International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(RESEARCH ARTICLE)

Evaluation of the anticonvulsant properties of the ethanol extract of *Detarium senegalense* leaves in mice

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International Journal of Biological and Pharmaceutical Sciences Archive, 2022, 03(02), 067–073

Publication history: Received on 25 March 2022; revised on 04 May 2022; accepted on 06 May 2022

Article DOI: https://doi.org/10.53771/ijbpsa.2022.3.2.0049

Abstract

Detarium senegalense, J.F. Gmelin (Fabaceae) is used in Nigerian folk medicine to treat different diseases including epilepsy, microbial infections, gastrointestinal diseases and inflammation; its efficacy is widely acclaimed among communities in South Eastern Nigeria. The leaf extract (100 mg/kg, 200 mg/kg and 400 mg/kg) was evaluated for its anticonvulsant activity in mice. Three different study models were used; pentylenetetrazole (PTZ), brucine and isoniazid (INH) convulsion methods. The acute toxicity study and the phytochemical analysis of the extract were also determined. The extract produced significant ($p<0.05$ and $p<0.01$) dose-dependent delay in onset, frequency and duration of seizures in mice in the three models of convulsion which is comparable to the standard anticonvulsant drug. The oral acute toxicity test was greater than 5000 mg/kg in mice. The phytochemical screening revealed that *D. senegalense* leaf extract contains bioactive principles that are relevant in the management of seizure disorders. These findings suggest that *D. senegalense* leaf extract possesses anticonvulsant properties and justifies its use in traditional medicine.

Keywords: Anticonvulsant activity; *Detarium senegalense* leaf; Pentylenetetrazole; Brucine; Isoniazid; Mice

1. Introduction

Epilepsy has been described as one of the most common chronic non communicable neurological ailments with no age, social, sexual or geographical boundaries [1]. Epilepsy, which has a high prevalence among people of all ages, is a serious and diverse set of chronic neurologic disorders characterized by spontaneously occurring seizures [2]. It has been estimated that about 50 million people worldwide live with epilepsy, and that greater than 85 % of this disease occurs in low-income and middle-income countries [3]. The stigmatization has long been recognized as a major challenge to people with this disease and their families especially in sub-Saharan Africa where the combination of poverty, social role expectations, limited medical care, and traditional beliefs blend to severely limit the lifespan of epileptics [4]. Synthetic drugs used for brain disorders are expensive and sometimes show serious and unavoidable side effects with poor patient compliance. Hence, herbal agents are preferred over synthetic drugs for neurological disorders like anxiety, epilepsy, depression schizophrenia Parkinson disease, Alzeheimer due to low cost, lesser side effects, and better therapeutic effect. The accessibility, negligible incidence of side effects, and cost effectiveness of plant products offer considerable benefits over synthetic drugs [5].

Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown activity when tested in modern bioassays for the detection of anticonvulsant activity [6]. Medicinal plants used for the therapy of

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epilepsy in traditional medicine have been shown to possess promising anticonvulsant activities and can be valuable source of new antiepileptic drugs [7].

Detarium senegalense, J.F. Gmelin which belong to the family Fabaceae, is a native to the West African region, particularly Senegal, where it was first discovered. The tree grows well in forests along the river banks and in the savannah [8]. *D. senegalense* tree is deciduous, with a relatively short trunk (ranging from 15-36 metres), and a wide, very leafy crown. The tree germinates from the stones or seeds, with the process taking about 6-10 weeks. The seeds are usually spread or propagated by animals after consuming the fruits. The trees are hardy, and can survive in harsh conditions such as unfavourable altitude, humidity and heat. It is commonly known as tallow tree and widely used in herbal medicine in Nigeria. It has a considerable commercial in food and pharmaceutical industries [9]. Among the Ibo tribe of south eastern Nigeria, the plant known as "Ofo" is believed to be a "religious" tree which grows in God's own compound, symbolizing truth and honestly [10]. It is the most investigated specie of the genus because of its popular use in African traditional medicine.

Different parts of the plant are used in folk medicine for wide variety of remedies such as fever, anaemia, treatment of diarrhoea, cough, ulcer, worm infestation, management of epilepsy, and cancer. Previous pharmacological studies revealed that extract of *D. senegalense* was found to possess antidiarrhoeal activity [11], antimicrobial activity [12, 13], antiproliferativ activity [14], Anthelminthic [15].

The current study evaluated the possible anticonvulsant effect of the ethanol leaf extract of *D. senegalense* to justify the traditional use of the leaves of this plant in epilepsy.

2. Material and methods

2.1. Plant Material Collection and Authentication

The fresh leaves of *D. senegalense* were sourced from Chaza, Niger State, by an ethnobotanist, Mallam Muazam in the department of Medicinal plants and traditional medicine (NIPRD, Abuja). The plant was identified and authenticated in the same department by a taxonomist.

2.2. Preparation of Plant and Extraction Procedure

The fresh leaves of *D. senegalense* were cleaned, cut into pieces and dried under room temperature. The dried leaves were ground into powder with the aid of pestle and mortar and sieved to obtain fine materials. Thereafter, 450 g of the powdered material was soaked in 1.5 litre of ethanol for 48 hours using maceration method. The solution was filtered through Whatmann (No. 25) filter paper into a conical flask. The filtrate was then concentrated to dryness on a water bath set at temperature of 40 ^{0}C.

2.3. Experimental Animals

One hundred and two (102) mature Swiss mice of both male and female gender weighing between 18-25 g were used for this study. They were sourced from Animal House of the Department of Veterinary Medicine, University of Nigeria, Nsukka. The mice were kept in plastic cages and allowed to acclimatize in laboratory environment for 14 days. During the period of study, animals were given pellets (Guinea Feeds, Plc Nigeria) and provided with clean water *ad libitum.*

2.4. Phytochemical analysis

The method as described by Inyang *et al*.,[16], Aziz, [17]) was adopted for the phytochemical analysis of the ethanol extract of *D. senegalense* leaves. The metabolites that were assayed include tannins, saponins, alkaloids, flavonoids, terpenoids, steroids, anthraquinones, glycosides, reducing sugars and resins.

2.5. Acute Toxicity Test

This was determined following the method described by Lorke [18]. The study was carried out in two phases. In the first phase, nine mice were divided into three groups of three mice each. They were given 10 mg/kg, 100 mg/kg and 1000 mg/kg of the leaf extract respectively. They were then monitored for signs of toxicity initially for first 4 hours, and then for 24 hours. The signs of toxicity that were looked out for include hyperactivity, paw licking, respiratory distress, and mortality. At the end of the first phase, there was no mortality. The study then proceeded to the second phase. In this phase, three mice were grouped into three with one mouse in each group, and given 1600 mg/kg, 2900 mg/kg and 5000 mg/kg of the extract respectively, and then monitored for signs of toxicity as stated earlier. The animals were further monitored for 48 and 72 hours for signs of late toxicity.

2.6. Anticonvulsant Studies

2.6.1. Pentylenetetrazole -induced convulsion in mice

The procedure described by Shimada and Yamagata [19] was employed. Thirty mice were randomized and separated into five groups of six mice each. Group one representing the negative control or drug free group was pre-treated with 20 ml/kg of distilled water (p.o.), while groups two, three and four were pre-treated with graded doses of the ethanol leaf extract of *D. senegalense*. All administrations were given with intragastric cannula. The fifth group of mice (positive control group) were pre-treated with Sodium Valproate. Thirty minutes after treatment with the extract, 90 mg/kg of pentylenetetrazole solution was administered subcutaneously to each mouse. The animals were monitored for 30 minutes for presence or absence of threshold seizures.

2.6.2. Brucine - induced convulsion in mice

The method of Chimbalkar and Vyawahare, [20] was adopted for this experimental study. Thirty mice were divided into 5 groups of 6 mice in a cage. Group 1 was orally treated with 20 ml/kg distilled water. Groups 2, 3 and 4 were administered graded doses of the ethanol leaf extract of *D. senegalense*, while group 5 was treated with Sodium Valproate. Thirty minutes after administration, convulsion was induced intraperitoneally in mice with 110 mg/kg of Brucine. Thereafter, each mouse was placed in a different cage and monitored for onset of convulsion, duration of convulsion, mortality and percentage protection for thirty minutes.

2.6.3. Isoniazid (INH) – induced convulsion in mice

This procedure was carried out following the method of Govindu and Adikay, [21] Thirty mice were divided into 5 groups of 6 mice per cage. Group 1 was treated with 20 ml/kg distilled water. Groups 2, 3 and 4 were orally administered graded doses of the ethanol leaf extract of *D. senegalense*, while group 5 was treated with Sodium Valproate. Thirty minutes post drug administration, convulsion was induced intraperitoneally in mice with 250 mg/kg of Isoniazid (INH). Thereafter, each mouse was placed in a different cage and monitored for onset of convulsion, duration of convulsion, mortality and percentage protection for thirty minutes.

2.7. Statistical Analysis

Data were expressed as mean± SEM and analysed with statistical package for social sciences (SPSS version 20), using one-way analysis of variance (ANOVA), followed by Dunnett's test. A difference in the mean $p<0.05$ was considered as statistically significant.

3. Results

3.1. Phytochemical analysis

It is important to know the chemical nature of plant products when their pharmacological responses are screened [17]. Phytochemical evaluation of *D. senegalense* extract showed the presence of the following secondary metabolites; alkaloids, saponins, tannins, flavonoids, terpenoids, steroids, cardiac glycosides, resins and balsam.

3.2. Acute toxicity test

There were no lethality or toxic reactions observed at any of the doses administered. All the mice were healthy and active during and after the period of study. Hence, oral acute toxicity result was greater than 5000 mg/kg in mice.

3.3. Effect of *D. senegalense* leaf extract on pentylenetetrazole-induced seizure in mice

The result of PTZ-induced convulsion showed that *D. senegalense* extract significantly ($p<0.05$ and $p<0.01$) delayed the onset and duration of seizures. Sodium valproate (200 mg/kg), the standard anticonvulsant used, completely protected the animals against PTZ-induced seizures in mice. (Table 1).

3.4. Effect of *D. senegalense* leaf extract on brucine-induced seizure in mice

The ethanol leaf extract of *D. senegalense* showed significant ($p<0.05$ and $p<0.01$) dose dependent protection against brucine-induced convulsion in mice, with highest percentage protection against seizure observed at 400 mg/kg. While the standard anticonvulsant drug, sodium valproate at 200 mg/kg produced significant ($p<0.01$) protection of all the mice from death (Table 2).

3.5. Effect of *D. senegalense* leaf extract on INH-induced convulsion in mice.

The result of INH induced seizure in mice showed significant ($p<0.05$ and $p<0.01$) dose-dependent mean onset of convulsion and death, and percentage protection among the groups that received 100 mg/kg, 200 mg/kg and 400 mg/kg of the extract respectively, with the greatest duration and highest percentage protection seen in the group that received 200 mg of Sodium Valproate (Table 3). However, a greater significance was observed in the groups of mice that were given 400 mg/kg of the extract and 200 mg of Sodium Valproate ($p<0.01$).

Table 1 Effect of the ethanol leaf extract of *D. senegalense* on pentylenetetrazole-induced convulsion in mice

Drug	mg/kg	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 ml/kg	7.24±0.30	8.05±0.59	0/6	6	0.00
D. senegalense	100 mg/kg	13.42±0.71	25.48±0.14	3/6	3	50[a]
D. senegalense	200 mg/kg	15.12±0.39	29.18±1.49	4/6	2	67[a]
D. senegalense	400 mg/kg	16.33±0.25	32.38±1.74	5/6	1	83[b]
Sodium Valproate	200 mg	-	-	-	-	100[b]

Results are expressed as mean± SEM; (n=6), by one-way ANOVA followed by Dunneet's Multiple Comparison Test (compared with control group)
[a] $p<0.05$, [b]$p<0.01$.

Table 2 Effect of ethanol leaf extract of *D. senegalense* on brucine-induced convulsion in mice

Drug	mg/kg	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 ml/kg	6.23±0.52	6.40±0.63	0/6	6	0.00
D. senegalense	100 mg/kg	13.32±0.24	23.35±0.82	3/6	3	50[a]
D. senegalense	200 mg/kg	15.19±0.53	26.52±0.46	4/6	2	67[a]
D. senegalense	400 mg/kg	16.25±2.22	31.38±2.11	5/6	1	83[b]
Sodium Valproate	200 mg	-	-	-	-	100[b]

Results are expressed as mean± SEM; (n=6), by one-way ANOVA followed by Dunneet's Multiple Comparison Test (compared with control group)
[a]$p<0.05$, $p<$ [b]0.01

Table 3 Effect of ethanol leaf extract of *D. senegalense* on INH-induced convulsion in mice

Drug	mg/kg	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 ml/kg	4.15±0.20	5.56±0.28	0/6	6	0.00
D. senegalense	100 mg/kg	14.35±0.38	25.16±0.35	3/6	3	50[a]
D. senegalense	200 mg/kg	14.56±0.43	29.02±1.60	4/6	2	67[a]
D. senegalense	400 mg/kg	16.12±0.28	34.07±0.18	5/6	1	83[b]
Sodium Valproate	200 mg	-	-	-	-	100[b]

Results are expressed as mean± SEM; (n=6), by one-way ANOVA followed by Dunneet's Multiple Comparison Test (compared with control group)
[a] $p<0.05$, [b]$p<$ [b]0.01

4. Discussion

The preliminary phytochemical screening of *Detarium senegalense* ethanol leaf extract revealed the presence of secondary metabolites like alkaloids, saponins, tannins, flavonoids, terpenoids, steroids and cardiac glycosides, which have been previously reported to have different neuropharmacological effects [22, 23]. The broad spectrum of the observed anticonvulsant effects in this study might be attributed to the presence of different biologically active components in the extract. The oral LD50 of the ethanol leaf extract of *D. senegalense* was greater than 5000 mg/kg in mice, suggesting its apparent safety.

Pentynelentetrazole-induced seizures test represents a valid model for human absence seizures [24], and has been employed experimentally to study seizure phenomenon and to identify agents that may raise seizure threshold [25]. The animal models used in this study were selected to represent different human seizure types (generalized tonic, clonic and myoclonic seizures; simple and complex partial seizures). The ability of the leaf extract to delay the onset of convulsions and/or shorten the frequency and duration of convulsions in three various models were considered as an indication of anticonvulsant activity. Inhibition of seizures induced by PTZ in laboratory animals is the most common predictive screening test used for characterizing potential anticonvulsant drugs [26]. Anticonvulsant activity against PTZ seizures also identifies compounds that can raise seizure threshold in the brain [27]. The anticonvulsant actions exhibited in the PTZ model therefore suggests that it may be effective against generalized myoclonic and absence seizures. *D. senegalense* may also have the ability to increase seizure threshold in the brain. The PTZ-induced seizures are similar to the symptoms observed in the absence seizures and drugs such as valproate, diazepam, and ethosuximide, which are useful in the treatment of the absence seizures and suppress PTZ induced seizures [28]. It has been found empirically that drugs which inhibit PTZ-induced seizures and raise the threshold for production of electrically induced seizures are generally effective against absence seizures [29]. The ability of *D. senegalense* extract to protect the animals against PTZ-induced seizures suggests anticonvulsant activity against absence seizures (petit mal) or myoclonic seizures. Thus, *D. senegalense* may be useful in the management of petit mal (absence) and/or myoclonic epilepsy.

In the brucine-induced seizure study, it is known that brucine directly antagonizes the inhibitory spinal reflexes of glycine [30]. *D. senegalense* leaf extract strongly protected the animals against brucine induced seizures. The convulsing action of brucine is due to the interference with postsynaptic inhibition mediated by glycine, an important inhibitory transmitter of the motor neurons and interneurons in the spinal cord [27]. Brucine acts as a selective, competitive antagonist at all glycine receptors [31]. The ability of the extract to inhibit brucine induced seizures demonstrates anticonvulsant effects mediated via glycine receptors [32].

D. senegalense delayed the onset of myoclonic seizure induced by INH in a dose-dependent manner. Since INH is a GABA synthesis inhibitor, it is likely that *D. senegalense* leaf extract produces its anticonvulsant effect by enhancing GABAergic neurotransmission action in the brain by augmenting the synthesis of GABA [33]. The standard anticonvulsant drug, valproate 200 mg/kg totally abolished the effects of INH induced convulsion in mice. It is well known that one of the factors responsible for isoniazid-induced convulsions is the decrease of GABA below a critical level in some neurons. Isoniazid was shown to lower the content of brain GABA to approximately the same extent in rats and mice [21]. Perhaps, the decrease in the amount of GABA stored presynaptically causes a reduction in the amount of GABA released by nerve impulses. Hence, the GABA receptors are regulated at the level of maximal sensitivity in order to maximize the action of GABA. INH induced convulsion in mice significantly delayed the onset of seizure, prolonged the duration of action and suggesting that *D. senegalense* extract has a stronger protective effect in mice.

5. Conclusion

The finding of this study suggests that *Detarium senegalense* ethanol leaf extract contains biologically active principles that are relevant to the management of convulsive disorders, thus justifying its use in herbal medicine for the treatment of seizures. Further studies are ongoing in our laboratory to isolate and characterize the bioactive compounds responsible for the anticonvulsant activity of this plant.

Compliance with ethical standards

Acknowledgments

The authors are grateful to Mr. Emmanuel Ogbonna and Mrs. Oby Onwura for their technical assistance.

Disclosure of conflict of interest

There is no conflict of interest associated with the authors of this paper.

Statement of ethical approval

The study protocol was carried out as per the rules and regulations of the Institutional Animal Ethical Committee, Faculty of Basic Clinical Sciences, Nnamdi Azikiwe University, Nnewi campus, as well the National Institute of Health Guide for the care and use of Laboratory Animals.

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