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Thrombolytic Property of Herbal Plants: A Short Review

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Since, ancient time medicinal plants have been using to treat various human ailments. Blood clotting causes various heart associated diseases like myocardial infarction, deep vein thrombosis and renal vein thrombosis. Thrombolytic drugs are being employed to lyse the thrombus (blood clot) formed in the arteries. The modern systems of medicines have certain limitations and serious consequences which can alter the normal hemostasis process. Herbal medicines are known for their safety and efficacy in treating diseases effectively without producing any untoward effects. The present review provides the medicinal importance of some plants as thrombolytic agents. The source for the present review was taken from literature survey carried through the findings from suitable keywords in databases, PubMed, Google Scholar and Web of Science and Scopus, etc. This review provides the detailed information on medicinal plants and phytochemical compounds as thrombolytic agents.

Keywords: Efficacy; Herbal Plants; Hemostasis; Thrombolytic Activity; Thrombosis.

Hemostasis means regulating the blood loss consequent to bleeding. It should not confuse with similar word homeostasis which means maintenance of the body's internal environment within physiological limits. In the blood vessels, the blood normally circulates in a fluid state. But if it is drawn from the body, it thickens and forms a gel called a clot. The process is called clotting or coagulation. Natural human circulatory or blood vessel systems are presented with two contending qualification to confirm the feasibility of the entity or organism: tissue intromission must be conserve at any movement, and the bleeding must be rapidly ceased at sites of blood vessel injury[1]. Cardiovascular illness caused by formation of thrombus is one of the most dangerous conditions which is rapidly increasing at an alarming rate in current times[2]. Hemostasis and fibrinolysis represent the important dynamics for stopaging the free flow of blood at sites of damage or injury and reinstate blood vessel capacity or potency during process of recovery of wound or healing correspondingly. The term hemostasis or coagulation refers to the transformation of

dispersible fibrinogen into insoluble fibrin. This technique occurs by step by step process of enhancing the enzymatic activation in which the formation of an inactive state of plasma proteins into an active protease (serine) product[3]. Thrombin serves as the central serine protease of the coagulation cascade[4]. Blood clot formation is a censorious step in the vascular related diseases which includes myocardial infarction, hypoxia (anoxia), hypertension[5], sudden heart blockage and infarction disorders that stand for a considerable number of mortality in Worldwide[6].Intense research activity in the antithrombotic field was devoted to compounds showing antiaggregatory potency during the last three decades of the 20th century. Among the huge number of synthetic molecules tested, only very few of them found in clinical use (Dupin*et al*., 2002). Intravenous tissue plasminogen activator infusion is the fastest way to initiate thrombolytic therapy; however, poor recovery can be expected in up to 50% of patients (Alexandrov *et al*., 2001). Tissue plasminogen activator delivery to the thrombus is dependent on the residual flow to and around the arterial obstruction when given intravenously (Alexandrov, 2004). Though, thrombolytics which includes aspirin, warfarin, antiplatelet (Clopidogrel) and heparin have shown efficacy and are widely dispensed medications in many cardiovascular and cerebrovascular diseases, the main adverse effects of use of these medications were an increased incidence of over bleeding(Bond *et al*., 2005). The recent epidemiological status from WHO has given the statement that ischemic related heart disease and sudden heart blockage alone caused 9.8 million deaths Worldwide. Cerebrovascular stroke is the stoppage of blood to some areas of the brain leads to brain dysfunction.

Clotting (coagulation) occurs through a process of a series of reactions and thrombin is the last enzyme that plays a vital role in the coagulation cascade which converts fibrinogen into insoluble fibrin (Fig 1)[7]. There are thirteen factors are involving in the coagulation and thrombin activates factor-XIII, enhance the formation of factor-V, which increases the thrombin formation and stimulates thrombocytes (platelets), and cause platelets aggregation[8]. Platelets respond to injury of blood vessels by first adhering to the vascular endothelial matrix as a single layer of cells. Throughout of lifetime in blood circulation, were exposed to a variety of external stimuli that control and regulate their state of activation[9]. The adhesion of platelets to the matrix is mediated by von Willebrand factor, a plasma glycoprotein that links platelets through their specific proteins (called surface glycoprotein) IX/lb receptors to collagen, by direct association with collagen through their surface glycoprotein Ia/IIa receptors. The primary extracellular molecule that increases platelet cAMP is prostaglandin I_2[10].

Animal survivallance on this earth has been made acceptable only because of the important role played by plants. Medicinal plants are the plants or their parts used for the protecting the health care of an individual as they probably contains a large number of functional groups which shows therapeutic activity against various dysfunctions of organs or tissues or systems in the body. The future of the plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is very promising. Herbal preparations contain a wide variety of chemical constituents like tannins, salicylate, and coumarins and proved as clot lysis or thrombolytic agents. Therefore herbal preparations would be used in the place of synthetic drugs to avoid unwanted effects.

The present scenario in thrombolytic therapy

To get cleanse of problems developed due to the formation of a clot in the blood or thrombus to remodify function to the affected area, fibrinolytic therapy is required[11]. The agent which is having the thrombolytic activity also known as clot busters which shows long term benefits for survivors, who have just a 5 % death rate at one year[12]. Fibrinolytic substance is being used in blood vessels or venous thrombosis, pulmonary (lung) embolism, myocardial infarction formation of clot in the arteries (arterial thromboembolism), and acute ischemic strokeetc[13].

Contraindications for thrombolytic therapy

Thrombolytics were predominantly safe and effective in correcting thrombosis, but excessbleeding (hemorrhage) is the major adverse effect. The current epidemiological data stated that 11% of all diseased persons who were administered thrombolytics have presented adverse effects like hemorrhage. About 0.3-1.3% had significant adverse drug reactions like intracranial hemorrhage. These drugs are contraindicated in

vascular lesions, severe uncontrolled hypertension, brain tumor, peptic ulcer and pregnancy.

Methodology

Published articles in connection with thrombolytic activity of various herbal plants were retrieved from PubMed, Science Direct, Taylor and Francis, BMC, ACS, Google scholar, Web of Science, Scopus and other literature database. Some articles were found by tracking citations from publications. The research key words used were thrombolytic activity and herbal plants. In this review briefly discussed the recent scientific findings regarding the thrombolytic activities of various herbal plants and indicatedtheareas where further study is required. The literature collections were restricted to publications in English language.

Medicinal plants having thrombolytic activity

Various studies have been reported the thrombolytic properties of plant parts and their isolated forms of few plants (**Table 1**). In the present review the scientific data of each reported medicinal plants were presented hereunder.

Camellia sinensis

C. sinensis belongs to the *Theaceae* family. *C. sinensis* is commonly known as green tea[18]. The herb is resident of the Asian and Southeast region for many years. *C. sinensis* is being widely consuming in countries like India, North Africa, North East Asia and China and Pakistan[19]. *C. sinensis* has been proved to have a wide variety of useful pharmacological and physiological actions[20]. Leaves were used as probiotic activities[21]. Warfarin effect is reduces in persons taking an excessive concentration of *C. sinensis* and also found hemorrhage development. *In vitro* thrombolytic potential *C. sinensis* reported that about 95.24% and 90.34% of clot lysis observed for methanolic extract and aqueous extract, respectively at 800 µg/mL concentration in dose dependent manner[22].

Allium sativum

A. sativum (garlic) represent the *Amaryllidaceae* family. *A.sativum* bulb is used in the conditions like hyperlipidaemia and heart related diseases. It blocks thromboxane formation and counteracts with thrombocytes functions and also reduces platelet aggregation. In addition, the plant has fewer complications like postoperative bleeding and epidural hematoma. Scientific studies, advises the avoidance of the supplements of garlic preparation with warfarin therapy, as this combination will causes serious complications[23]. Anti-coagulant property of garlic extract was achieved by preventing or prolonging the time required for clot formation thereby alters the coagulation mechanism[24]. Ethanolic extract at 10 µg/mL dose displayed the potential fibrinolytic activity and time factors exposure was influenced[25].

Terminalia bellerica

It belongs to the *Combretaceae* family. It is one of the compositions of well-established preparation known as "Triphala" which is being using in a wide variety of pharmacological and physiological actions like in hair care, as a laxative, leucorrhoea, liver diseases and gastrointestinal

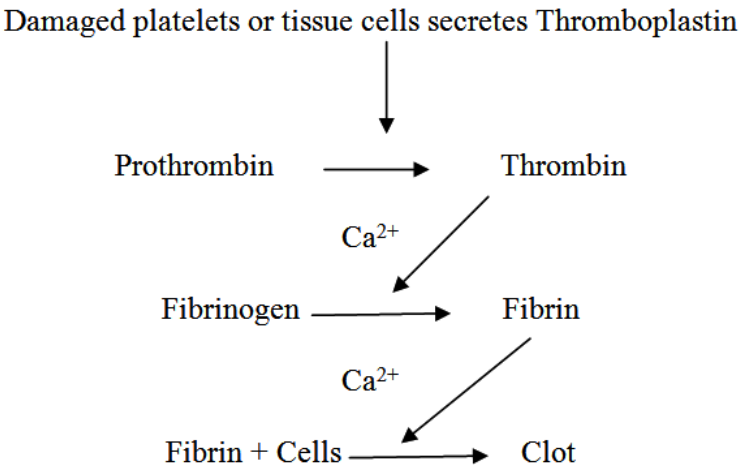

Fig. 1. Coagulation process

Table 1. List of medicinal plants having active constituents responsible for thrombolytic activity

No	Plant name	Family	Active constituents	Reference
1	*Cyamopsistetragonoloba*	*Fabaceae,*	Gum residues, saponins and polyphenol	14
2	*Pulmonaria officinalis*	*Boraginaceae*	Flavonoids, vitamins like C and B, Al^{+}, Mn^{+}, nickel and Fe^{+2}	15
3	*Petroselinumcrispum*	*Apiaceae*	Flavonoids, dihydroxycoumarin, apiin, and apigenin	15
4	*Tridax procumbens* L.	*Asteraceae*	Taraxasterylacetate, lupeol, oleonic acids.	15
5	*Paeonia anomala*	*Paeoniaceae*	Acid like ellagic, Acetophenone, *t*-butylhydroperoxide, methyl and ethyl gallate, quercetin, fischeroside B	15
6	*Ferula communis*L.	*Apiaceae*	Ferulenol, fertdin,anisate, oxajaeskeanadioyl and costic acid	15
7	*Panax notoginseng*	*Araliaceae*	Ginsenoside Rh4, Rh1, notoginsenoside S, notoginsenoside T ginsenoside Re	15
8	*Cinnamomum cassia*	*Lauraceae.*	Derivatives of coumarin, cinnamyl acetate, hydroxyl cinnamaldehyde, and *N*-acetyl-l-cysteine	16
9	*Filipendulaulmaria*	*Rosaceae*	Flavonoids, tannins and vitamins, tannins, polyphenol, ellagitannins, phenolic acids, methyl gallate	17

Table 2. Plants proved as thrombolytic agents and their mode of action

Plant name	Family	Part used	Functions	Mode of action	Reference
Cyamopsis tetragonoloba	*Fabaceae,*	Seeds	Thrombolytics	Increases prothrombin time	62
Panax notoginseng	*Araliaceae*	Roots	Thrombolytics	Increases prothrombin time	63
*Ferula communis*L.	*Apiaceae*	Leaves	Thrombolytics	Increasing the clotting time	64
Paeonia anomala	*Paeoniaceae*	Fruits and roots	Anti coagulants	Antithrombotic and thrombolytic	65
Filipendula ulmaria	*Rosaceae*	Flowers	Thrombolytics	Antithrombotic and thrombolytic	66
Pulmonaria officinalis	*Boraginaceae*	Aerial parts	Anticoagulants	Antithrombotic and thrombolytic	67
Cinnamomum cassia	*Lauraceae.*	Bark	Thrombolytics	Antithrombotic and thrombolytic	68
Petroselinum crispum	*Apiaceae*	Aerial parts	Thrombolytics	Antithrombotic and thrombolytic	69
Careya arborea	*Lecythidaceae*	Bark	Thrombolytic	Prolongs the thrombin time by decreasing the clotting factors	70, 71
Terminalia bellerica	*Combretaceae*	Fruit	Thrombolytic	Antithrombotic and thrombolytic	72
Allium cepa	*Amaryllidaceae*	Bulb	Thrombolytic	Prolongs prothrombin time	73
Molineria recurpata	*Hypoxidaceae*	Leaves	Antithrombotic	Increases the prothrombin time	74
Curcuma longa	*Zingiberaceae*	Root and rhizome	Antithrombotic	Suppresses the ability of platelet adhesion	75

disorders. Fruits are being reported as anticoagulant and thrombolytic activity[26]. In addition it also acts as anthelmintic[27, 28] antidepressants[29], antianxiety[30] and antiplasmodialactivity[31]. *In vitro* thrombolytic activity of methanolic leaf extract showed moderate amount of (32.95%) of clot lysis when compared with standard streptokinase.

Typha angustifolia

T. angustifolia belongs to the family of *Typhaceae* and it is commonly known as elephant grass or cattail. Various parts of the plant are edible; including dormant sprouts on the roots and bases of the leaves, ripen pollens, the stem, and the starchy roots[32, 33]. The medicinal use of the plant includes treatment of renal calculi[34], uncontrolled bleeding in uterus, abscesses, infection with tapeworm, diarrohea, and dysentery. Modern research on pollen grains of angustifolia showed that presence of sterols, terpinoids, flavonoids and glycosides[35] and these secondary active metabolites possess various pharmacological activities like immune suppression[36], antiplatelet aggregation[37], anti microbial[38] and lipid lowering property[39]. *In vitro* fibrinolytic activity of methanolic leaf extract *T. angustifolia* showed 58±2.32 % of clot lysis [40].

Zingiber officinale

Z. officinale belongs to the family of *Zingiberaceae.* Roots used in the treatment of motion sickness disorder and rheumatism. It inhibits the thromboxane synthetase and thereby reduces the platelets aggregation. Excess intake of ginger in the diet may cause bleeding with warfarin[41]. The methanolic extracts of *Z. officinale* showed moderate thrombolytic activity (30.13% clot lysis) at test concentration of 10 mg/mL [42].

Salvia miltiorrhiza

This *S. miltiorrhiza* belongs to the *Lamiaceae* family. Rhizomes possess variouspharmacological and physiological actions. It shows beneficial pharmacological uses in the various circulatory disorders. The complications are gastric cancer, bleeding and pleural hemorrhage with warfarin. Previous studies suggested that blood clotting mechanism is altered by various factors like enhancement of fibrinolytic efficacy, promotion of antithrombin III like action and inhibition of platelet aggregation[43]. A purified extract of this plant containing its major constituents, cryptotanshinone, tanshinone I, and tanshinone IIA can protect against liver toxicity *in vivo* and *in vitro*[44]. *S. Miltiorrhiza* was shown to possess unique efficacy in treating thromboangiitis obliterans[45].

***Wedelia trilobata* L.**

Is a flowering plant belongs to the family of *Asteraceae*. It is used to treat hepatitis infections and to reduce the menstrual pain and unspecified female complaints[46].The plant has various medicinal activities, such as antidiabetic, antimicrobial, antitumor, liver protectant, and CNS depressant[47].The reports indicated the maximum blood clot lysis (57.89%) effects of leaf extracts of *W. trilobata* [48].

Triclisia dictyophylla

T. dictyophylla belongs to the family of *Menispermaceae*. The aqueous root extract of *T. dictyophylla* showed anti-platelet activity. The aqueous root extract of *T. dictyophylla* prolonged the *in vitro* whole human blood clotting time at concentrations of 50 and 100 mg/mL, complete anticoagulation effect was achieved [49, 50].

Aporosa wallichii Hook. f

This plant belongs to Th *Phyllanthaceae* family. This study showed that this plant has an acceptable level of the free radical scavenging property and thrombolytic property along with cytotoxic activity. In a thrombolytic model the methanolic extract exhibited 24.5% of clot lysis at 100 µL[51].

Melissa officinalis

It is belongs to the family of *Lamiacea*e is a perennial aromatic herb, it is generally applied for the preparations of food and cosmetics related products. An *in vitro* thrombolytic model of methanolic extracts of leaves and stem showed 25.87±1.089, 41.482 ± 0.948 % clot lysis, respectively [52].

Enhydra fluctuans* Lour *(Leaves)

E. fluctuans Lour belongs to the family *Asteraceae* is a small genus of marsh herb, available in tropical and subtropical regions. Leaves of the plant are used as a laxative and also used in the treatment of the skin and nervous system. The phytochemical analysis displayed that the crude extract contains tannin, alkaloid, and saponins; it could be predicted that these phytochemicals may be responsible for its clot lysis activity. An *in vitro* thrombolytic model of methanolic extract showed 31.25% of clot lysis [53].

Luffa cylindrica linn

L. cylindrica Linn belongs to the family of *Cucurbitaceae*. Originally the literature report revealed the folk claims of *L. cylindrica*. The plant is having a potent thrombolytic property which is beneficial in treating heart attacks and pulmonary embolism and atherothrombosis. In an *in vitro* study the ethanolic extract showed 45% of clot lysis[54].

Angelica sinensis

A. sinensis is herbal plant belongs to family *Apiaceae*. Primarily it is used in menses in females. The plant also exhibits a fibrinolytic activity by blocking the activation and aggregation of platelets.A study on rabbits revealed that prothrombin time was increased after its consumption[55].

Wedelia chinensis (Osbeck) Merr

The family of *W. chinensis (Osbeck) Merr* is *Asteraceae*. It is also known as ChineseWedelia and herb of sunflower. Fruits, stems and leaves possess medicinal importance [56]. The plant leaves possess pharmacological activities in the conditions of kidney dysfunction, cold, wounds, and amenorrhea. The other medicinal uses are treatment of wounds, seminal weakness, astringent, bitter, acrid, anti-inflammatory and cardio protection and hepatitis[57]. The methanolic leaf extract of *W.chinensis (osbeck) Merr* showed significant clot lysis 24.48 % at 100 µg/mL concentration with reference to streptokinase as standard [58].

Vigna unguiculata Linn (seed)

V. unguiculata Linn is a herbal plant of *Fabaceae* family. It possesses a wide variety of physiological and pharmacological properties. Few reports suggest that methanolic extract of *V. unguiculata Linn* (seed) showed significant thrombolytic activity with 40.33% of clot lysis at 10 mg/mL concentration[59].

Punica granatum

Punica granatum belongs to the family of *Lythraceae*. Pomegranate fruits has been considered as a healing food owing to its vast advantageous biological effects against several diseases since ancient times. It is widely used in the preparation of ayurvedic blood tonic [60]. Ethanolic and aqueous extract of fruit and peel of plant was used for *in vitro* thrombolytic activity by using streptokinase as standard. Ethanolic extract of fruit and peel showed moderate amount of *in vitro* clot lysis (59%) at 100 µg/mL concentration.

Murraya koenigii

It belongs to the family of *Rutaceae.* Leaves and roots are medicinally useful. Leaves possess promising thrombolytic property. In an *in vitro* thrombolytic model of an aqueous extract exhibited the remarkable clot lysis (22.14 %) effect at a concentration of 10 mg/mL[61].

On extensive literature search, the reports suggest majorly the plant constituents have possessed their antithrombotic properties through prolonging the prothrombin time or by preventing the platelet aggregations. As per literature information's few other antithrombotic plant sources with their probable mode of actions are depicted in the Table 2.

CONCLUSION

This review helps to understand the effect of various medicinal plants having thrombolytic activity. The accessibility of treating the thrombotic diseases with herbal medicine or plant derived compounds and not necessity of laborious pharmaceuticals synthesis seems that the approach is highly attractive. As per the presented data, many literature studies offered the thrombolytic importance of crude and/or solvent extracts of the various plants parts. Though the thrombolytic property was proved in these investigations, further much attention and an extensive study is required in exploring the phytochemical and pharmacological profile of the active principles. It will be helpful to the pharmacologists, scientists and health professionals to develop new safer pharmaceutical products with thrombolytic properties.

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Conflict of interest

The authors declare that there is no conflict of interest.

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