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IN VITRO EVALUATION OF THROMBOLYTIC ACTIVITY AND MEMBRANE STABILIZING ACTIVITY OF ETHANOLIC EXTRACT OF SYZYGIUM CUMINI LEAVES IN DIFFERENT DOSES.

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Abstract:

Aims: *In the present study, the The present study was commenced to judge ethnomedicinal worth of the plant Syzygium cumini (Family: Myrtaceae). Crude ethanolic extract of leaves was investigated for membrane stabilizing and thrombolytic activities.*

Place and Duration of Study: *The study was carried out for 0ne year from July 2017 to August 2018 in the Department of Pharmacy, Southeast university, Dhaka-1216, Bangladesh.*

Methodology*: In vitro membrane stabilizing activity was assessed by hypotonic solution and was compared with standard acetyl salicylic acid (ASA). In thrombolytic activity, percentage of inhibition of clot was carried out against Streptokinase.*

Results: Inhibition: *Significant clot lysis were revealed by 2 mg & 4 mg of S. cumini by 29% (P<0.001) & 35.5% (P<0.001) where standard streptokinase shown maximum clot inhibition (70.5%) (P<0.001). Dose dependent ihibition in RBC rupture causing membrane stabilizing activity were 30.87% (P<0.01) & 45.71% (P<0.01) by 2 mg & 4 mg of plant extract where acetyl salicylic acid shown maximum inhibition by 82.75% (P<0.001).*

Conclusion: *Leaves extract of the Syzygium cumini could be considered as potential source of compound(s) of thrombolytic and membrane stabilizing activities. The plant possesses significant bioactivities which rationalize it's use as folk medicine.*

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INTRODUCTION:

Phytomedicine refers to the use of any part of plant for medicinal & health purposes [1]. Now a days about 25% drugs are prescribed that derived from plants. Thrombus or embolus hinders the blood flow by blocking the blood vessel leading to lack of normal blood flow and oxygen & causes consequence necrosis. Thrombin formed blood clot from fibrinogen and is lysed by plasmin, which is activated from plasminogen by tissue plasminogen activator (tPA). The purpose of a fibrinolytic drug is to dissolve thrombin in acutely occluded coronary arteries & to restore blood supply to myocardium, to limit necrosis and to improve prognosis ali. Most commonly used thrombolytic agents for dissolving clots are alteplase, anistreplase, streptokinase, urokinase, and tissue plasminogen activator [2, 3]. Almost each and every thrombolytic agent have significant shortcomings, including limited fibrin specificity, bleeding tendency, and required large doses to have a maximum therapeutic effect [4]. Membrane stabilizing effects involve the inhibition or total abolishing or blocking propagation of action potentials from being propagated across the membrane. Anesthesia & some beta blockers possess membrane stabilizing activity (MSA) [**5].** This is the non-specific immune response that occurs in any type of bodily injury or sometimes manifested due to the complex biological response of vascular tissues to harmful stimuli [6, 7].

Syzygium cumini (L.) Skeels (Myrtaceae) commonly known as Indian blackberry or Jamun or black plum or jambolan Jaman. Originality in India It is a large tree distributed throughout West Bengal, all forest district of India [8,9] also grown in Thailand, Philippines, Madagascar It grows commonly along streams and damp places and in evergreen forests. The tree is planted as an ornamental in gardens and at roadsides [10**, 11].** The fruit pulp contains essential vitamins and minerals such as calcium, copper, iron, sulphur, NA, Mg, potassium, vitamin A, thiamin, riboflavin, nicotinic acid and ascorbic acids choline folic acid [12,13]. Fruit of *S. cumini* contains Malic acid as the major acid [14]. The plant is rich in oxalic acid, betulinic acid, friedelin, epi-friedelanol, β-sitosterol, eugenin, fatty acid ester of epi-friedelanol [15], β-sitosterol, quercetin kaempferol, myricetin gallic acid and ellagic acid [16], caffeic and ferulic acids derivaties, guaicol, resorcinol dimethyl ether, corilaginin **[17],** bergenins [18], flavonoids and tannins [19], isoquercetin (quercetin-3-glucoside), acetyl oleanolic acid [20], flavonoid glycosides [21], isorhamnetin 3-O-rutinoside [22], raffinose, glucose, fructose [23] citric acid [24], cyanidin diglycoside, petunidin and malvidin [25]. The color of the fruits might be due to the presence of anthocyanins [26], cyaniding diglycosides [27]. The peel powder can be employed as a colorant for foods and pharmaceuticals [28].

Syzygium cumini is used traditionally in cure of cough, diabetes, dysentery, inflammation [29] digestive complaints, piles, pimples, stomachache [30] as well as used for blood purification strengthening of teeth and removing ringworm infection of the head [31] Pharmacological effects were established by the plant like antihyperglycemic effect [32], antidiabetic [33,34] antioxidant [35], anti-microbial [36] nitric oxide scavenging, gastroprotective [37], free radical scavenging [38], anti-inflammatory [39,40], antineurgenic [41] , antileishmanial, antifungal [42], anti-diarrheal [43], antifertility [44], anorexigenic [45], behavioural effects [46], anti-ulcerogenic [47] and radioprotective activities [48]. Anorexigenic, antibacterial [49] anti-infective [50] anti-malarial [51], antiallergic [52], lipid peroxidation inhibition [53], hepatoprotective [54], cardioprotective [55], chemoprotective [56] anticancer activity [57] are also reviewed from this plant. Moreover, leaf extracts of the plant on the radiation-induced micronuclei formation was studied by Jagetia and Baliga [58].

METHODOLOGY:

Collection of Plant Material and Preparation of Extracts:

C. gigantea plant was collected from the natural population growing in the Gazipur, Dhaka, Bagladesh & authenticated by the expert taxonomist from Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh (Accession number: 34008.). Leaves were washed and shade dried for several days followed by grinding using mechanical grinder. About 200 gm dried powder were soaked in 800 ml ethanol and kept for a period of about 7 days with occasional shaking and stirring. The whole mixture is then filtered through Whitman No.1 filters paper and concentrated by a rotary evaporate under reduced pressure at 50^0C temperature to afford crude extract with gummy or semisolid appearance. The concentrate was stored in an airtight container and kept in a cool, dark and dry place until the next course of action.

Chemicals:

All used chemicals were of analytical grade and were obtained from standard commercial suppliers.

Thrombolytic Activity:

Streptokinase:

Commercially available lyophilized Altepase (Streptokinase) vial (Beacon pharmaceutical Ltd) of 15, 00,000 I.U., was collected and 5 ml sterile distilled water was added and mixed properly. This suspension was used as a stock from which 100µl (30,000 I.U) was used for in vitro thrombolysis [59].

Study design:
Whole blood (n=10) was drawn from healthy human volunteers without a history of oral contraceptive or anticoagulant therapy and 1 ml of blood was transferred to the previously weighed sterile vials and was allowed to form clots. Aliquots (5 ml) of venous blood were drawn from healthy volunteers who were distributed in ten different pre weighed sterile vials (1 ml/vial) and incubated at 37 °C for 45 minutes. After clot formation, the serum was completely removed without disturbing the clot and each vial having clot was again weighed to determine the clot weight. To each vial containing pre-weighed clot, 100 µl aqueous solution ethanolic extract (2mg/ ml & 4 mg/ml) added separately. As a positive control, 100 µl of streptokinase (SK) and as a negative non thrombolytic control, 100 µl of distilled water were separately added to the control vials. All the vials were then incubated at 37 °C for 90 minutes and observed for clot lysis. After incubation, the released of fluid was removed and vials were again weighed to observe the difference in weight after clot disruption. Difference obtained in weight taken before and after clot lysis.

% clot lysis = (Weight of the lysis clot / Weight of clot before lysis) × 100

Membrane Stabilizing Activity:
The erythrocyte membrane resembles to lysosomal membrane and as such, the effect of drugs on the stabilization of erythrocyte could be extrapolated to the stabilization of lysosomal membrane [60]. The membrane stabilizing activity of the extractives was assessed by using hypotonic solution-induced and heat-induced mice erythrocyte haemolysis [61].

Stock erythrocyte (RBC) suspension:

Human RBCs were collected from the female with 55 kg and free from disease. The collected RBCs were kept in a test tube with an anticoagulant EDTA under standard conditions temperature 23±2° C and humidity 55±10 %. The blood was washed tree times with isotonic (154 Mm NaCl) in 10 Mm sodium phosphate buffer (PH 7.4) through centrifuge action for 10 min at 3000g. Thus the suspension finally collected was the stock erythrocyte (RBC) suspension.

Hypotonic solution –induced hemolysis:

Standard acetyl salicylic acid (ASA) was used as standard drug & hypotonic-buffered saline solution was used as negative control. The test sample (2mg/ ml & 4 mg/ml) consisted of stock erythrocyte(RBC) suspension (0.50ml) with 5 ml of hypotonic solution (50 Mm NaCl in 10 mM sodium phosphate buffer saline (pH 7.4) containing either the different ethanolic extract (1.0 mg/ ml) or acetyl salicylic acid (0.10 mg/ml) . the acetyl salicylic acid was used as as reference standard. The mixture were incubated for 10 minutes at room temperature, centrifuge for 10 minutes at 3000 g and the absorbance (0.1) of the supernated was measured at 540 nm using UV-spectrophotometer [62]. The percentage inhabitation of either haemolysis or membrane stabilization was calculated by using following equation:
% inhibition of haemolysis = 100 x $\{(OD_1 - OD_2)/OD_1\}$

Where,
OD1 = optical density of hypotonic-buffered saline solution alone (control) and
OD2 = optical density of test sample in hypotonic solution

RESULTS & DISCUSSION:

Thrombolytic Activity:
Thrombolytic activity were revealed by 2 mg & 4 mg of *S. cumini* with significantly inhibition of blood clot by 29% (P<0.001) & 35.5% (P<0.001) where standard streptokinase shown maximum clot inhibition (70.5%) (P<0.001). Inhibition of blood clotting was revealed as dose dependent manner.

Table 01: % of clot lysis of S. cumini leaves

Concentration	% of blood clot lysis
Syzygium cumini (2 mg/ ml)	29±1.41***
Syzygium cumini (4 mg/ ml)	35.5±2.12***
Streptokinase (30,000 I.U.),	70.5±2.01***
Control (normal saline)	14.20±1.35

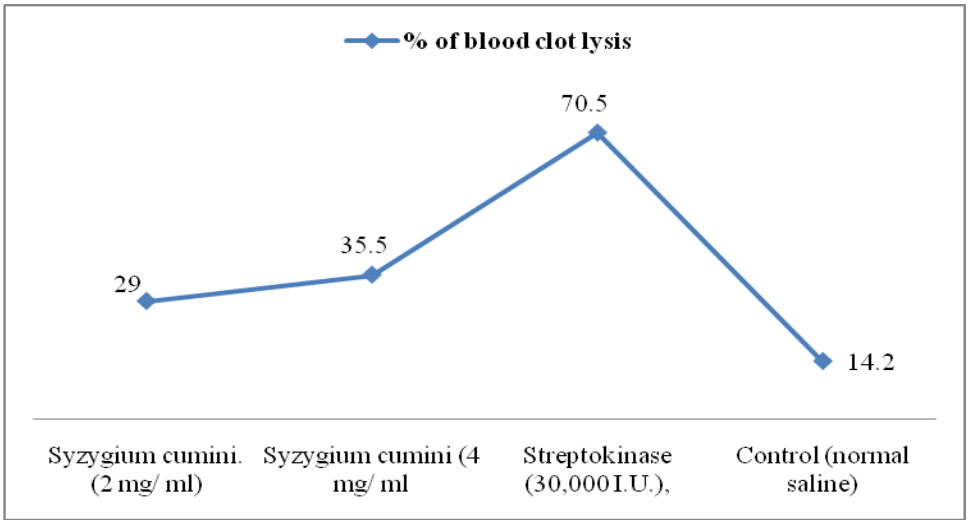

Figure 01: % of clot lysis of *S. cumini* leaves

Membrane stabilizing activity:

The present study shown that 2 mg & 4 mg of *S. cumini* significantly inhibited RBC hemolysis by 30.87% (P<0.01) & 45.71% (P<0.01) where acetyl salicylic acid shown maximum inhibited by 82.75% (P<0.001). Slight increase in inhibition was found for increased dose (Table 02 & Figure 02).

Table 02: Percentage of inhibition of hemolysis of different ethanolic extract of *S. cumini* leaves.

Concentration	% of Inhibition of Hemolysis
Syzygium cumini (2mg/ml)	30.87±0.19**
Syzygium cumini (4mg/ml)	45.71± 2.60**
Acetyl salicylic acid (0.1 mg/ml)	82.75± 2.42**
Control (normal saline)	-----

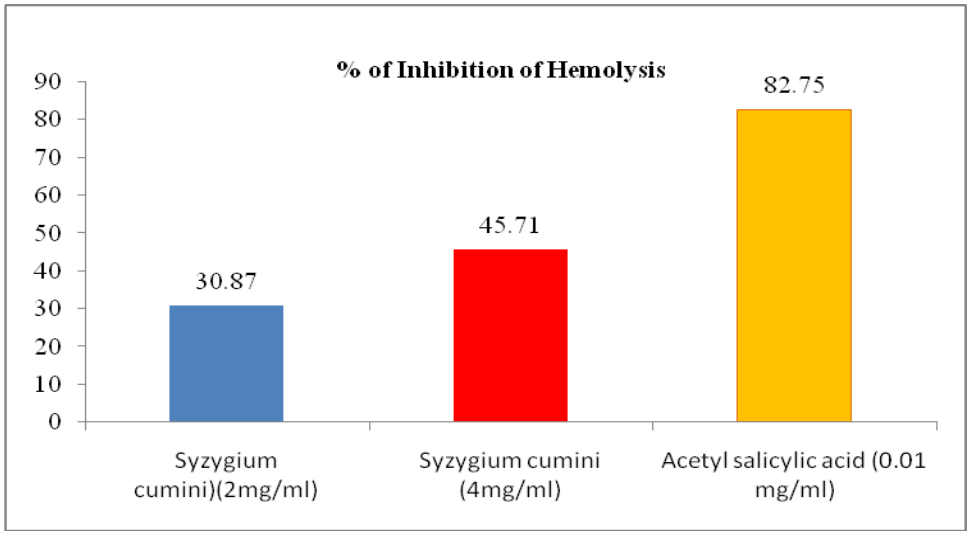

Figure 02: Percentage of inhibition of hemolysis of different ethanolic extract of *S. cumini* leaves.

Thrombus development leads to many vascular myocardial infraction, stroke, deep vein thrombus, renal vein thrombosis, portal vein thrombosis et, which might result in death. Tissue plasminogen activator, urokinase, streptokinase etc are used currently for treating thrombosis but better thrombolytic agents are still a demand of time. The plant is rich source of alkaloids, flavonoids, saponins, steroids, reducing sugar and phenolic compounds which witness the ample of medicine potential of the herb. Significant Thrombolytic activity were were revealed by 2 mg & 4 mg of *S. cumini* by 29% (P<0.001) & 35.5% (P<0.001) where standard streptokinase shown maximum clot inhibition (70.5%) (P<0.001). The thrombolytic activity is probably due to the plant`s diverse composition like flavonoids, tannins and terpenoids [63]. It has been demonstrated that certain herbal preparations were competent of stabilizing the red blood cell membrane and this may be indicative of their ability to exert anti-inflammatory activity [64] that is probably due to the inhibitory effect on enzymes involved in the production of the chemical mediators of inflammation and metabolism of arachidonic acid. Membrane stabilization causes prevention of leakage of serum proteins and fluids into the tissues during the period of increased permeability which is caused by inflammatory mediators. In hypotonic solution induced condition, samples were found to inhibit lysis of erythrocyte membrane where 2 mg & 4 mg of *S. cumini* significantly inhibited RBC hemolysis by 30.87% (P<0.01) & 45.71% (P<0.01) where acetyl salicylic acid shown maximum inhibited by 82.75% (P<0.001). Membrane stabilization of plant confirms the presence of flavonoids, tannins [65] escinol, rutin & butadion [66] in the plant.

CONCLUSION:

Although plants were using as a medicine from the ancient during but these days the term alternative medicine become very famous, it focus on the idea of using the plants for medicinal purpose. But the current belief that medicines which come in capsules or pills are the only medicines that we can trust and use. Based on the result of the present study, we can confirm that the ethanolic extract of *S. cumini* leaves possesses remarkable thrombolytic, antioxidant and membrane stabilizing activities. However, further studies are indispensable to examine underlying mechanisms and to isolate the active compounds responsible for these pharmacological activities. In future experiments, studies with expensive solvent soluble fractions of extract can be conducted for further pharmacological activities and to discover potential lead compound.

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