Thrombolytic, CNS Depressant and Anti-Diarrhoeal Activities of Ethanolic Extract of Bark of *Syzygium cumini* L. Skeels: An *In-Vivo* and *In-Vitro* Study

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Abstract: The present study was aimed to create scientific insights that validate the traditional use of bark of ethanolic extract of *S. cumini* in thrombosis, CNS depression and in diarrheal cases. The CNS depressant activity was evaluated by observing the locomotor activity of the animals in the open field and forced swim methods at a dose of 200 and 400 mg/kg body weight and the anti-diarrheal activity was evaluated through castor oil induced method and charcoal induced GI motility tests. Finally thrombolytic activity assessment was done by employing Streptokinase as standard. In this study, among the five different concentrations 10 mg/ml showed maximum clot lysis that was 48.5%, whereas standard showed 51.05% lysis of clot. In case of open field test, the mean number of movement at 60 min were 20 and 31.11 at a dose of 200 and 400 mg/kg respectively. In case of castor oil induced method the above two doses of bark extract of *S. cumini* exhibited 23.07% and 36.67% of diarrheal inhibition compared to the standard Loperamide (5mg/kg) was 50%. For charcoal induced GI motility test, diarrheal inhibition was 23.07% and 36.67%. The present revealed that ethanolic bark extract of bark of *S. cumini* justify its traditional uses through good thrombolytic, CNS depressant and anti-diarrheal activity.

Keywords: *Syzygium cumini*, Thrombolytic, CNS depressant, Anti-diarrhoeal.

1. INTRODUCTION

Nature has been an inseparable part of life from the very beginning of civilization. That not only provides life-saving oxygen but also providing various essential remedies to cure diseases of human [1]. Since ancient times Plants are considered as one of the major raw materials in drugs for treating various ailments of the human being. Though the final two decades, significant adjustments have taken vicinity inside the medicinal gadget everywhere in the international, however a standard cognizance of the big toxicity and harmful after-results emerge as keep the primary situation inside the long time use of artificial tablets and antibiotics. All of those shortening projected over drugs from herbal assets are being favored [2]. The term herbal stands for using the part/parts of a plant for making ready drug treatments (for examples: leaves, vegetation, seeds, roots, barks, stems, etc.) [3]. Plants containing biologically energetic chemical materials which include saponins, tannins, crucial oils, flavonoids, alkaloids and other chemicals are considered as the feasible applicants for the herbal therapy [4, 5]. Again Tyler [6], has pronounced that vegetation also contain positive different compounds that modulate the effects of the active ingredients. Accordingly, extensive studies on plants are going on to explore medicinal values. But many plants are still unexplored of their medicinal potentials [7]. Because of such great opportunities in medicinal plants, we liked to work on a medicinal plant called *S. cumini* L. Skeels of Myrtaceae family [8]. The plant is locally known as Java plum, Black plum, Jaman, Jambu, Jambul and Indian blackberry [9, 10]. The bark of the plant has the astringent effect and its decoction is used in gargle [11]. The plant extract has antifungal, anticancer, antioxidant, and hypoglycemic, anti-inflammatory, sedative, anticonvulsant, ulcer protective, and antiviral activities [12-19]. But till now there is no report on thrombolytic, CNS depressant and anti-diarrheal activity of *S. cumini*, though it is used in traditional medicine. Thus the objective of this present investigation is to explore the above three unexplored activity of ethanolic bark extract of *S. cumini*.

2. METHODS AND MATERIALS

2.1. Drugs and Chemicals

Standard Diazepam, Loperamide, Streptokinase were purchased from Square Pharmaceuticals Ltd.,

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Bangladesh. Other reagents of analytical grade for conducting this research work were supplied from ethno pharmacology laboratory of Pharmacy department of Noakhali Science and Technology University.

2.2. Plant Material

For this present investigation the bark of *S. cumini* was collected from East Eklashpur, Begumgonj, Noakhali in April, 2015. The local name of *S. cumini* is Jam. After collection of barks of *S. cumini* and whole barks of *S. cumini* were thoroughly washed with water. The plant was identified by expert of Bangladesh National Herbarium Institute, Mirpur, and Dhaka, Bangladesh. (Accession number-47751). The collected plant parts were then air-dried by using mechanical graded e aluminum foil and finally kept at room temperature for 14 days [20]. The plant parts were ground into a coarse powder with the help of a suitable grinder. The powder was stored in an airtight container and kept in a cool, dark and dry place until analysis commenced.

2.3. Extract Preparation

The dried and powdered bark of *S. cumini* (500 g) were soaked in 1500 ml of 99% ethanol for about 7 days at room temperature with occasional stirring. After 7 days the solution was filtered using filter cloth and Whatman's filter paper. The filtrate (ethanol extract) obtained was evaporated in rotary evaporator and subsequently under ceiling fan until dried. These procedures rendered extract into dark chocolate granular. The dark chocolate granular was designated as crude extract of ethanol that was transferred to clean petri dish for further use and storage.

2.4. Preparation of Animal

Adult White albino mice weighing between (25-30) gm of either sex were collected from Pharmacology Laboratory, Jahangirnagar University, Savar, Dhaka and used for the studies. The animals were maintained under normal laboratory condition & kept in standard cages at room temperature of 30°C±2°C and 60% to 65% relative humidity and provided with standard diet & water. The experiment was done in the Physiology Laboratory of Department of Pharmacy at Noakhali Science and Technology University.

2.5. Thrombolytic Activity Test

In vitro thrombolytic activity test of ethanolic bark extract of *S. cumini* was carried out according to the method described by Prasad *et al*. with minor modification [21]. According to the method, venous blood was withdrawn from five healthy volunteers (5 ml from each of them) having no history of smoking, taking no oral contraceptive, anti-coagulant therapy and transferred to different pre weighed sterile micro-centrifuge tube (1ml/tube).The micro-centrifuged tubes were subjected to incubation at 37°C for 45 min. After the formation of clot, serum was completely removed from the tubes without disturbing the clot and each tube having clot was again weighed to determine the weight of the clot. To each micro-centrifuge tube containing pre-weighed clot, 100 µl solution of five different concentration (2, 4, 6, 8 and 10 mg/ml) of ethanolic bark extracts of *S. cumini* were added accordingly. As a positive control, 100 µl of streptokinase and as a negative control, 100 µl of sterilized distilled water were separately added to the control tubes. Then all the tubes were incubated again at 37°C for 90min and observed for clot lysis. After incubation, the obtained fluid was removed from the tubes and they were again weighed to observe the difference in weight after Clot disruption.

Then percentage of clot lysis is calculated using the following equation.

% of clot lysis = (wt of released clot/clot wt) × 100

2.6. CNS Depressant Activity Test

2.6.1. Open Field Method

CNS depressant activity tests were evaluated by method described by Gupta [22]. According to this method, mice were randomly divided into four group such as standard, Control, and two sample groups. Where control group was treated orally with distilled water (10 ml/kg) and two sample group were treated orally with 200 and 400 mg/kg of plant extract and Standard group was treated intraperitonially with Diazepam (1mg/kg) body weight. Each mice was observed at a time interval (on 0, 15, 30, 45 and 60 minutes after administration) for 3 minutes to note the number of fields crossed by each mouse in all group. The mean number squares of open fields crossed by mice of each groups were compared with standard group to detect Neuropharmacological activity.

2.6.2. Forced Swimming Test

The method described by Porsolt *et al*. [23] was used in our study. Each animal was placed individually in a 5 L glass beaker, filled with water up to a height of 15 cm and was observed for a duration of 6 min, last 4

min values were taken for calculation. The mouse was considered immobile when it floated motionless or made only those moments necessary to keep its head above the water surface. The water was changed after each test.

2.7. Anti-Diarrhoeal Activity Test

2.7.1. Castor Oil Induced Method

The experiment was carried out by the slightly modified procedure previously described by Uddin and Awouters [24, 25]. The anti-diarrhoeal activity of the ethanolic bark extract of *S. cumini Linn*. was evaluated using the method of castor oil induced diarrhoea in mice. According to this method, each mouse was fed with 1ml of highly pure analytical grade of castor oil which would induce diarrhoea. Each animal was constantly observed for consistency of faecal matter and frequency of defecation. The feces were collected with an absorbant sheet of paper placed beneath the transperant cages [26]. The wet feces were read at the end of the experiment by lifting up it from the open upper part of the cage containing the sheet of paper and animals. The observations of the experimental groups were compared against that of the control to evaluate the anti-diarrhoeal activity of the samples.

The percentage of inhibition of defecation was measured using the following formula:

% inhibition of defecation = (1-B/A) X 100

Where,

A = Mean number of defecation by castor oil.

B = Mean number of defecation by drug or extract.

2.8. Gastrointestinal Transit Test

The castor oil induced gastrointestinal transition test was carried out according to the method described by Bakare *et al*. [27] In this method, all of the mice (25-35 g) in all groups (I-VI) were fasted for 18-24 h, but allowed free access to water. The animals were treated with distilled water, plant extract or standard drug (castor oil) and after 30 minutes, each animal was administered 1 ml of marker (10% charcoal suspension in 5% gum acacia) orally by gavage to all groups. All the animals were sacrificed after 15 minutes of marker administration and the small intestine was rapidly dissected out and placed on a clean surface. The intestine was carefully inspected and the distance travelled (traversed) by charcoal meal plug from the pylorus to caecum was measured by a measuring scale. The length of the whole intestine was also measured. The distance travelled by the charcoal plug from the pylorus to the caecum was expressed as a percentage of the total length of the small intestine [28-31].

2.8.1. Percentage of Inhibition

Compared with the control group was determined by using the following equation [32, 33].

IP % = (LM/LSI) x 100

% Inhibition = {IP % (control) – IP% (treatment)}/ IP % (control)

Where,

PI = Peristaltic index

LM = Length of charcoal meal

LSI = Length of small intestine

2.9. Statistical Analysis

All values were expressed as the mean ± standard error of the mean (SEM) and the result were analyzed statistically by one way analysis of variance (ANOVA) followed by Dunnett's t-test by using SPSS version 19. $P < 0.05$ was considered to be statistically significant.

3. RESULTS

3.1. Thrombolytic Activity Test

Human blood clot lysis activity of bark ethanolic extract of *S. cumini* remarkable clot lysis at 10mg/dl (38.5%) concentration when compared to standard streptokinase's clot lysis potentiality (59.6%) and the result is represent in Table **1**. Here, bark ethanolic extract of *S. cumini* showed clot lysis potentiality at dose dependent manner.

Table 1: Effect of Different Concentrations of the Ethanolic Extract of *S. cumini* and the Controls on *In vitro* Clot Lysis

Treatment	% of clot lysis (mean± S.D)
EE (2mg/ml)	17.3±0.375
EE (4mg/ml)	22.9±0.448
EE (6mg/ml)	27.2±0.342
EE (8mg/ml)	33.3±0.408
EE (10mg/ml)	38.5±0.381
SK	51.05±0.383

Here, SK =Streptokinase, EE= ehanolic extract, values are represented as mean ± SEM (n=6).

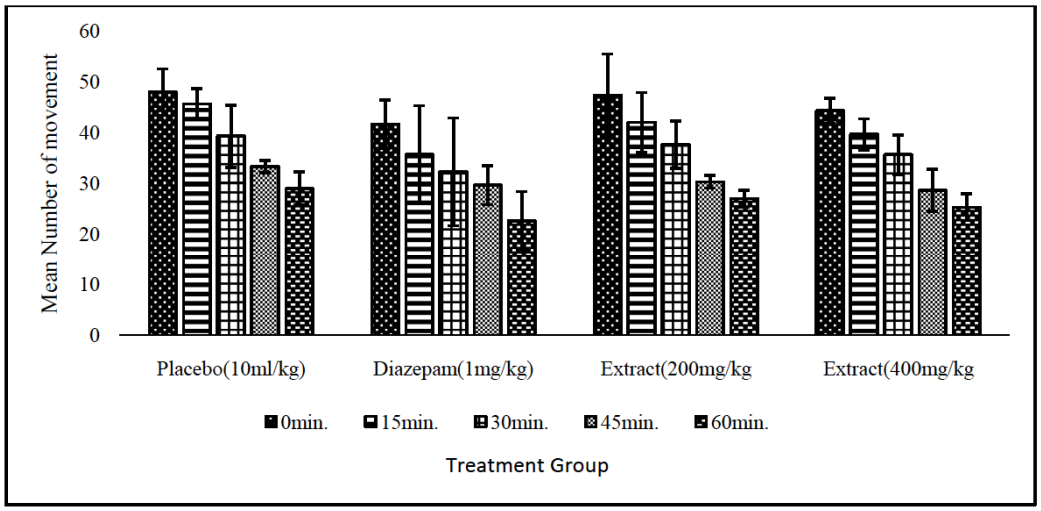

Figure 1: Effect of ethanolic extracts of *S. cumini* on Open Field Test.

3.2. CNS Depressant Activity

The crude ethanolic extract of *S. cumini* was assayed for CNS depressant activity by using open field and Forced swim methods results are represent in Figure **1**. From Figure **1** it is seen that, number of movement generated by the mice in arm was decreased for both doses (200mg/kg, 400mg/kg) when compared to control group. The validation of experiment on CNS depressant effect of *S. cumini* was carried out by measuring external signs, through Forced Swim Test. Where administration of different concentration of ethanolic extract of *S. cumini* (200, 400mg/kg) results decreased mice's response rate.

3.3. Anti-Diarrheal Test

3.3.1. Castor Oil Induce Method

The effect of *S. cumini* (stem barks) on castor oil induced diarrhoeal method in mice shown in Table **2**. The results obtained indicates that, 200 mg/kg of *S. cumini* (stem barks) at 5th hours showed significant ($p<0.05$) inhibition of 23.07%. Again at the dose of 400 mg/kg, showed mild inhibition of 34.62 % respectively while the standard Loperamide inhibited 50.00% at the same time, both of this data was found to be statistically significant.

3.3.2. Gastrointestinal Transit Method

The total lenth of intestine for each mouse was measured with the distance travelled (traversed) by charcoal meal plug from the pylorus to caecum by a measuring scale and then the data evaluated statistically to find its significance. Percent of inhibition for gastrointestinal motility found for the ethanolic crude bark extracts of *S. cumini* is 26.6% & 37.7% at the dose of 200 mg/kg& 400mg/kg respectively, while compared to standard loperamide that showed 61.5% of inhibition of diarrhea (Table **3**). But none of this value was found to be statistically significant.

4. DISCUSSION

Our present observation became a try to discover if the ethanolic extracts of *S. Cumini* possess clot lysis potentiality or now not. The assessment of the standard (streptokinase) with control (distilled water) sincerely verified that clot dissolution does not occur when water changed into delivered to the clot. Encouraged by the result of the standard streptokinase, we as compared 5

Table 2: Effect of Methanolic Extract on Castor Oil Induced Diarrhea in Mice

Treatment	Dose (mg/kg)	No. of Diarrheal feces (Mean ± SEM)	% Reduction of diarrhea
CTL	10 ml/kg	10.00 ± 0.58	----
STD	5.0mg/kg	7.00 ± 0.58	50.00*
EE	200mg/kg	4.33 ± 0.33	23.07
EE	400mg/kg	3.67 ± 1.33	34.62***

Here, CTL=control, STD= Loperamide, EE= ethanolic extract, Values are expressed as Mean ± SEM (n=3). ***P<0.001, **P< 0.01, *p<0.05 compared to control (One way ANOVA followed by Dunnett's 't'-test).

Table 3: The Data Representing Total Length of Isolated GIT with the Charcoal Transition Length and the Percent of Inhibition of Motility for the Selected Plant Samples Comparing Against Control

Group	Treatment	Number of mice(n)	MTLI (cm) Mean ± SEM	MDTC (cm) Mean ± SEM	Peristaltic Index %	% of Inhibition
1	Control (10 ml/kg)	4	44±0.92	34.75 ± 1.25	78.98	--
2	Loperamide (5mg/kg)	4	39.5 ± 1.21	12 ± 1.04	30.38	61.5
3	EE (200mg/kg)	4	43.25 ± 3.56	25 ± 1.47	57.80	26.6
4	EE (400mg/kg)	4	46.75 ± 1.49	23 ± 1.92	49.19	37.7

Here, EE= Ethanolic Extract, MTLI=Mean Total Length of Intestine, MDTC=Mean Distance Travelled by Charcoal, Values are presented as mean ± SEM (n=4).

exclusive concentrations at pattern inside the same manner with the terrible manipulate and located extensive thrombolytic hobby. Nowadays, mobile floor or blood vessel are blocked with the aid of the deposition of platelets, tissue aspect, and fibrin via thrombosis or blood clot formation has become an important event [32]. During this organic system platelets are playing the important role inside the process of thrombosis is initiated when the activated platelets shape platelets to platelets bonds. Finally, a complex method of plaque formation and growth activated platelets is generated whilst similarly Activated platelets bind to the leucocytes [33]. Most of the thrombolytic retailers lyse clot by disrupting the fibrinogen and fibrin contained in a clot. Among they all, plasmin is one of the herbal anti-thrombotic drugs, that is itself activated from mobile floor plasminogen that is then in the long run ends in fibrinolysis [34]. Other to be had fibrinolytic agents are urokinase, tissue plasminogen activator, and streptokinase used for clinical intervention for pathological development of blood clots. Very currently large quantity of research works had been undertaken to discover antithrombotic retailers (anticoagulant and antiplatelet) from flora and natural food sources that allows you to the prevention of coronary occasions and stroke [35]. Nowadays, recombinant generation is employed to make the ones capsules greater effective and location unique. A widely used thrombolytic agent known as Streptokinase (a bacterial plasminogen activator) has the potentiality to changing additional plasminogen to plasmin, with a few significant destructive consequences like bleeding and embolism which lead to similar complications. To solve those headaches a number of studies were performed by diverse researchers with a purpose to find out new assets of herbs and natural ingredients and their supplements having antithrombotic effect with minimal detrimental effect [35]. Nowadays, recombinant technology is employed to make those drugs more effective and site specific. A widely used thrombolytic agent called Streptokinase (a bacterial plasminogen activator) has the potentiality to converting additional plasminogen to plasmin, with some considerable adverse effects like bleeding and embolism which lead to further complications. To solve these complications a number of studies have been carried out by various researchers in order to discover new sources of herbs and natural foods and their supplements having antithrombotic effect with minimal adverse effect [35]. At our present locating, we attempted to find whether or not the natural arrangements of ethanolic bark extract of *S. cumini* own clotlysis potentiality or not. When we in comparison the end result of standard (streptokinase) with that of control (distilled water), we located that there was a negligible quantity of clot disruption whilst water was brought to the clot. This distinguished result encouraged us to evaluate four special take a look at samples inside the equal manner towards the terrible control and take a look at giant thrombolytic hobby. It became suggested that phytochemicals like saponin, alkaloids, and tannin are answerable for thrombolytic hobby [36]. As the seed and bark ethanolic extract of *S. cumini* possesses saponin, alkaloids [37, 38] consequently due to the presence of these phytochemicals within the bark ethanolic extract may be the possibly cause of demonstrating the thrombolytic activity. Rodents are displayed immobility when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair, which in turn may reflect depressive disorders in humans. In fact, there is a significant correlation between the potency of antidepressants in both forced-swimming and Open Field Test and clinical potency of the drugs [39]. Comparing the effects acquired by means of the two fashions hired in this examine, which use one of a kind strain situations to set off states of terror and melancholy, it can be found that the impact of the extract at the discount of immobility time turned into expressed greater strongly inside the pressured-swimming version than inside the Open Field Test (Tables **2** and **3**). The plant extract showed marked

CNS depressant activity in the open field and forced swim methods in comparison to the control drug and the effects were dose dependent. Gamma-amino-butyric acid (GABA) is well known as a major inhibitory neurotransmitter in the central nervous system [40] it is evidence that many anxiolytic, muscle relaxants and sedative-hypnotic drugs exert their actions via GABA [41]. Some previous researchers in this area showed that phytoconstituents like flavonoids act as ligands for the GABAA receptors in the central nervous system, which led to figure out a major hypothesis that these compounds may act as benzodiazepine like molecules [40] Therefore it may be suggested that the plant extract may exert its action by potentiating GABAergic inhibition in the CNS via membrane hyperpolarization [41, 42]. The phytochemical assessment showed the presence of alkaloids, flavonoids, saponins and steroids in the plant [37, 38], which supports the result its CNS depressant activity of our present study. Thus, it could be concluded that ethanolic bark extract of the selected plant may have CNS depressant activity. Again in this present study, crude ethanolic extracts of selected plants displayed slight activity against castor oil-induced diarrhea. Loperamide is widely used in the management of diarrheal diseases which effectively antagonizes diarrhea induced by castor oil [43]. Ethanolic crude extracts of *S. cumini* showed the slight anti-diarrhoeal activity of 23.07% at 200mg but extracts of *S. cumini* showed the anti-diarrhoeal activity of 34.62% at the dose of 400 mg/kg. At the same time, the reference standard loperamide exhibited 50.00% inhibition at a concentration of 5 mg/kg body weight. The antidiarrhoeal properties may be due to the presence of tannins, alkaloids, saponins, flavonoids, steroids, terpenes in those vegetation. Previous research have proven that antidysenteric and antidiarrhoeal properties have been commonly because of the presence of tannins, alkaloids, saponins, flavonoids and triterpenes [44]. The activity of the extract may also be due to the presence of denatured proteins which shape protein tannates. Protein tannates make the mucosa extra resistant and hence, lessen secretion [45]. This can be because of the reality that the extract increased the reabsorption of water by way of lowering intestinal motility within the isolated rabbit ileum. Phytochemical screening found out the presence of flavonoids, tannins, saponins, cardiac glycosides and triterpenes. Hence, tannins and triterpenes can be responsible for the mechanism of movement of lowering the impact on GI motility of the selected plant samples [46]. Thus, Bioactivity-guided isolation can be needed to carry out to separate the bioactive metabolites to define these biological actions more specifically.

5. CONCLUSION

The findings of the present study indicate that the bark ethanolic extract of *S. cumini* possess thrombolytic, CNS depressant activity and antidiarrheal activity. All these present results validated the traditional use of the plant parts in the treatment of diarrhea, anxiety and cardiovascular disorder etc. However, further researches are required to establish the potential mechanism of action of these activities and elucidate structure of the active phytoconstituents responsible for these bioactivities.

COMPETING INTERESTS

Authors have declared that no competing of interests exist.

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ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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