lysis model. The results showed a maximum clot lysis of 84.24% at a concentration of 800 ug/ml after 72 hours of incubation. The results clearly indicate that the concentrations of leaf extract improved the percentage of clot lysis. However, SK and water were used as positive and negative controls, showing a maximum clot lysis of 96.63% and 41.32% after 72 hours of incubation, respectively. Some studies suggest that the thrombolytic activity is likely due to the diverse composition of plant extracts as phytoconstituents, including rich sources of alkaloids, flavonoids, tannins, and terpenoids (Sherwani et al, 2013).

Table 1 showcases various plant varieties employed in in vitro screening for thrombolytic activities. The table includes information about the specific plant parts used, the regions

wherethe plants are found, the active principal compounds present, and the in vitro assays conducted to assess their thrombolytic activities, along with corresponding references.

Table1. Efficacy of Plants as Thrombolytic Agents

Scientific name	Commonly Name	Family	Used Part	Region	Active Principle	Percentage of Thrombolytic Activity	References
Withania somnifera	winter cherry	Solanaceae	Roots	Savar, Dhaka, Bangladesh	Withaniol, acyl-steryl-glucoside, reducing sugar, hentriacontane, dulcitol,	68.14% for the methanolic extract, 21.15% for the ethanolic extract, and 17.46% for the chloroform extract, respectively.	Shahriar et al, 2014
Plumbago zeylanica L	Lead wort-white flowered	Plumbaginaceae	leaves	Talakona Forest in India	Flavonoids, phenolic compound	96.83% for the methanolic extract, 92.73% for the hydroalcoholic extract	Guguloth et al, 2022
Spilanthes paniculata	toothache plant	Asteraceae	leaves	Local Zone Narayanganj (Bangladesh)	Glucides, Alcaloïdes, Flavonoïd, saponines	42.77±6.14% for the methanolic extract	Tabassum et al, 2017
Eleocharis dulcis	Chinese waterchestnut	Cyperaceae	fruits	Near the fields of Jahangirnagar University, Dhaka, Bangladesh	alkaloid, carbohydrate, Glycoside, tannins, flavonoids, Saponin protein, and diterpenes Triterpenoids.	The clot lysis for the methanolic extract (200mg) and the methanolic extract (100mg) is 86.87% and 84.15% respectively	Islam et al, 2019
Wedelia chinensis	Chinese Wedelia	Asteraceae	leaves	Dhaka in Bangladesh	Flavonoids, Alkaloids, Glycosides	The fraction of methanolic extract exhibited 24.48±5.23%clot lysis	Tabassum et al, 2017
Centella asiatica L	Thankuni	Apiaceae	whole plant	Rural areas of the Narayan-ganja district (Bangladesh)	Phenolic compound, Flavonoïde	Maximum clot lysis activity (43.94 ± 0.62%) for the chloroform extract	Rashid et al, 2023
Litsea glutinosa	Maida Lakri	Lauraceae	leaves	Rural areas of Bangladesh	Saponine, alcaloïdes et tanins	46.78 ± 0.90% for the methanol extract	Bhowmick et al, 2014
Gardenia coronaria	Kannyari	Rubiaceae	leaves	theforest of Chittagong , Bangladesh	coronalolide, coronalolic acid, coronalolide methyl ester, ethyl coronalolate acetate triterpenes	26.79% % for the methanol extract	Rahman et al, 2020.
Capparis decidua Edgew	Caper berry	Capparaceae	fruits	New Delhi in India	Stachydrin, alcaloïdes	23.16 ± 1.26% and 32.39 ± 2.10 for the methanol extract	Kunwar et al, 2022
Albizia lebbeck	Lebbeck tree	Fabaceae	bark	Chittagong	alkaloid, flavonoid, tannin, phenol, saponin, glycoside and free amino acid	54.13 ± 0.30% for the methanol extract	Sohaily et al, 2014 ;Kamala Lakshmi et al, 2020.
Pergularia deamia	velipparuthi	Asclepiadaceae	stem	Inde	Tanins, alcaloïdes, saponines	62.22% for the hexane extract	Sakthipriya, and Vidhya, 2015
Viburnum foetidum	Khailzakhori	Adoxaceae	leaves	Mountainous region of Sylhet	Iridoids	62.30% for the petroleum ether extract and 60.10% for the n-hexane extract	Roy et al, 2015 ; Wang et al, 2020
Typha	Elephant	Typhaceae	leaves	Gulbarga	flavonoid	58% for the methanolic extract and 51.76	***Londonkar et***

angustifolia	grass or Cattail			University campus, Gulbarga,Karnataka, India	glycosides, terpinoids, long chain hydrocarbons,sterols, and cerebrosides	% for the aqueous extract	***al. 2014***
Achyranthes aspera L.	devil's horsewhip, prickly chaff flower	Amaranthaceae	leaves	Gaibandha District of Bangladesh	flavonoides, tannins, saponins, and alkaloids	36.49% for the methanol extract	Rishikesh et al, 2013.
Protium serratum	Nihor	Burseraceae	leaves	Mountainous region of Bangladesh	Terpenoids and coumarin	59.653 ± 8.626% for the methanol extract	Sayeed et al, 2014
Ficus hispida	Dumoor	Moraceae	whole plant	Botanical Garden, Dhaka, Bangladesh.	steroids, triterpenoids, phenols, tannins and flavonoids	50.12 ± 1.91% for the methanolic extract	Shahriar et al, 2013
Cassia siamea L	kassod tree	Leguminosae	leaves	Rural region of Vijayawada, India	chromone alkaloids, anthraquinone glycosides, flavonoids, and gallic acid, Phenols	The ethanol extract showed 18% clot lysis, and the aqueous extract showed 14.5% clot lysis	Vani et al, 2019
Cyperus rotandus	purple nut sedge or nut grass	Cyperaceae	Rhizome	India	Tanins, flavonoïde terpénoïde polyphénol	60.00 ± 5.18% for the ethanol extract	Gajendran et al, 2022
Sonneratia caseolaris	mangrove	Sonneratiaceae	leaves	Barisal District (Bangladesh).	triterpenoids, phenolic compound, steroids, flavonoids and benzene carboxylic derivatives	44.67% for the methanol extract	Munira et al, 2019
Syzygium malaccense	Malay apple	Myrtaceae	leaves	Medicinal Plants Garden of Pioneer Medical & Paramedical Campus in India."	saponins, flavonoids, tannins, steroids and glycosides	At various concentrations of 100, 200, 300, 400, 500 µg/mL, the clot lysis percentages were 20.15%, 23.64%, 32.12%, 55.21%, and 40.65% respectively for the hydroalcoholic extract	Patel et al, 2019
Dysophylla auricularia	Buntot pusa	Lamiaceae	leaves	Saraf-bhata Hill (Bangladesh).	Glycoside, Alcaloïdes, Tannins, Flavonoïdes	42.1208% for the methanol extract	(Rana et al, 2015 ; Nur et al, 2015)
Erythrina variegate	Palitamadar	Fabaceae	stem bark	The campus of University of Dhaka, Bangladesh	Alkaloids, isoflavones, triterpines, lupeol and stigmasterol	The aqueous and petroleom ether fraction showed highest clot lysis activity (56.78 and 57.78 %, respectively)	TABASSUM et al, 2019
Byttneria pilosa	Harjora	Sterculiaceae	whole plant	the forest ofthe University of Chittagong, Bangladesh	Flavonoids, saponins alkaloids, gums, glycosides, terpenoids, reducing sugars, steroids, and tannins	Ethanol extract exhibited clot lysis capability ranging from 8.83 ± 0.20% to 51.32 ± 0.73% at concentrations of 10 to 320 µg/mL. The maximum clot lysis observed was 51.32 ± 0.73% at the concentration of 320 µg/mL.	Sikder et al. (2022).
Pandanus odoratissimus	Umbrella tree	Pandanaceae	hole plant	Botanical Garden, Mirpur, Dhaka	pyridine alkaloids, the volatile	46.58 ± 0.21% for the aqueous extract.	(Penu et al, 2020)

					oil, Lignans and benzofurans		
Fagonia Arabica	Kharasan	Zygoplyllaceae	hole plant	India	Tannins, coumarins, flavonoids, saponins, Alkaloids, and phenolic compound	75.6 ± 2.7% for the aqueous extract.	[146], (Shahid et al, 2022).
Litsea monopetala	meda	Lauraceae	leaves	Village in Laxmipur District, Bangladesh	alkaloids, carbohydrates, tannins, flavonoids, steroids	At concentrations of 2.5, 5, 10, and 20 mg/ml, the clot lysis rates were 9.52, 9.49, 13.64, and 17.50%, respectively, for the methanol extract	Dewanjee et al, 2022
Moringa oleifera	drumstick tree	Moringaceae	leaves and flowers.	Open land in Arvind Nagar, India	flavonoids, terpenoids, cardiac glycosides, saponins,tannins, amino acids,and carbohydrates	41.40 ± 2.02% for the methanol extract	Kunwar et al, 2022
Bougainvillea spectabilis Willd	paper flower	Nyctaginaceae	leaves	Karachi, Pakistan's city of roads	phenolics, flavonoids, alkaloids, anthocyanin, tannins, saponins, phytate, and oxalate	84.24% for the aqueous extract	[148], Kenari et al, 2022.
Manilkara zapota	the sapodilla	Sapotaceae	leaves	Botanical Garden of Anurag College of Pharmacy, Kodaden, India	triterpènes, flavonoïdes, glycosides, glucides, tanins, and Alcaloïdes	23.94% for the hydro-ethanolic extract	Barbhuiya et al, 2019
Polygonum hydropiper	Bishkatali	Polygonaceae	hole plant	Dhaka, Bangladesh	Flavonoids, Carbohydrates, saponines, steroides,	43.08% for the ethanolic extract	Sharif et al, 2014
Murraya paniculata	Kamini	Rutaceae	leaves	Dhaka, Bangladesh	total phenolic and flavonoids compound	58.06% for the hexane extract	Laboni et al, 2015 ; Zhu et al, 2015

Comparative analysis of thrombolytic activity and factors influencing variation among various plants and their active constituents

This section aims to compare the thrombolytic activity of different plant species, including Bougainvillea spectabilis, Fagonia arabica, Erythrina variegata, Cyperus rotundus, Protium serratum, Capparis decidua Edgew, Centella asiatica, Pergularia daemia, Albizia lebbeck, Plumbago zeylanica, and Withania somnifera. The strengths and weaknesses of each plant's thrombolytic potential, as reported in the available literature, will be analyzed. Additionally, potential factors influencing the variation in thrombolytic activity among these plant species will be discussed.

Several factors may contribute to the variation in thrombolytic activity among different plant species. These factors include:

Phytoconstituents: The diverse composition of plant extracts, including alkaloids, flavonoids, tannins, terpenoids, and polyphenols, may influence their thrombolytic potential.
Extract Solvents: Different solvents used for extraction may yield varying levels of active constituents, leading to differences in thrombolytic activity among extracts from the same plant.
Concentration and Incubation Time: The thrombolytic activity may vary depending on the concentration of the plant extract and the duration of incubation, as observed in the results.
Synergistic Effects: Some plants may exhibit higher thrombolytic activity due to synergistic effects between multiple phytochemical compounds present in the extracts.

Mechanism of action of Active Constituents as thrombolytic agent
The thrombolytic agents that lyse clot by disrupting the fibrinogen and fibrin contained in a clot. Plasmin is one of the natural anti-thrombotic agents. The cell surface bound plasminogen is easily activated to plasmin which ultimately leads to fibrinolysis (Pantzar et al, 1998).
Medicinal plants have been used for centuries to treat various diseases and conditions. Thrombolytic activity is one of the important properties of medicinal plants that can help in the treatment of thrombotic disorders. Thrombolytic agents are used to dissolve blood clots that can cause heart attacks, strokes, and other serious conditions.
The following are some of the components present in medicinal plants that may contribute to their thrombolytic activity: Flavonoids: Flavonoids are a group of polyphenolic compounds that are widely distributed in plants. They have been shown to possess thrombolytic activity by activating plasminogen to plasmin, which is responsible for the dissolution of blood clots.

Flavonoids such Epicatechin : possess fibrinolytic activity, which may offer a potential strategy for mitigating thrombotic complications. Although there have been limited reports on the fibrinolytic effects of flavonoids, Xue et al. (2017) proposed, based on molecular docking studies, that flavonoids can activate plasmin by forming hydrogen bonds with u-PA. Consequently, it becomes crucial to conduct further research on the fibrinolytic properties of flavonoids(Quintal Martínez and Segura Campos,2023).
Tannins: Tannins are a group of polyphenolic compounds that are widely distributed in plants. They have been shown to possess thrombolytic activity, It has been shown that corilagin (ellagitannin, 7.5–60 μM) increased t-PA activity and decreased PAI-1 activity in plasma collected from healthy rats and also reduced the activity of PAI-1 released from thrombin-stimulated rat platelets in vitro (Marcińczyk et al, 2022)
Glycosides: The docking simulation study indicates that glycoside plays a crucial role in the thrombolytic mechanism. It interacts with the activation site of tissue plasminogen activator, which converts plasminogen to plasmin, leading to the breakdown of extracellular matrix proteins or clots. This interaction facilitates thrombolysis (Mahmud et al, 2015).
Alkaloids: Alkaloids are a group of nitrogen-containing compounds that are found in many medicinal plants. They have been shown to possess thrombolytic activity by inhibiting platelet aggregation and promoting fibrinolysis (Lee, et al 2016).
Terpenoids: Terpenoids are a group of compounds that are widely distributed in plants. Andrographolide, a bicyclic terpenoid lactone, has demonstrated thrombolytic activity by effectively dissolving blood clots in vitro (Prakash et al, 2013).
Coumarins: a significant group of natural compounds present in various plants and microorganisms, have been the subject of noteworthy research, which has demonstrated their

antithrombotic activity. These studies have shown that coumarin derivatives effectively inhibit platelet aggregation induced by adenosine diphosphate (ADP), thromboxane A2 (TXA2), thrombin (Thr), collagen (Coll), and arachidonic acid (AA) (Gao et al, 2021).

There are other fibrinolytic compounds from various organisms:In previous studies, Zhang et al. (2008) and Wang et al. (2012) isolated a novel fibrin(ogen)-olytic agent from the marine microorganism Stachybotrys longispora FG216 (CCTCC M 2012272), temporarily named fungi fibrinolytic compound 1 (FGFC1). FGFC1, a pyranoindole compound with a low molecular weight and a chemical name of 2,5-bis-[8-4,8-dimethyl-nona-3,7-dienyl)-5,7-dihydroxy-8-methyl-3-keto-1,2,7,8-tertahydro-6H-pyran[a]isoindol-2-yl]-pentanoic acid (Table 1), enhances Plg activation through promoting the effect by single urokinasetype Plg activator and plasminogen, thereby inducing thrombolysis (Wu and Bao 2005; Qu et al. 2009; Wu and Bao 2006). Furthermore, fibrinolytic compounds, 1-O-Palmitoyl-2-O-oleoyl-3-O-(a-D-glucopyranosyl)-glycerol (POGG), and 1-O-myristoyl-2-O-oleoyl-3-O-(a-D-glucopyranosyl)-glycerol (MOGG), were isolated from the brown alga S. fulvellum. Wu et al. (2009) demonstrated that POGG and MOGG enhance reciprocal activation of pro-u-PA and plasminogen in vitro. Tachikawa et al. (1997) isolated complestatin, a chlorine-containing peptide metabolite from Streptomyces sp. They characterized it as an active component that effectively elevates Glu-Plg-fibrin binding. Moreover, FGFC1 exhibits linear pharmacokinetics and rapid distribution in most tissues except the brain in Wistar rats (Su et al. 2013). In previous studies, Zhang et al. (2008) and Wang et al. (2012) isolated a novel fibrin(ogen)-olytic agent from the marine microorganism Stachybotrys longispora FG216 (CCTCC M 2012272), temporarily named fungi fibrinolytic compound 1 (FGFC1). FGFC1, a pyranoindole compound with a low molecular weight and a chemical name of 2,5-bis-[8-4,8-dimethyl-nona-3,7-dienyl)-5,7-dihydroxy-8-methyl-3-keto-1,2,7,8-tertahydro-6H-pyran[a]isoindol-2-yl]-pentanoic acid (Table 1), enhances Plg activation through promoting the effect by single urokinasetype Plg activator and plasminogen, thereby inducing thrombolysis (Wu and Bao 2005; Qu et al. 2009; Wu and Bao 2006). Shinohara et al. (1996) discovered a novel triprenyl phenol compound named staplabin from a culture of the fungus Stachybotrys microspora. Its activities are quite similar to those of complestatin.

Conclusion

In our bibliographic study, we conducted a detailed investigation into the thrombolytic activity of 31 carefully selected medicinal plants. Through a thorough examination of relevant scientific literature, we assessed the potential of these plants to dissolve blood clots and reduce the risk of thrombotic diseases. According to the results of this study, a variety of plants exhibited thrombotic activity. Traditional treatments using known plant species showed that these plants exert this activity through active compounds present in their extracts. We observed that the methanolic extract displayed the highest thrombolytic activity for the majority of the plants. The active principles responsible for clot dissolution are primarily flavonoids, phenolic compounds, and alkaloids.

Although the examination of these references allowed us to confirm that these plants have the ability to dissolve clots, it is not enough as we still do not fully understand how the active compounds of these plants work in the clot dissolution process. Further research and studies are

needed to determine the role of these botanical species in the activity of clot decomposition. Combining conventional treatments with modern therapies may help researchers elucidate the mechanisms of action of these plants with thrombolytic activities. This study has also revealed the potential for developing new herbal-based medications in the thrombolytic field. Conducting further in-depth research on these plants in the future will enable us to rely on them for treating and reducing thrombotic diseases and promoting overall health.

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