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OVERVIEW ON MEDICINAL PLANTS IN THE TREATMENT OF CARDIO VASCULAR DISEASES ILLNESS

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ABSTRACT

Hemostasis is retarding or stopping the flow of blood within a blood vessel which leads to thrombosis. Thrombosis occurs when there is damage in blood vessels due to an internal or external injury. Complications depend upon the thrombosis is located. Heart attack, stroke, and some breathing problems are some of the severe consequences. Anticoagulants such as streptokinase, Urokinase, t-PA are introduced to reduce or break the clot. There is considerable interest in the role of natural products and their bioactive components in preventing and treating thrombosis-related disorders. This paper describes the mechanism of thrombosis formation, thrombolysis, and case studies.

Keywords: CVD; Thrombolysis; Antithrombolytics; Anticoagulant; Embolism

INTRODUCTION

Cardiovascular illness is still the Grim Reaper's primary source of revenue. Cardiovascular diseases (CVD) and associated diseases are the leading cause of mortality in the world's population **[1]**. India and China account for more CVD instances than the rest of the developing world combined. Premature onset, high mortality, increased burden, and geographical variability are all unique features of CVD in poor and medium-income nations like India **[2]**. According to the American Heart Association's 2015 update on cardiovascular disease, 40.5percent of males and 35.5 percent of females are affected **[3]**. Hemostasis is a process that protects the integrity of the circulatory system after injury. It's a

complex, closely controlled process that has yet to be fully comprehended. Under normal circumstances, vessel wall damage triggers a cascade of coordinated actions to seal the breach caused by the lesion. Clotting is caused by these events, which necessitate platelet recruitment and activation and the generation of thrombin and fibrin **[4]**. Haemostasis, on the other hand, is a physiological response to stop bleeding. Thrombosis is a medical word describing the abnormal increase of a thrombus (fibrin). When an embolus forms in the bloodstream, it is known as embolization because it decreases or stops blood flow to a tissue, with profound effects **[5]**.

Coronary artery diseases such as venous thromboembolism, Deep Vein Thrombosis (DVT), cerebrovascular accident (CVA), the myocardial infarction are caused by thrombosis, which is a fundamental pathophysiological mechanism **[6]**. Thrombolytic medicines such astreptokinase, tissue plasminogen activators [tPA], and urokinase [uPA], among others, are essential in treating cerebral venous sinus thrombolysis. Only three agents have been granted permission to work in the USA. Streptokinase, t-PA, uPA are some of the enzymes that may be found in the body. In the United States, urokinase is not currently available for usage **[7]**. Tenecteplase and reteplase are two of the most commonly utilized medicines because they provide enough benefit with a concise [2 hours] infusion time. With careful evaluation of contraction, risk formation of embolus is crucial for deciding which cases are best suitable for fibrinolytic activity **[8]**.

As a result, any thrombolytic drug that has both antioxidant and thrombolytic properties would be of interest. Oral anticoagulants are the most promising since they are easy to use and may be administered in set dosages. It improves the uptake of anticoagulant prophylaxis in stroke patients, lowering mortality and disability. Herbal remedies have been resurrected thanks to developments in phytochemistry and the detection of plant components helpful in healing specific ailments **[9]**. Antioxidants are essential nutrients that protect the body from the harm caused by oxidative stress produced by free radicals. Certain artificial antioxidants, such as butylated hydroxy methoxy benzene and butyl hydroxy methyl benzene toluene, phenylmethane, must be substituted by neutral antioxidants, mostly plant phenolics found in fruits, vegetables, nuts, seeds, leaves, roots, and bark **[10]**.

Plant-derived compounds play a fundamental role; about 79 percent of medicinal plants have cytotoxicity, whereas 75 percent of non-medicinal plants have

bioactivity. In large dosages, bioactive substances are nearly always hazardous **[11]**. Toxicology is just pharmacology at lower dosages, while pharmacology is simply toxicology at larger ones. The bio function and health-promoting characteristics of phenolic chemicals, which are extensively dispersed in plants, have piqued scientific attention **[12]**. Fruits are a good source of natural phenolic compounds. Antioxidants are used as food additives to keep lipids from oxidizing. The phenolic composition and antioxidant activity of several fruits have been studied **[13]**.

REVIEW OF LITERATURE

The following headings are used to discuss the review of literature related to the current study.

Components of the Blood

- Clot — Characteristics and Methods of Clot Formation
- The Triad of Virchow
- A clot's characteristics
- Thrombosis Mechanism
- Fibrinolysis and thrombolysis
- Thrombolytic
- Antioxidants

Components of Blood

William Harvey created the phrase "Blood." Blood makes up around 8% of an adult's total weight, has a mean temperature of 380°C, and has a pH of 7.35–7.45, making it somewhat essential. The viscosity of whole blood is approximately 4.5–5.5 times that of water, indicating that it is more resistive to flow than water. Blood viscosity is vital for its operation because if blood flows too quickly or with too much resistance, it puts a burden on the heart and can cause serious cardiovascular problems. Transport, protection, and regulation are the three primary roles of blood. Blood is a connective tissue that is made up of two primary components

a. Plasma is an extracellular fluid that is transparent.
b. Forming elements are blood cells and platelets.

a. The plasma

Proteins, enzymes, nutrition, wastes, hormones, and gases are all present.

The following are the components' specific compositions and functions

Proteins: By weight, proteins are the most common substances in plasma, and they have a number of activities in the body, including clotting, defence, and transport. There are three main categories to consider -albumins, globulins, and fibrinogens are examples of plasma proteins.

- **Amino acids** When tissue proteins are broken down or digested, they produce these substances.

- **Nitrogenous waste** These are dangerous by-products of chemical breakdown in the body, and they are usually expelled by the kidneys after being cleared from the bloodstream.
- **Nutrients** Those absorbed through the digestive system travel through the blood plasma. Glucose, amino acids, lipids, cholesterol, vitamins, and minerals are among them.
- **Gases** Plasma transports some oxygen and carbon dioxide. There is also a significant amount of dissolved nitrogen in plasma.

b. Formed Elements

Formed elements are encased in a plasma membrane and have a defined structure and shape. Except for platelets, which are small fragments of bone marrow cells, all produced constituents are cells.

CLOT - COAGULATION CHARACTERISTICS AND FORMATION

The Virchow's Triad:

Huang, a Chinese physician, described pathologic haemostasis as early as 2650 BC. However, the German pathologist Rudolph Virchow's contribution to the triad of conditions led to the formation of thrombosis. The three elements, dubbed Virchow's triad, were anomalies of the blood vessel wall, blood components, and blood flow.

Even after 150 years, the most significant general account of the participants in the pathophysiology of thrombosis remains Virchow's triad. Endothelium and endocardium abnormalities ("abnormalities of vessel wall"); The coagulative and fibrinolytic processes, as well as platelets ("abnormalities in blood constituents"); and stenotic areas, big vessels burdened by uneven atheroma, and haemorheology and turbulence at bifurcations ("abnormalities in blood flow") are all accounted for in a recent update of the three factors **[14]**.

Clots Characteristics

The primary clotting process in arteries is platelets, which stick to the injured blood vessel's wall and close the bleeding site. A thrombus rich in platelets is known as a "white clot" because it looks like a white clump. Antiplatelet drugs are commonly used to treat thrombi that form in the arteries.

The thrombin system is the principal clotting mechanism in veins. This system is made up of many proteins that, once activated, initiate a series of chemical processes that result in the formation of fibrin. Fibrin strands form a web that traps red blood cells and platelets, resulting in a red clot. Anticoagulants, which function by interfering with various parts of the coagulation cascade, are used to prevent and cure thrombi in veins.

THROMBOSIS MECHANISM

The three principal functions of active blood constituents are the creation of fibrin coagulum by the coagulation cascade, platelet adhesion and aggregation, and fibrinolysis. A thrombotic event can be triggered by damage to the blood vessel and endothelial lining **[15]**. When a ship is wounded, a series of intertwined interactions between the injured vessel, platelets, and coagulation factors occurs, leading to blood vessel constriction and a platelet and fibrin coagulum formation. Between blood and the blood artery, endothelial cells create a purely passive layer **[16]**. Although it is a passive layer, it is critical for haemostasis, Migration of tissue fluid and WBC into the Arterial wall, as well as vascular tone regulation. The loss of thrombomodulin and a compromised endothelium that generates excellent quantities of thrombin von willebrand factor (VWF) induce thrombosis **[17]**.

COAGULATION CASCADE

The clotting cascade is a series of events that occur in opposite directions and lead to the formation of a fibrin mesh clot:

The intrinsic clotting pathway is activated when blood comes into touch with a damaged blood vessel lining. The extrinsic clotting pathway is activated when damaged vascular tissue produces tissue factors, encouraging platelet adhesion, activation, and aggregation. Two paths eventually come together at a point known as the ultimate familiar road. Factor X is activated at this stage, causing prothrombin to be converted to thrombin, which subsequently causes fibrinogen to be converted to fibrin. Heart attacks, strokes, severe leg pain, and difficulties walking can all be caused by a thrombus that forms in the aorta.

Blood clots in the capacitance vessels cause deep vein thrombosis in the bony pelvis, lower limb, and basilica or cephalic capacitance vessels. When these Deep Vein Blood clots break off and travel via the bloodstream to the heart and subsequently to the blood vessels in the lungs, an acute pulmonary embolism occurs **[18]**.

THROMBOSIS AND FIBRINOLYSIS BASIC CONCEPTS

Fibrinolysis is the process of a plasmin cleaving fibrin at specified sites into smaller water-soluble components. The thrombi contain inactive plasminogen, and plasminogen activators, such as t-PA, must enter the clot to initiate fibrinolysis. Because of its size, tPA can diffuse freely. However, this is hampered by the enzyme's increased affinity for fibrin. The tPA from the bloodstream binds to the fibrin surface, raising its concentration by many folds and triggering fibrinolysis. TPA activates plasminogen in the presence of fibrin. The fibrin is digested by the produced plasmin, which exposes additional binding sites on

the fibrin, resulting in the build-up of plasminogen molecules on the clot's surface **[19]**.

The plasmin cleaves the fibres crosswise, forming thick bundles. In these conditions, fibrinolysis occurs in the thin outer layer of fibrin, followed by layer-by-layer breakdown. The fibrin network topology, the size of the pores, and other fibrin–occluded components that can interact with the fibrinolytic enzymes all influence the pace of fibrinolysis. Blood flow rate is another crucial component that impacts the diffusion of fibrinolytic enzymes and the elimination of breakdown products from the clot's surface **[20]**.

CLOT FORMATION AND LYSIS IN BLOOD VESSELS

Both coagulation and fibrinolysis are accurately regulated under physiological settings by the measurable participation of substrates, activators, inhibitors, cofactors, and receptors. Thanks to molecular connections between these systems, localized, timely clearance of on-going or acutely generated fibrin deposits is possible. Blood fluidity is ensured by these coordinated chemical activities, which also limit blood loss **[21]**.

CONSTITUENTS OF THROMBOLYTIC SYSTEM

- Plasminogen - Zymogen (N-terminal glutamic acid and lysine variants)
- Tissue plasminogen activator - Plasminogen activators (tPA)

Inhibitors

- Inhibitors of plasmin
- 2-plasmin inhibitors (2-PI) and 2-macroglobulin (2-MG) are two proteins that inhibit plasmin.

Nexin of the protease

- Inhibitors of plasminogen activator
- Inhibitors of plasminogen activator-1 and -2 (PAI-1, PAI-2)
- Protease nexin inhibitor - C1-esterase inhibitor

The attenuator is a fibrinolysis inhibitor that is activated by thrombin (TAFI)

The most important receptors are

- ✓ Initiating: Urokinase receptor Annexin 2 M2 integrin (uPAR)
- ✓ Accessibility: Mannose receptor LRP (low-density lipoprotein receptor-related protein)

THROMBOLYTICS

Thrombolytic compounds were initially utilized for myocardial infarction in 1959 to establish patterns of efficacy and safety for thrombolytic drugs and determine the true impact of early thrombolytic therapy on mortality **[22]**.

i. Clot busters (thrombolytic agents) such as streptokinase may be used to treat arterial clots.

ii. Clopidogrel and aspirin (oral antiplatelet agents)

iii. Antiplatelet drugs are given intravenously

iv. Tissue plasminogen activators (a blood thinner and anticoagulant)

v. Heparin (a blood thinner and anticoagulant)

Special interventional catheters, in addition to drugs, may be utilized to remove or compress these artery blockages.

DETERMINATION OF ANTIOXIDANT

Antioxidants are essential for human health, and supplementation is indicated to protect cells from the de tolerance effect of high ROS levels. Plant cells are covered by an antioxidant system that includes both non-enzymatic and enzymatic antioxidants.

ENZYMIC OXIDANTS

Antioxidant enzyme activities such as superoxide dismutase, Peroxidase, and catalase are vital in cellular defence strategies against oxidative stress **[23]**.

a. CAT stands for catalase.
b. POD stands for Peroxidase
c. PPO stands for polyphenol oxidase.
d. GPX stands for glutathione peroxidase

NON ENZYMIC ANTIOXIDANTS

Both enzymic and non-enzymic strategies are used in antioxidant defence. Vitamin A, C, E, glutathione, coenzyme Q10, various bioflavonoids, and antioxidant minerals [Cu, Zn, Mg,Se] are all examples of non-enzymic antioxidants **[24]**.

Table 1: List of plant parts showing thrombolytic activity

S. No.	Plant name	Family	Plant part
1	*Justica gendarussa* *Hydnocarpus kurzii* *Sansevieria trifasciata* *Mesua nagassarium*	Acanthaceae Achariaceae Agavaceae Clusiaceae	Leaf Extract [25].
2	*Cassia senna leaves*	Fabaceae	Leaf Extract [26].
3	*Andrographis paniculate*	Acanthaceae	Aerial Parts [27].
4.	*Spinacia oleracea*	Amaranthaceae	Leaf Extract [28].
5.	*Lanneacoromandelica*	Anacardiaceae	Bark and Leaves [29].
6.	*Gymnema Sylvestre*	Apocynaceae	Stem,Leaves,Roots [30].
7.	*Artemisia dracunculus*	Asteraceae	Leaf Extract [31].
8.	*Crassocephalum crepidioides*	Asteraceae	Leaf Extract [32].
9.	*Eclipta alba Hassk* *Emilia sonchifolia* *Spilanthes paniculata Wall.*	Asteraceae Asteracea Asteraceae	Leaf Extract [33].
10.	*Tridax procumbens* *Vernonia cinerea*	Asteraceae Asteraceae	Leaf Extract [34].
11.	*Brassica oleracea*	Brassicaceae	Flowers [35].
12.	*Jatropha gosipiifolia L*	Euphorbiaceae	Leaf Extract [36].
13.	*Sida acuta.*	Malvaceae	Leaves [37].
14.	*Punica granatum*	Punicaceae	Fruit and Peel [38].
15.	*Citrus assamensis*	Rutaceae	Leaves [39].
16.	*Citrus hystrix*	Rutaceae	Leaves [40].
17.	*Murraya koenigii*	Rutaceae	Leaf Extract [41].
18.	*Cestrum nocturnum L*	Solanaceae	Leaves [42].
19.	*Typha angustifolia*	Typhaceae	Plant Fiber [43].
20.	*Typha angustifolia*	Typhaceae	Leaves [44].

CONCLUSION

Thrombosis paves way for the most common disease such as myocardial infraction and stroke. However, considerable amount of studies have been done for understanding pathological and pharmacological functions. Natural products have shown attributable operations on thrombotic diseases in both experimental and clinical stages, giving a useful adjunct to the current pharmacological treatment and thrombotic disease. Advances in the knowledge of natural products will provide awareness to promote human health.

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Conflict of interest

Authors declare no conflicting interest

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