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AN OVERVIEW: NATURAL HERBS AS AN ATHERO-THROMBOLYTICS

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ABSTRACT
Atherosclerosis is the preliminary lipid disorder in which arterial blood vessels become hard and thicken due to multiple plaque formation within blood vessels. These soft multiple plaques suddenly ruptures out, leading to the formation of thrombus that rapidly slow down or stop the blood flow and obstruct the oxygen supply to the targeted tissues. These free floating thrombi can be circulated anywhere in the cardiovascular system including lung, brain, heart or deep veins of leg and leads to serious complications as atherothrombotic diseases (myocardial or cerebral infarction), coronary artery diseases (CAD), peripheral vascular diseases, pulmonary thrombosis, cerebro-vascular disease and heart failure. Pulmonary thrombosis is a inexorable condition commonly appear in Covid-19pneumonia patients due to fully or partially block blood supply to artery of lung and is characterized by inexplicable breathing difficulties, hemoptysis and chest pain. Similarly cardiac arrhythmias is on rise worldwide and is leading cause of morbidity, mortality and disabilities, is associated with shortness of breath, synapse, angina or finally even death. A Cardio vascular disease (CVD) is the highly implacable disease and often impacting most productive and precious years of individuals throughout the world and hence requires very accurate diagnosis and treatment. Commonly used conventional antithrombotic drugs suchas t-PA, Urokinase, Streptokinase, Ateplase, Anisteplase and so forth, play deciding role in CVD management and other related disorders. However, available thrombolytics still have noticeable shortcomings including bleeding, lysis of hemolytic plug, antigenicity, defective coagulation, gastrointestinal and cerebral hemorrhage. In view of the inadequacies of conventional thrombolytics, efforts have made to understand significant value of herbal drugs for treating coronary arterial disease and related problems. As diabetes mellitus, hypertension, smoking cigarettes, dislipidemia, dyspnea and pneumonia are the prime causes of increasing severity of atherosclerosis and Covid-19 diseases, includes aggregation of platelets which eventually results in thrombus formation and hypoxia. Moreover, covid- 19 death rate is more common among people with such diseases and disorders. Hence food and dietary herbals with antithrombotic characteristics may be used to improve such diseases which ultimately maintain the health and regain healthy state of mind. The present review is focused on the availability of medicinal plants that have antithrombotic, anti- platelets and fibrinolytic potential, which can be explored for the effective treatment of thrombotic diseases, lifestyle disorders and future pandemics like Covid-19.

KEYWORDS: Atherosclerosis, Blood thrombus, Natural herbs.

1. INTRODUCTION

Nature has contrived a system, the body uses to maintain and restore itself, when the vascular system is injured, body responds very quickly to cease the bleeding and repair the damage. Platelets and certain proteins in plasma work together to stop the bleeding by initiating a clot formation over the injury.[1] The process of coagulation occurs through the cascade of several sequential reactions that forms enzyme thrombin, which in turn transform soluble fibrinogen into insoluble fibrin.[2] Thrombin activate platelets in order to enhance platelet aggregation thereby initiate the process of coagulation by converting the blood prothrombin in to thrombin to form a clot.[3] The activation of the coagulation cascade and platelets is usually made possible by atherosclerotic plaque rupture or cardio embolic thrombosis. In the cascade, free floating inactive coagulation factor zymogens converted into an activated factor by interaction with atherosclerotic plaque. Further activated platelets induce the interaction within activated factors to assist in the generation of thrombin by transformation of the soluble protein fibrinogen to insoluble fibrin thus forming a blood clot.[4] Likewise addition to the zymogens, protein cofactors and surface membrane of phospholipids and calcium ion take part in development of the fibrin clot.[5] Thrombus is established

by attaching/sticking of the damaged regions of the endothelial cell surface where platelets play a significant role in the formation process. The process of thrombosis get started when the activated platelets forms platelets bonding and further binds to leucocytes and carry them into a complex process of plague formation.[6] A large number of factors are responsible for the initial stage of arterial thrombosis such as blood vessel injury, platelets adhesion and aggregation which is followed by blood obstruction / blockage that habitually forms vein thrombus.[7,8] Occlusion of each of two, arterial supply and venous drainage bring about ischemic necrosis of the area which leads to infarction. Additionally formed thrombus may play vital role in the development of atherosclerotic plaques. Atherosclerotic and its thrombotic issue are the paramount cause of morbidity mortality and disabilities in the cardiovascular diseases.[9] Elevated level of serum lipid in diabetes mellitus represents a major risk factor for coronary heart diseases.[10] Thrombus formed within blood vessel when it breaks away from the vessel wall and freely go round may becomes fatal if it blocks the oxygen supply to vital tissues. Blood thrombus builds inarterial system can leads to stroke, myocardial infarction, pulmonary embolism, angina pectoris while thrombus in venous system gives rise to renal vein thrombosis, deep vein thrombosis, portal vein thrombosis.[11] In addition, blood clots may results into ischemic stroke and cardiac ischemia, which is characterized by shortness of breath, syncope, cardiac arrhythmias or even death.[12] Cardiovascular diseases are reported to be a leading cause of 17.6 million people death and it is a prediction that by 2030 more than 23 million people will die per year.[13]

1.1 Current scenario of Atherosclerosis

Atherosclerosis is a typically established disease in most of the principal arteries, yet it is a asymptomatic and not easily detected by symptomatic test during adult life, however it start early in the childhood.[14] Hyperlipidemia is the most commonly prevailing indicator for vulnerability to atherosclerotic heart disease. It is marked by elevated lipid and lipoproteins levels in the blood. The frequency indication of atherosclerosis around the world has experienced an exponential increase in coronary heart disease. The authentication mark for atherosclerosis is the atherosclerotic plaque which usually consists of lipids, inflammatory cells, smooth muscle cells, connective tissues, thrombi and calcium deposits. Athero- sclerotic plaque are possibly stable or unstable in nature. The unstable plaques are susceptible to spontaneous degradation, fissure or rupture leading to formation of acute thrombosis.[15] A key step in the pathogenesis of atherosclerosis is accepted to be oxidative modification of low density lipids.[15] Atherosclerosis normally initiated from low density lipoproteins molecules becoming oxidized by reactive oxygen species (ROS). The cholesterol plaques bring about the muscles cells to enlarge and give rise to hard cover over the affected part, these results to narrowing of arterial vessel wall which reduces flow of blood and eventually increase in blood pressure.[17] The current essential and auxiliary prevention strategies for atherosclerosis is to emphasize the control of atherosclerotic hazardous components including cigarette smoking, a diet of high in saturated fats, hypertension, hypercholesterolemia, diabetes mellitus, weight and homocysteine.[18]

2. Conventional antithrombotic and Anticoagulants

The most frequently used thrombolytic drugs are Ateplase, Anistreplase, Streptokinase, Urokinase and tissue plasminogen activator (t-PA).[19] They solubilize the blood clots in vascular bed by activating plasminogen into cleaved product known as plasmin. Plasmin is a proteolytic enzyme formed in blood, capable of destroying blood clots by breaking cross linking in between fibrin molecules that provide strong structural integrity in clots.[20] A 1:1 stoichiometric complex of streptokinase with plasminogen is effective in converting additional plasminogen to *plasmin*.[20]

2.1 Categories of antithrombotic agents

Antithrombotic agents mainly consist of anti-platelets, anticoagulants and fibrinolytics drugs. These are further classified as[21]

1. Drugs which stop platelet adhesion or aggregation
2. Drugs which prevent fibrin formation
3. Drug which causes fibrin degradation

Thrombolytic (Enzymes / platelets) are additionally grouped into two class based on theirworking mechanism[22, 23]

1. Enzyme which degrades fibrin through activation of plasminogen: t-PA, urokinase,strepto-kinase
2. Proteins which directly degrades fibrin: Plasmin

2.2 Currently used Thrombolytic drugs[24]

Sr. No.	Thrombolyticdrugs	Thrombolytic drugs side effects
01	Aspirin	Bleeding, GIT-Nausea, stomach pain, heart burn, constipation,Reye's syndrome
02	Coumarins	Skin necrosis, causes spontaneous abortion embryoabnormalities.
03	Heparin	Major bleeding, heparin induced thrombocytopenia (HIT),paradoxical thrombosis.
04	Streptokinase	Severe bleeding, decreased RBC and platelets
05	Urokinase	Severe bleeding, heart attack, pulmonary embolism, decreasedRBC and platelets, excess sweating.
06	Warfarin	Bleeding during pregnancy, hypersensitivity, loss ofconsciousness and coma, purple toe syndrome, warfarin necrosis, osteoporosis.

2.3 Methods for thrombus dissolution.

Blocked arteries and blood clots can induce heart attacks and strokes. So their therapy may be similar in several aspects. In both the situations, a physician may prescribe a clot busting drugs in the hospital. Specifically for ischemic strokes, therapies preferred remains very expensive and time limiting.

1. Thrombolytic therapy [25]: The therapy is adapted for breaking up dangerous clot in blood vessels. The clot busting agents must be given within three hours after the start of stroke symptoms.

Therapy cost: - Intravenous thrombolytic therapy (IVT) cost around Rs. 25,000 - 40,000.

2. Mechanical thrombectomy[26]: This is a faster technique than thrombolytic therapy. It takes around 30 minutes for the complete treatment, where small mechanical device is to be attached at the catheter site.

Therapy cost: It is highly upgraded technique. Private hospitals providing such kind of intervention charge about Rs. 10 lacs and above.

3. Carotid endarterectomy[27]: It includes surgery that unlock the insides of narrowed neck carotid artery by removing the thromboembolic debris, thereby reduces recurrence. Therapy cost: The total average expenses for therapy is up to USD 15000.

2.4 Contraindications for thrombolytic therapy

Thrombolytic drugs gives rise to untoward effects or harm to patient thereby, accepted treatment for clot dissolution would be withhold or it is prohibited.

Absolute contraindications: Events that causes a life threatening situations like vascular lesion, severe uncontrolled hypertension, brain tumor, bleeding and ischemic stroke in twoor three month.

Absolute contraindications: Events initiated when the two drugs or procedure followed together, such as active peptic ulcer, ischemic stroke three month prior, current use of anticoagulant drugs, pregnancy and internal bleeding are the inflexible condition which may be developed.[28]

2.5 Challenges in Therapy

Implementation of Thrombolytic therapy unit in India is a great task because of following reasons[29]

a) Inadequate number of skilled and trained staff.
b) Lack of awareness and proper infrastructure, limited access to tertiary stroke care, scarceuse of t-PA.
c) Poor affordability contributes inadequate management of stroke.

2.6 Shortcomings of anti-thrombotic agent

However all available antithrombotic drugs have quite remarkable shortcomings involving need of large doses, restricted fibrin specificity, bleeding tendency, gastrointestinal and cerebral hemorrhages and severe anaphylactic reactions.[30] Now a days, standard practice in primary care to prevent adverse effects of coronary artery diseases is a combination of aspirin and clopidogrel which inhibits cyclo-oxygenase and antagonizes P2Y12, respectively. In spite of their significant effectiveness, there are cases of recurrent cardiovascular diseases with those who are seeking antiplatelet drugs. GIT bleeding and gastric ulcers are the common adverse effects observed during therapy.[31] Certain anti-platelets drugs holdback the platelet aggregation by discontinuing the formation of ADP and thromboxane, participating in platelet aggregation process. Despite their efficacy remains unmattered, the deleterious life threatening side effects of such drugs have been documented.[32,33] Tissue plasminogen activator is a serine protease enzyme involved in the breakdown of blood clot. Although intravenous thrombolysis with t-PA (IV t-PA) is the quality of care in the treatment of acute ischemic stroke, but its application in pregnancy is not clearly specified. Even though t-PA does not travel across the placenta, still there are many possible potential complications in pregnancy which can restrict its utility. Uterine bleeding can take place leading to premature labor and placental abruption.[34] Streptokinase is a first generation antithrombotic drug, isolated and obtained from purified Streptococci bacteria. Streptokinase gives rise to more fibrin degradation product (fibrin genesis), thus consequently widespread lytic action takes place in the body. It may also cause thrombus formation, hemorrhage or tissue oedema; thereby make streptokinase less useful in acute ischemia stroke treatment.[35] Experimental studies associated with antithrombotic therapy revealed that 11% of all patients who go through thrombotic treatment have reasonable bleeding. Among them 0.3-1.3% showing intracranial hemorrhage.[36] Apart from that, if thrombolytic remedial measures are not operated within suitable time window due to prehospital delay, intrahospital delay or decision delay, it may produce unexpected outcomes.[37,38]

In view of the inadequacies of conventional thrombolytic therapy, endeavors are undeway to create enhanced recombination variations of these medications in order to make them more site specific and effective. Recombination is a process where pieces of DNA are broken and recombined to produce new combination of alleles which create genetic diversity at the levelof genes that reflects differences in the DNA sequence of different organisms.[39]

3. NATURAL REMEDIES FOR THROMBOLYSIS

3.1 Role of herbal drugs to mankind

Prehistoric man in scouring of food and to manage diseased condition in humans initiated to distinguish those plants having medicinal properties from others with précised pharmacological response. This correlation between human being and plants has thoroughly expanded and many plants came to light likewise and

which is to be used as medicines.[40] Further it has been noticed that many plants have therapeutic value because of the presence of the secondary metabolites which involve alkaloids, glycosides, flavonoids, saponins, tannins, volatile oils, terpenoids, and steroids.[41] Alkaloid holds antimalerial, anticancer, antimicrobial, antispasmodic, antiarrythmic, analgesic and diuretic properties. Glycosides accounted for antifungal, antibacterial activities and they are more readily used in enhancingcardiac output and lower heart diseases such as congestive heart failure and cardiac arrhythmia. Phenol and flavonoids reported as anti-oxidants, anti-inflammatory, anti-allergic and antibacterial effects. Saponins have anti-inflammatory, antiviral, antibacterial activities and act as antifeedant. Steroids act as signaling molecules.[42] The WHO listed around 4 billion people (80% of world population) utilize herbal medicine for primary health care and herbal medicine identified as a essential components for human health care.[43]

Herbal drugs and its preparations are practiced since ancient times to treat several diseases and to maintain health and retrieve healthy state of mind. Around 30% of the pharmaceutical preparations are prepared worldwide from the plant origin itself.[44] Plants are the principal source of the multiple range of bioactive components and hence the basis for their therapeutic potential.[45] Leaves, fruits, barks and seeds of a greater number of a species were established to possess rich ethno medical value. Furthermore, potential biological activity represents broad scope for discovery of new drug molecules from the plant origin. So, there is a wide scope for researchers to recognize and isolate several biological active constituents with thrombolytic activity and prove to be a superior option for management of coronary atherothrombotic diseases.[46]

3.2 Herbals and their traditional utility

Many plants, minerals and dietary components since long may used as the optional source for the expansion of new thrombolytic agents. A number of studies have been carried out by various investigators to search out the herbs, natural food sources and their supplements having antithrombotic, anticoagulant and anti-platelets properties and there is solid documentation that consuming such food gives rise to prevention of coronary events and stroke.[47] As different medicinal plants and their parts are utilized to treat several diseases from ancient time, thus here we would like to explore the herbs having thrombolytic possessions.[48] This review indicates following documented natural herbs were used as antithrombotic or anticoagulants in folklore medicine.

Punica granatum

It is often called as Pomegranate (family- Punaceae) contains alkaloids, flavonoids, tannins, saponins, terpenoids, glycosides, anthocyanins, punicalagin, punicalin. Traditionally it deals with stomachic disorders, diabetes, cardiac diseases, haemorrhages, dental disorders, fever and anaemia.[49,50] Pomegranate peels consist of anthocyanides having salutary effects in cardiovascular diseases. It also contains catechin and quercetin which shows modulate endothelial cell fibrinolytic protein (t-PA, uPA) expression at different levels designating fibrinolytic activity.[51]

Zingiber officinale

It is a rhizome of *Zingiber officinale* (family-Zingiberaceae) which contains flavonoids, tannins, zingirone, zingiberone and shagaol, used for the treatment of ulcers, osteoarthritis, rheumatoid arthritis, heart and lung diseases, hypolipidemic, anti-inflammatory and analgesic.[52,53] Principal constituents of ginger is gingerols, shagaols and paradols which hampers arachidonic acid induced platelets aggregation as well as thromboxane activity suggesting its beneficial properties in heart problems.[54]

***Phyllanthus emblica*:**

It is usually called as Indian gooseberry (family-Euphorbiaceae), contains alkaloids, flavonoids, flavonols, gallitannins, saponins, steroids, triterpenoids, anthocyanins, anthraquinones, coumarins, glycosides, vit. C and rutin.[55] Vit C is the major constituent which lower plasma fibrinogen levels while rutin inhibits platelets aggregation and fibrin generation. Rutin also play vital role in blocking earliest phase in thrombus formation by inhibiting protein disulphide isomerase.[56] Aqueous extract of these herbal drugs reveals 37.42%, 30.03% and 34.31% of average clotlytic properties suggesting potent nature of herbals. Selective 1:1:1 proportion of these three aqueous herbals extract was found to be competent to lyse 40.19% of blood clot.[57]

Azadirachta indica

It is commonly called as Neem (family-Meliaceae), the tree is regarded today as “Village dispensary” in India as it offers solution to the major concerns faced by human. It contains azadirachtin, meliacin, gedunin, salanin, nimbin, valassin and many more derivatives of these principles. The various parts of the tree has analgesic, anticholinergic, antihelmintic, antihistaminic, antiprotozoal, antipyretic, antiviral, insecticidal and insect repellant properties.[58]

Allium sativum

It is usually named as Garlic (family-Liliaceae), it contain biologically important secondary metabolites like alliin, allinase, alllicin, S-allyl cysteine, diallyldisulphide, diallyltrisulphide and methyl allyl trisulphide. It is widely used to treat the several conditions such as acne, arthritis, diabetes, emphysema, insomnia, pneumonia, rheumatism, warts and wound.[59]

Withania somnifera

It is commonly called as asgandh (family-Solanaceae), in ayurveda it is well mentioned as adaptogenic. Major biochemical constituents of aswagandha root are alkaloids, steroidal lactones and saponins. Among the

alkaloids, withanine is the biologically important one. It is beneficial as sedatives, anti-inflammatory, antidiabetic, antiepileptics, anti-stress and blood tonic. The thrombolytic assay of *Azadirachta indica*, *Allium sativum* and *Withania somnifera* extract reported significant thrombolytic activities and it may be used for the inhibition of cardiovascular events and stroke.[60]

Curcuma longa

It is known as Turmeric (family-Zingiberaceae), contain chief chemical constituents as curcumin and curcuminods. Artermorone- a fraction of curcumin oil reported anti-platelet activity by affecting the cyclooxygenase (Cox) pathway in platelets at membrane/receptor level. It is most important Indian spice used in Southest Asia for the treatment of various conditions such as stomachic, wounds and in joints. Turmeric extensively used for its antioxidant, antimicrobial, anti-inflammatory and antiproliferative properties.[61]

Berberis vulgaris

It is commonly known as barberry (family-Berberidaceae), native in Europe and Asia. It shows the presence of alkaloids, tannins, phenolic compounds, sterols and triterpenes. In TCM, it is suggested to have wide potential effects including antimicrobial, antiemetic, antipyretic and antipruritic properties. Scientifically, it may provide antihypertensive and vasodilator activity. Berberine, an alkaloidal components of the drug inhibit the platelet aggregation in blood vessels which gives maximum inhibition of 52.5 %.[62,63]

Osmanthus fragrance

It is a sweet osmanthus, native to Asia (family-Oleaceae), encases linalool and its oxides alpha ionone, beta ionone. It's high content of phenolic acid regulate the free radicals (a unstable atom damages cells) that causes chronic cataracts, atherosclerosis and other cardiovascular diseases. Osmanthus fragrance seed extract using ethyl acetate and n-butyl alcohol solvent shows greatest platelet aggregation inhibition at a concentration of 1.4 mg/ml and 2.8 mg/ml respectively.[64]

Gardenia jasminoides

It is also called as common gardenia or cape jasmine (family-Rubiceae), natively distributed in East Asia. The iridoid glycoside i.e. geniposide and its aglycon genipine has anti- inflammatory, antioxidant, antiplatelet aggregation and antidiabetic propertities. Scientifically gardenia jasminoides extract reveals anti-atherosclerotic and anti-adhesive activity.[65]

Inula racemosa

Inula racemosa is an Asian plant (family-Asteraceae), contains sesquiterpenes such as alantolactone, isoalantolactone and alloalantolactone, are the major phytoconstituents. It also shows the presence of flavonol glycosides, terpenes, allantoids, germacranolides and eudesmenes.[66,67] Its cardioprotective properties are mostly attributed to antioxidant sesquiterpenes by inhibition of lipid peroxides. Several experimental and clinical studies of *Inula racemosa* has established high potential against hypertension, coronary heart diseases, atherosclerosis, thrombosis and myocardial infarction.[68,69]

Crataegus monogyna

It is commonly known as hawthorn (family-Rosaceae), hold prime chemical constituents like flavonoids, proanthocynidins, organic acids and amines. Several other constituents like epicatechin, hyperoxide and chlorogenic acid are responsible for radical scavenging activity.[70,71] Hawthorn extract is a popular herbal medicine traditionally practiced for averting and treating the cardiovascular diseases involving hypertension, arrhythmias and congestive heart failure. Moreover, *Crataegus oxycantha* tincture and their isolated flavonoids and oligomeric proanthocynidine inhibit the formation of thromboxane A_2 (TxA_2)

- a potent inflammatory mediator) which induces the platelet aggregation.[72]

Honey

It is plant product obtained from the honey bee (family-Apidae), has a major source of antioxidants mainly flavonoids, phenolic acid like quercetin, caffeic acids, acacetin and apigenin which have wide range of promising effects in chronic diseases.[73] Scientific study communicate that honey has significant therapeutic value in dealing with cancer, heart diseases, cataracts and many inflammatory diseases.[74]

4. CONCLUSION

As only about 10% of the surviving higher plant species have been chemically identified the broad diversity of the plant kingdom is an immense reservoir with potential value which still have to be characterized. In India, there is vast reserve of natural resources and rich history of traditional medicine, so there is enormous scope for new researcher to explore and isolate countless biologically active components with thrombolytic activity to improve the health status and can prove to be a better alternative for the treatment of cardiovascular diseases. Looking to the emerging challenges and future pandemics like Covid-19 in health care system there is need to integrate the Ayurveda in medical system for the proper management of several diseases and lifestyle related disorders. Finally it may be concluded that the ayurvedic system of herbal medicine is unquestionably a treasure of plant drugs which bring back hope for the complete and permanent remedy of coronary atherothrombotic diseases through natural means with minimum side effects as compared to the allopathic drugs. We have to personally promote the integration of herbal medicine with modern medicine in natural health care systems where it is appropriate.

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