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Serotonergic and noradrenergic response of ethanol extract; opioidergic response of ethyl acetate extract of *Dicranopteris linearis* L. leaf

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Abstract

Background: *Dicranopteris linearis* L. is among the popular tribal plants used for various ailments, although many of its pharmacological potentials have not been investigated yet. The neuropharmacological potentials of the leaf, including sedative-anxiolytic potential, were previously studied however, the antidepressant activity was yet to be examined. Thus, this study was aimed to investigate the serotonergic, noradrenergic and opioidergic response of *D. linearis* leaf extracts.

Methods: The plant leaf was extracted in three solvents- water (DLAQ), ethanol (DLET) and ethyl acetate (DLEA) and applied each in 200 and 400 $mg.kg^{-1}$ per body weight of Swiss Albino mice. Forced Swim Test (FST) and Tail Suspension Test (TST) were conducted to evaluate antidepressant potential. In FST, latency and duration of immobility, swimming and climbing time were recorded. In TST, immobility, swinging, curling and pedaling were observed. Alongside, preliminary screening through acute toxicity study and pentobarbitone induced sleep test were performed.

Results: Both in FST and TST, the duration of immobility was reduced by the standard imipramine and DLET 200 and 400. In FST, DLEA 200 and 400 increased the climbing time suggesting noradrenergic mechanism of action and decreased the swimming time suggesting deficit of serotoninergic mechanism of action. Interestingly, DLET increased both the parameters presenting a dual action. However, in TST, DLEA decreased immobility but increased swinging and curling response which indicated its opioidergic mechanism. On the other hand, DLET proved to mediate through serotonin and/or NA reuptake mechanism by having decreased curling time.

Conclusion: Among the three extracts, the ethanol extract proved to be more potent. DLET mimicked the standard imipramine in all parameters except for the curling behavior. The result thus suggests *D. linearis* as a potent antidepressant agent however, recommends its medicinal use after further investigation to identify bioactive compounds.

Keywords: *Dicranopteris linearis*, Forced swim test, Tail suspension test, Antidepressants

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Introduction

Dicranopteris linearis is a popular healer member of the Gleicheniaceae family of medicinal plants. It is prescribed for various ailments in different parts of Bangladesh in different localities. The plant is characterized as forking fern by its segmented leaves in linear shape which grows up to 7 cm in length and by a few millimeters in width with hairy and waxy underside [1]. Studies found that the Garo tribes of Haluaghat (Mymensingh) prescribes a juice prepared from the young leaf for the treatment of cough, allergic symptoms and respiratory troubles [2]. Traditional uses around the globe were found reported in literature supporting its efficacy to alleviate fever (Malaysia); to treat ulcers, boils and topical wound (Papua New Guinea); to protect against intestinal worms (Indochina) and to pacify asthma and treat woman's sterility (India) [3]. Scientifically investigated pharmacological activities include analgesic, antipyretic, anti-inflammatory, antibacterial, antioxidant, hepatoprotective, gastroprotective and cytotoxic response whereas more potential activities are still under investigation [3–7]. The leaf processed as a drink or as poultice for external use is often prescribed [8].

The search for neuropharmacological potential of medicinal plants has always been crucial due to the limited numbers of agents in the therapeutic line with proven efficacy. The ability of leaf of *D. linearis* to control muscarinic receptors proposes for new therapeutic use against Alzheimer's disease and schizophrenia [9, 10]. Though other studies have focused on the anxiolytic and sedative responses [1], no studies have been reported on the antidepressant investigation of the *D. linearis* leaf. Moreover, finding effective pharmacotherapy for major depressive disorders has been a major challenge for long. The time demand together with the proven neuropharmacological efficacy of this plant makes it a potential candidate for evaluating antidepressant activities as well. The present study was thus designed to investigate the antidepressant potential of the leaf of *D. linearis* by a comparison of three different solvent extracts.

Methodology

Preparation of extract

Approximately 6–7 kg of *D. linearis* leaf was collected from the district of Mymensingh (24°45′14″N 90°24′11″E) of Bangladesh in Jun, 2014. After collection the leaf was identified by Bangladesh National Herbarium and a sample specimen was kept with the accession number DACB 42009. The leaf was first washed thoroughly to clean from dust and dirt. These are sun dried and crushed in to powder (approximately 600 g) with a grinder. Then the powder was immersed separately in three different solvents for 7 days to get aqueous (DLAQ), ethanol (DLET) and ethyl acetate (DLEA) extracts. Finally, the solution was filtered with cellulose filter paper and condensed with the help of rotary evaporator to make viscous leaf extracts [11].

Drugs and reagents

Imipramine Hydrochloride (Incepta Pharmaceuticals Ltd.), Sodium Pentobarbitone (Sigma-Aldrich Inc.), Diazepam (Square Pharmaceuticals Ltd.), Caffeine (Square Pharmaceuticals Ltd.), Ethanol (Merck, Germany) and Ethyl Acetate (Merck, Germany) were obtained for the experiments.

Preliminary screening

Acute toxicity study

Sixteen groups ($n = 5$) of male-female Swiss Albino mice were isolated for acute toxicity test and those were not re-selected for any further investigation. They were exposed to high strengths (250 mg/kg, 500 mg/kg, 1000 mg/kg, 2000 mg/kg, 3000 mg/kg per body weight) of the test agents alongside a control group (did not receive any extract) by oral administration and observed for next 72 h for any lethality.

Pentobarbitone induced sleeping time test

The test was performed to investigate the sedation and stimulation potential of the extracts in doses to be tested on mice. Female mice were randomly assigned to nine groups ($n = 6$) and orally received either *D. linearis* extracts (DLAQ 200, DLAQ 400, DLET 200, DLET 400, DLEA 200, DLEA 400 $mg.kg^{-1}$ b.w.) as test agents, diazepam (1 $mg.kg^{-1}$ b.w.) as sedative standard, caffeine (5 $mg.kg^{-1}$ b.w.) as stimulating standard, or 1% tween in distilled water (10 $ml.kg^{-1}$ b.w.) as negative control. Sleep was induced to the rodents by intraperitoneal injection of 50 $mg.kg^{-1}$ sodium pentobarbitone, 1 h after respective drug treatments. The observation of latency to sleep as defined by the time between pentobarbitone injection and loss of righting reflex and duration of sleep as the time between loss of and regaining of righting reflex were recorded [12].

Acute antidepressant tests

Animal groups

Fresh Swiss Albino mice with sound health and mental conditions, female aged 40–45 days, weighed 25–30 g were selected for the studies. Prior each experiment, eight groups were formed consisting six mice in each depending upon the treatment they received. The groups were as followed: control (dH2O), standard (imipramine hydrochloride 3 ($mg.kg^{-1}$), DLAQ 200 ($mg.kg^{-1}$), DLAQ 400 ($mg.kg^{-1}$), DLET 200 ($mg.kg^{-1}$), DLET 400 ($mg.kg^{-1}$), DLEA 200 ($mg.kg^{-1}$) and DLEA 400 ($mg.kg^{-1}$) as per body weight. Standard animal handling

and treatment guideline was followed for all the investigations [13].

Forced swim test

In this experiment mice were subjected to forced swim when dropped in a water filled (15 cm) top open glass cylinder (25 × 15 × 25 cm) to check the immobility [8]. Sixty minutes after oral administration of the test agents, mice were placed in the water (24 ± 1 °C) and observed for the duration of immobility, latency to immobility, climbing, and swimming for the next four minutes to check the anti-depressant activity. First one minute of this study were excluded to avoid handling shock. Imipramine hydrochloride and distilled water served as the positive and negative controls respectively for this study. After the exposure period, animals were withdrawn from the cylinder and gently dried with a towel and kept in a warm place until completely dried. The increase in latency and decrease in duration of immobility typically indicate antidepressant-like activities. Whereas the escape-oriented behavior like climbing and swimming give clues to predict possible mechanisms of action of the test agents [14].

Tail suspension test

Tail suspension is another mode of investigation of immobility exhibited by the mice when they are hanged by the tail [9]. One hour after the oral gavage of the test agents, mice were marked at 1 cm from the tip of the tail. Imipramine hydrochloride was used as the positive standard for this experiment. They were hanged at the tip 50 cm above the ground and kept suspended for the next four minutes where the last three minutes were observed for the immobility time (without engaging in any active behavior), swinging time (continuously moving its paws in vertical position keeping body straight and/or moving body side to side), curling time (engaged in active twisting movements of entire body) and pedaling (moved its paw continuously without moving its body). During the experiment, any mice climbed by its tail, was gently pulled down and allowed to proceed with the experiment [15].

Statistical significance

One-way analysis of variance (ANOVA) followed by Dunnett's t tests were performed for statistical analysis of data using SPSS 20 for windows. All results were compared with the negative control where P values < 0.05, 0.01 and 0.001 were considered to be statistically significant.

Results

Acute toxicity study

Oral administration of high doses of the test agents produced no lethal effect however were associated with abnormal conditions. Table 1 showed that the aqueous, ethanol and ethyl acetate extracts at 3000 $mg.kg^{-1}$ per body weight caused indigestion. The toxicity study aided to design safe dose line for further investigation.

Pentobarbitone induced sleeping time test (PIST)

After pentobarbitone pretreatment the acute administration of *D. linearis* extracts showed decrease in latency of losing the righting reflex in which DLAQ 400, DLEA 200 and 400 $mg.kg^{-1}$ were found significant ($p < 0.5$) compared to control. Maximum reduction in latency was observed by Diazepam (1 $mg.kg^{-1}$) in 4.2 min whereas the CNS stimulant caffeine (16 $mg.kg^{-1}$) prolonged the onset till 26.4 min (Fig. 1a).

Figure 1b showed diazepam significantly ($p < 0.001$) increased the duration of sleep (126.75 min) in comparison with control (48.24 min). DLEA 200 followed the same pattern (86.00 min, $p < 0.5$). On the contrary, caffeine exhibited the shortest sleeping time (29.45 min) among all groups.

Antidepressant tests

Forced swim test (FST)

The duration of the animals exhibited with no physical action in the swimming cylinder was found minimum (53.25 s) with imipramine 1 $mg.kg^{-1}$ (Fig. 2a). DLET 400 closely mimicked (59.5 s) the standard. Both DLAQ and DLEA found to have mild effect on decreasing the activity at higher dose (400 $mg.kg^{-1}$). Figure 2b demonstrated that the latency to immobile condition was significantly increased by DLET 200 ($p < 0.05$) and 400 ($p < 0.01$) next to imipramine ($p < 0.001$).

The climbing response was found highest with DLEA 200 (57.85 s, $p < 0.01$) compared to control (20.75 s). Imipramine exhibited the lowest response (10.25 s) and DLET 400 followed to reduce the forced activity (Fig. 2c). The standard also significantly ($p < 0.01$) increased the swimming activity while DLET 400 showed similar response (Fig. 2d).

Tail suspension test (TST)

Like forced swim test, DLET (400 mg/Kg b.w) showed a decrease in the immobility time (51.35 s $p < 0.05$) compared to the standard drug imipramine (46.50s, $p < 0.01$) (Fig. 3a). All other test groups could not establish significant difference with the control (108.75 s). Figure 3b depicts that control mice did not produce much swinging activity. On the contrary, imipramine, DLET 400 and DLEA 400 significantly increase the activity.

Figure 3c showed that the curling response in tail suspension test was increased by imipramine, DLAQ 200 and DLEA 400. DLET inversely acted to decrease the activity. Among the three extracts DLAQ 400 was able to reduce the pedaling time by the mice in comparison

Table 1 Acute Toxicity Study Report of *D. linearis* leaf extract

Groups	Test Agents	Dose Strength (mg.kg^{-1} b.w.)	Lethality (D/T)	Abnormal Effect
1	d.H_2O (control)	0	0/5	–
2	DLAQ	250	0/5	–
3	DLAQ	500	0/5	–
4	DLAQ	1000	0/5	–
5	DLAQ	2000	0/5	–
6	DLAQ	3000	0/5	Indigestion
7	DLET	250	0/5	–
8	DLET	500	0/5	–
9	DLET	1000	0/5	–
10	DLET	2000	0/5	Indigestion
11	DLET	3000	0/5	Indigestion
12	DLEA	250	0/5	–
13	DLEA	500	0/5	–
14	DLEA	1000	0/5	–
15	DLEA	2000	0/5	–
16	DLEA	3000	0/5	Indigestion

D = Deaths recorded, T = Total numbers treated, DLAQ = Aqueous extract of *D. linearis*, DLET = Ethanol extract of *D. linearis*, DLEA = Ethyl Acetate extract of of *D. linearis*

with the control though having no significant difference (Fig. 3d).

Discussion

Acute toxicity study is often considered a determinant for safe dose lining. The present study suggested that *D. linearis* leaf extracts were free from the risks of mortality at the given doses. However, abnormalities in digestion were observed at very high doses (3000 mg.kg^{-1}) which was also evident in comparatively lower doses (2000 mg.kg^{-1}) but particularly for ethanol extract. The indigestion was characterized by slightly olive to greenish stools compared to that of observed in mice administered with lower doses.

The leaf of *D. linearis* contains high total phenolic content (TPC), flavonoids (particuarly of flavonol 3-Oglycosides types), triterpenes, saponins and high content of steroids [16, 17]. Preparation of the leaf in three different solvents potentiate the chance of extracting maximum number of the bioactive components. Aqueous extract contained polar; ethanol held slightly polar to nonpolar while ethyl acetate obtained the nonpolar compounds [1]. The presence of phenolic compounds demonstrates good antidepressant-like activity [18–20]. Flavonoids plays a vital role in exhibiting antidepressant-like activity [21]. Direct evidences of such activity by triterpenes and saponins through FST and TST were reported in the literatures [22, 23]. Moreover, studies

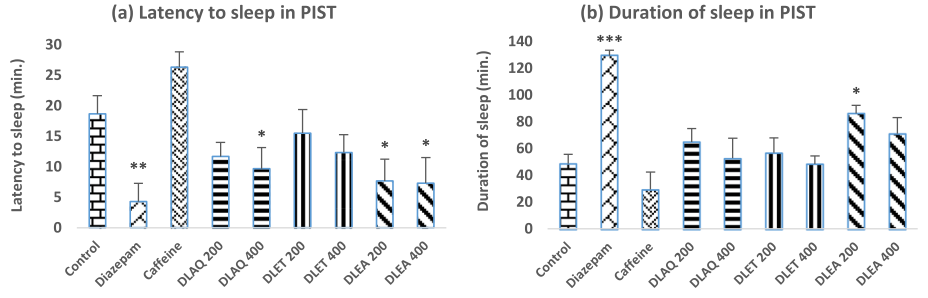

Fig. 1 a-b: Observation parameters of Pentobarbitone Induced Sleeping Time Test (PIST). Figure represented the latency to sleep (**a**) and duration of sleep (**b**) in minutes exhibited by the respective groups of mice. DLAQ = Aqueous extract of *D. linearis*, DLET = Ethanol extract of *D. linearis*, DLEA = Ethyl Acetate extract of of *D. linearis*. Data represented as mean + SEM and analyzed by one-way ANOVA followed by Dunnett t test where *, **, *** denoted $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively and statistically significant. All groups ($n = 6$) were compared to control

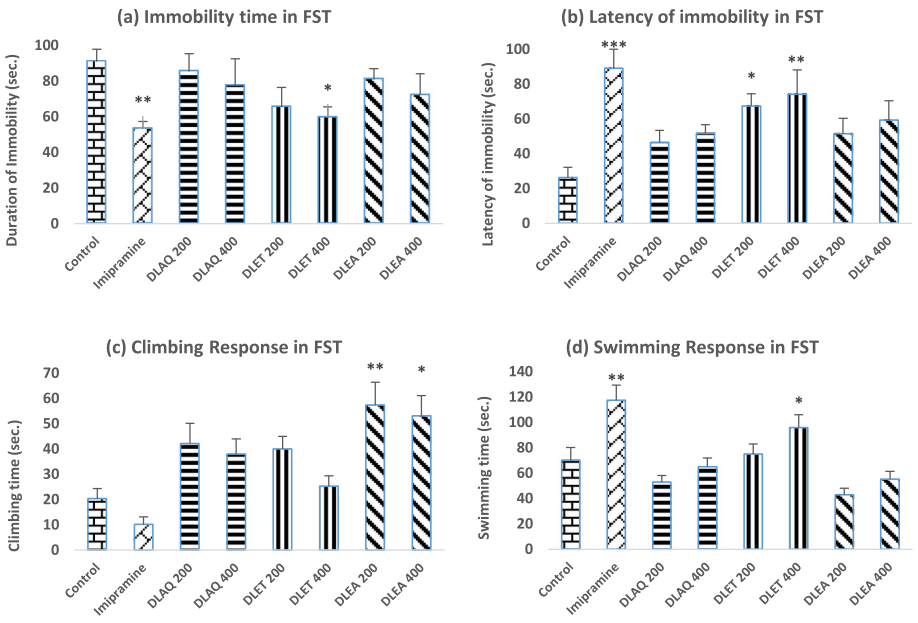

Fig. 2 a-d: Observation parameters of Forced Swim Test (FST). Figure represented the duration of immobility (**a**), latency of immobility (**b**), climbing time (**c**) and swimming time (**d**) measured in seconds exhibited by the respective groups of mice. DLAQ = Aqueous extract of *D. linearis*, DLET = Ethanol extract of *D. linearis*, DLEA = Ethyl Acetate extract of of *D. linearis*. Data represented as mean + SEM and analyzed by one-way ANOVA followed by Dunnett t test where *, **, *** denoted $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively and statistically significant. All groups ($n = 6$) were compared to control

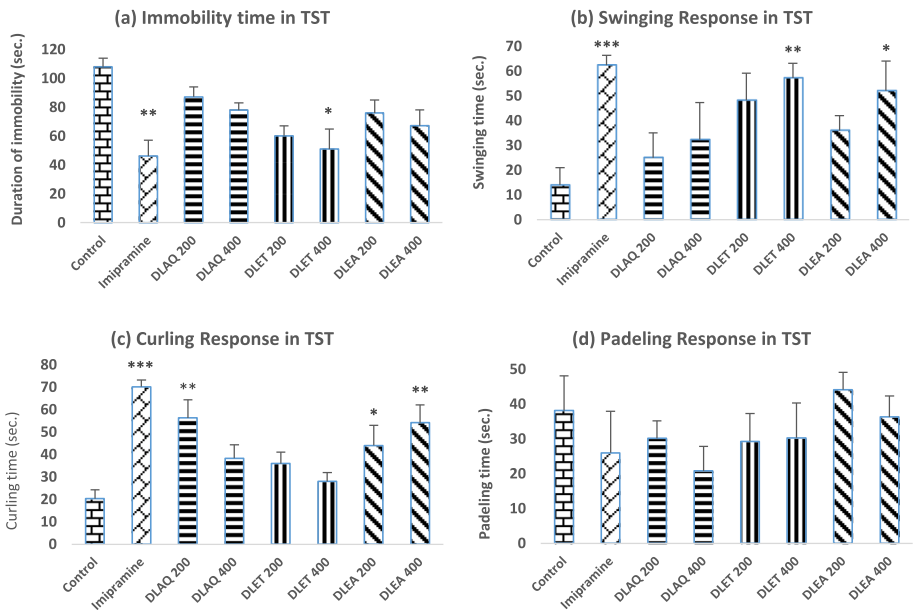

Fig. 3 a-d: Observation parameters of Tail Suspension Test (TST). Figure represented the duration of immobility (**a**), swinging response (**b**), curling time (**c**) and pedaling time (**d**) measured in seconds exhibited by the respective groups of mice. DLAQ = Aqueous extract of *D. linearis*, DLET = Ethanol extract of *D. linearis*, DLEA = Ethyl Acetate extract of of *D. linearis*. Data represented as mean + SEM and analyzed by one-way ANOVA followed by Dunnett t test where *, **, *** denoted $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively and statistically significant. All groups ($n = 6$) were compared to control

proved that steroids are found to reduce the immobility in FST [24, 25]. Further investigation is required to identify the particularly responsible bioactive compounds which can validate the claims of this study.

In FST, antidepressants acting through the serotonergic system decrease the immobility period and selectively increase the swimming response [26]. In addition, increase in climbing behavior is observed with the drug acts through noradrenergic mechanism [27, 28]. The data showed DLEA 200 and 400 had an increase in climbing response suggesting the involvement of noradrenergic mechanism however, the decrease in swimming activity reversed the possibilities of a serotonin mediated response. On the other side, DLET in both cases increased the response indicating dual effects [29, 30]. Like imipramine, DLET increased the latency to immobile condition but significantly reduced the duration of immobility resulting in antidepressant-like activity.

Similarly, in TST, antidepressants act through inhibiting serotonin and/or NA reuptake, decrease immobility and increase swinging behavior of the animal [26]. One the contrary, opioids result in decreased immobility and increased curling behavior [31]. DLEA was found with decreased immobility but increased swinging and curling response as like imipramine suggesting the possible involvement of opioidergic mechanism. DLET increased the swinging response and reduced the immobility time but unlikely also reduced the curling activity. Arbitrary pedaling activity was observed with no significant difference with the control.

Pentobarbitone is a barbituric acid derivative which help induces sleep in rodents by binding GABA receptor complex. The drug is used for GABA mediated hyperpolarization of postsynaptic neurons. Pentobarbitone induced sleep test involves mechanism of GABA potentiation and hindrance of excitatory glutamate receptor, which all together produces molecular action lead to abate neuronal activity [32]. In this study, none of the extracts exhibited extreme duration of sleep which can be attributed to a sedative potential. The antidepressant-like activity of the extracts thus seems not to be associated with the sleep.

Conclusion

Antidepressant-like activity was measured with forced activity tests where inactivity represented the development of confidence level which was an indication of antidepressant-like activity. Standard drug imipramine showed a decrease in the duration of immobility alternatively increasing the swimming time. In search of the antidepressant-like activity by the extracts of *D. linearis*, ethanol extract proved to be highly potent among others. Ethyl acetate extract resulted in some interesting findings regarding the hypothesis of its mechanism which eventually demanded a new area of investigation. Further phytochemical screening and in vitro analysis is recommended to establish the scientific basis of its activity.

Abbreviations

DLAQ: Aqueous extract of *D. linearis*; DLET: Ethanol extract of *D. linearis*; DLEA: Ethyl Acetate extract of of *D. linearis*.; b.w: Body weight; i.p: Intraperitoneal; p.o.: Per oral; GABA: Gamma-Amino Butyric Acid; TST: Tail Suspension Test; FST: Forced Swim Test; CNS: Central Nervous System; NA: Noradrenaline

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MMB and KN designed coordinated and supervised the project. ASC performed in vivo experiments and prepared the graphical presentations. MSM participated in the experiments and analyzed the data. Authors MAR prepared the extracts, coordinated the preliminary screening and prepared the manuscript. MRA participated in interpretation of data to reach a scientific discussion and critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All experiments associated with animal handling were performed in accordance with the Guide for the Care and Use of Laboratory Animals, 8th ed.; The National Academies Collection adopted by the institutional guideline for animal handling (Ref. no. IPSDRLAB/AHCP/01/18). The experimental design was authorized by the Institutional Ethical Committee Clearance (Ref. No. IPSDRLAB/IECC/17/19) of Institute for Pharmaceutical Skill Development and Research, Bangladesh (project approved on 20/11/2019).

Consent for publication

Not applicable.

Competing interests

All authors agreed on the article before submission and had no conflict of interests.

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