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(RESEARCH ARTICLE)

The anti-seizure and anti-nociceptive potential of hexane fraction from the leaves of *Detarium senegalense*

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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. This study aimed to evaluate the anti-seizure and anti-nociceptive potential of hexane fraction from the leaves of *D. senegalense* The hexane fraction of *D. senegalense* leaf was evaluated to determine the effect of the oral administration of the extract (100 – 400 mg/kg) against seizure using the pentylenetetrazole (PTZ), brucine, isoniazid (INH) induced seizure models and analgesic activity using the writhing and water tail immersion tests in mice. The hexane fraction of the extract significantly ($p<0.05$) increased the latency period in seizures induced by PTZ, brucine and isoniazid, and significantly reduced the duration of seizures induced by these three inducing agents. The extract also protected 67 % of animals against death. In acetic acid-induced writhing models and tail immersion models, the fraction showed a good analgesic effect characterized by a significant ($p<0.05$ – $p<0.01$) reduction in the number of writhes when compared to the control and a significant ($p<0.05$ – $p<0.01$ increase in the latency in a dose-related manner. The findings of the present study validated the folkloric use of *Detarium senegalense* leaves in seizure disorders as well as painful conditions.

Keywords: Herbal medicine; Antiseizure activity; Analgesic; Hexane fraction; *Detarium senegalense* leaf; Mice

1. Introduction

Detarium senegalense, J.F. Gmelin which belongs to the family Fabaceae, is native to the West African region, particularly Senegal, where it was first discovered. The tree grows in forests along the river banks and the savannah [1]. *D. senegalense* tree is deciduous, with a relatively short trunk, and wide and leafy crown. The tree germinates from the stones and seeds, with the process taking over 9 weeks. The seeds are always propagated by animals after consuming the fruits. The trees are hardy but can survive in harsh conditions such as unfavourable altitude, humidity and hot environment. *D. senegalense* plant is widely used in herbal medicine in Nigeria. It has a considerable commercial in the

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food and pharmaceutical industries [2]. Among the Igbo 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 [3]. *D. senegalense* 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 a great variety of remedies such as fever, anaemia, diarrhoea, cough, ulcer, worm infestation, and management of epilepsy and cancer. Previous pharmacological studies revealed that extract of *D. senegalense* possesses antidiarrhoeal activity [4], antimicrobial activity [5, 6], antiproliferative activity, Anthelminthic and anticonvulsant [7, 8, 9].

The present work was undertaken to evaluate the antiseizure and antinociceptive activities from the hexane fraction leaf extract of *D. senegalense* to justify its traditional use in epilepsy and painful condition.

2. Materials and Method

2.1. Plant 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. A voucher sample number with NIPRD/H/7082 was prepared and deposited in the herbarium of department for reference.

2.2. Preparation of plant and extraction procedure

The fresh leaves of *D. senegalense* were cleaned, cut into pieces and dried at room temperature. The dried leaves were ground into a powder with the aid of a pestle and mortar and sieved to obtain fine materials. Thereafter, 350 g of the powdered material was extracted in 1.5 litres of 96 % ethanol. The crude ethanol extract was fractionated using n-hexane and concentrated in a rotary evaporator at 40 ℃ under reduced pressure.

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 the Animal House of the Department of Veterinary Medicine, University of Nigeria, Nsukka. The mice were kept in plastic cages and allowed to acclimatize in a 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-Agha, [10], Aziz, [11] was adopted for the phytochemical analysis of n-hexane fraction extract of *D. senegalense* leaves.

2.5. Acute toxicity test

This was determined following the method described by Lorke [12]. 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 the 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. Pentylenetetrazole –induced seizure test

The anticonvulsant activity of *D. senegalense* was evaluated using the method of Nagaraja et al. [13] was used in the study. Adult Swiss mice were randomly divided into five groups (n=6). Animals in group one representing the negative control (drug-free) were given 10 mL/kg normal saline via the intraperitoneal route, the second (reference drug) group was treated with 200 mg/kg Sodium Valproate, while groups two, three and four were pre-treated with the N- hexane fraction of *D. senegalense* at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight. All doses were through the oral route. Thirty minutes after, 90 mg/kg of pentylenetetrazole solution was administered subcutaneously to each mouse. The animals were observed for thirty minutes for the presence or absence of threshold seizures. The onset,

duration of seizures, quantal protection and mortality were recorded for each group. These parameters were compared in treated animals with those of control animals, to ascertain the anticonvulsant activity of the leaf extract.

2.7. Brucine-induced seizure in mice

The method described by Yakubu et al [14] was adopted. Thirty male mice were grouped into five, each consisting of six mice. The first group received normal saline (10 mL/kg). The mice in the second, third and fourth groups received graded doses (100 mg/kg, 200 mg/kg and 400 mg/kg) of the ethanol leaf extract of *D. senegalense*, intraperitoneally. Mice in the fifth group received 30 mg/kg of the standard drug, Phenobarbital. Thirty (30) minutes post-treatment, 110 mg/kg of Brucine was administered to each mouse via the intraperitoneal route. The mice were subsequently observed for hind limb tonic seizures for thirty minutes. The absence of tonic hind limb extension or prolongation of the latency of tonic hind limb extension was considered an indication of anticonvulsant activity.

2.8. Isoniazid (INH) – induced convulsion in mice

This procedure was performed as per the method of Chitra et al. [15]. Thirty adult Swiss mice were divided into 5 groups (n=6. Group 1 was treated with 20 ml/kg of distilled water. The administration of the extract and the standard drug on different groups of animal was as described above. Thirty minutes post drug administration, convulsion was induced intraperitoneally in mice with 250 mg/kg of Isoniazid (INH). This was followed by placing each mouse in a different cage and observing for the onset of tonic-clonic seizure and death. Animals which survived the 30 minutes observation were considered protected.

2.9. Acetic acid-induced abdominal writhing in mice

Antinociceptive activity of hexane fraction from *D. senegalense* leaf against acetic acid-induced writhing was carried out according to the procedure of Xu et al., [16] with slight modification. Thirty Swiss mice of both sexes were divided into 5 groups of 6 mice each. One group served as drug- free control (saline 10 mL/kg). The second group was administered 150 mg/kg of acetylsalicylic acid (aspirin), as a reference drug. The remaining three groups were given the extract (100 mg/kg, 200 mg/kg and 400 mg/kg respectively. All administrations were done orally. The animals were given 10 mL/kg of 1% acetic acid in distilled water intraperitoneally 30 minutes after treatment. . Thereafter, each mouse in all the groups was individually observed by counting the number of writhings in 30 minutes commencing five minutes after administration of the acetic acid solution. Writhing movements are indicated by abdominal constriction and stretching of at least one hind limb.

2.10. Tail immersion test

Antinociceptive activity of the extract was evaluated by the water tail-flick method described [17, 18]. Mice used for this experiment were randomly grouped into five with six in each cage. The animals were pretreated 60 minutes before tail immersion with 10 mL/kg distilled water for the negative control (group 1), 10 mg/kg of morphine being the standard drug, was administered to each mouse in the second group, while the remaining three groups were given hexane fraction extract (100 mg/kg, 200 mg/kg, 400 mg/kg) respectively. Thereafter, 4 cm of the tail of each mouse was dipped into a water bath thermo-statically maintained at 50±1°C, and the time in seconds taken to flick its tail or withdraw it from the warm water due to pain was recorded for all the animals. The reaction time was recorded at 15, 30, 45 and 60 minutes and the highest reaction cut-off time was at 15 seconds to prevent tissue injury.

2.11. Statistical analysis

Results were expressed as mean± SEM and analyzed with a 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 statistically significant.

3. Results

3.1. Phytochemical analysis

Phytochemical evaluation of *D. senegalense* extract reacted positively to the following secondary metabolites; alkaloids, saponins, tannins, flavonoids, terpenoids, steroids, cardiac glycosides, resins and balsam.

3.2. Acute toxicity test

The n-hexane fraction of the leaf extract of *Detarium senegalense* did not produce any lethality or significant signs of toxicity in rats up to 5000 mg/kg body weight after 24 and 72 hours.

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

Pre-treatment of n-hexane fraction of *D. senegalense* significantly ($p<0.05$) prolonged the onset of a seizure and shortened the duration of convulsion against PTZ-induced convulsions in mice as shown in Table 1. The maximum protection was observed at the dose of 400 mg/kg. However, the standard drug valproic acid significantly ($p<0.01$) protected the animals from death.

Table 1 Effect of n-hexane fraction of *D. senegalense* leaf on pentylenetetrazole-induced convulsion in mice

Drug	mg/k	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 mL/kg	3.93±0.17	3.57±0.36	0/6	6	0.00
D. senegalense	100	14.15±0.91	25.40±0.63	3/6	3	50[a]
D. senegalense	200	14.17±1.01	28.11±1.33	4/6	2	67[a]
D. senegalense	400	16.08±0.33	30.08±1.24	5/6	2	67[a]
Sodium valproate	200	-	-	-	-	100[b]

Data 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$p<0.01$

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

Table 2 indicates the effect of the extract against convulsions induced by brucine in mice. Administration of the extract significantly ($p<0.05$) showed a dose-dependent anticonvulsant effect against brucine-induced clonic seizures by significantly reducing the onset and duration of convulsions as well as reducing the frequency of clonic seizures. Phenobarbital, the reference drug also significantly ($p<0.01$) reduced the onset and duration of convulsions and the frequency of clonic convulsions.

Table 2 Effect of n-hexane fraction of *D. senegalense* leaf on brucine-induced convulsion in mice

Drug	mg/k	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 mL/kg	6.50±0.69	7.07±0.69	0/6	6	0.00
D. senegalense	100	14.13±0.24	24.2.5±1.11	3/6	3	50a
D. senegalense	200	17.02±0.73	26.40±0.64	4/6	2	67a
D. senegalense	400	16.49±0.34	29.43±1.65	5/6	2	67a
Valproic acid	200	-	-	-	-	100b

Data 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$p<0.01$

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

The results of Isoniazid-induced convulsion test showed that the n-hexane fraction from *D. senegalense* leaf extract significantly ($p<0.05$) delayed the onset and duration of convulsion in mice against INH-induced convulsion when compared with distilled water treated group. The standard anticonvulsant drug, phenobarbitone significantly ($p<0.01$) abolished the effect of isoniazid-induced convulsion in mice (Table 3).

3.6. Effect of n-hexane fraction of *D. senegalense* leaf extract on acetic acid-induce writhing in mice

The administration of n-hexane fraction from *D. senegalense* leaf extract significantly ($p<0.05$) exhibited dose-dependent reduction of abdominal constrictions and hind limb stretching induced by intraperitoneal administration of

acetic acid in mice. The maximum inhibition of writhing was observed at 400 mg/ kg which was significant at ($p<0.01$) and comparable to the standard acetylsalicylic acid at 150 mg/kg (Table 4).

3.7. Effect of n-hexane fraction of *D. senegalense* leaf extract on tail immersion test in mice

The result of the thermal nociception activity of the extract is shown in Table 5. The extract exhibited a dose-dependent effect on thermally-induced pain in mice. This inhibition was statistically significant ($p< 0.05$) when compared to the control. The effect of the extract was significant at ($p<0.01$) comparable to that of morphine, the standard drug.

Table 3 Effect of n-hexane fraction of *D. senegalense* leaf on INH-induced convulsion in mice

Drug	mg/k	Mean onset of Seizures (min)	Mean onset of death (min)	Quantal protection	Mortality	%Protection
Control	20 mL/kg	5.39±0.20	6.33±0.87	-	6	0.00
D. senegalense	100	15.61±0.18	24.18±0.44	3/6	3	50a
D. senegalense	200	16.98±0.40	26.32±1.08	5/6	3	50a
D. senegalense	400	17.57±0.78	31.11±2.03	5/6	2	67a
Phenytoin	200	-	-	-	-	100b

Data 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 4 The effect of n-hexane fraction of *D. senegalense* leaf on acetic acid- induced writhing in mice

Drug	Dose (mg/kg)	Writhes	inhibition
Control	20 mL/kg	19.00±1.26	-
A. senegalensis	100	12.67±1.43	33a
A. senegalensis	200	5.83± 0.87	67a
A. senegalensis	400	17.57±0.78	83a
Aspirin	150	2.50± 1.59	87b

Data 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 5 The effect of n-hexane fraction of *D. senegalense* leaf on tail immersion in mice

		Time Interval (mins)				
Drug	**Dose (mg/kg)**	**0**	**15**	**30**	**45**	**60**
Control	20 mL/kg	7.17±0.87	8.17±0.04	9.67±1.65	9.83±1.62	11.67±071
A. senegalensis	100	7.67±0.49	10.00±0.45	12.33±1.17	13.17±1.10	16.00±0.86a
A. senegalensis	200	8.17±0.06	12.67±1.09	13.5±0.72	15.17±1.30	18.83±1.05a
A. senegalensis	400	8.49±0.87	14.34±0.23	16.90±0.36	18.05±0.74	20.95±0.37b
Morphine	10	8.67±1.05	17.67±1.33	19.67±1.70	20.67±1.26	23.67±1.09b

Data 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$p<0.01$

4. Discussion

The antiseizure and antinociceptive activities of hexane fraction extract from D. senegalanse were studied in three experimental models of PTZ, Brucine and INH-induced convulsions in mice. The effects of the extract were also observed on analgesic activity using the acetic acid-induced writhing and water tail immersion technique in mice, respectively.

Epilepsy is one of the most common global neurological disorders. Seizures have been traditionally recognized as a symptom of abnormal neuronal synchronization, and until recently have been thought to be due to abnormal synaptic communication [19]. Despite numerous advances in research on the disease, its pharmacological management remains largely empirical probably due to the lack of understanding of the underlying disorder. Moreover, over 30 per cent of people with this disorder do not satisfactorily respond to conventional anticonvulsant drugs [20]. These limitations alone make it imperative to explore the agents that could potentiate the action of currently used antiepileptic drug to make the treatment of epilepsy more effective. The results of this study showed that extract fraction exhibited anticonvulsant activity by delaying the onset of PTZ-induced seizures and protected treated mice from mortality induced by seizures. PTZ is the most frequently used experimental model to test potential anticonvulsant drugs [21]. The mechanism by which PTZ is believed to exert its action is by acting as an antagonist at the GABAA receptor complex [22]. PTZ prevents GABAmediated Cl− influx in the Cl− channel via an allosteric interaction, leading to convulsions in animals [23]. Deficiencies in GABA neurotransmission in both experimental animal models and human syndromes are associated with epilepsy [24]. Agents protecting against tonic-clonic seizures induced by PTZ are considered to be useful to control myoclonic and absence seizures in humans [25, 26]. The N-hexane extract produced significant inhibition of PTZ-induced seizures, which helps to confirm its traditional use in epilepsy management. It was observed that the extract especially at 400 mg/kg delayed the onset of clonic and tonic convulsions and also decreased its frequency and duration. The potent effect of valproic acid as evident in PTZ-induced convulsions agrees with its enhancing effects in GABAergic neurotransmission [27]. GABA is a major inhibitory neurotransmitter in the central nervous system in humans (Katzung and Trevor, 2004). Inhibition of pentylenetetrazol-induced seizures could indicate that the anticonvulsant effects of extract fraction may be linked with GABA activity modulation in the central nervous system.

The glycine receptor is responsible for the regulation of strong inhibitory neurotransmission in the mature central nervous system [28], which makes the receptor a prospective target for anticonvulsant drugs [29]. Brucine induces seizures by blocking the activity of brucine-sensitive glycine receptors, and increased postsynaptic excitability and sustained action in the brainstem and spinal cord neurons [9]. Brucine increases the concentration of amino acid and glutamic acid in the brain, which acts as a neurotransmitter for excitatory nerve impulses leading to myo-contraction [30]. In this study, the extract exerted anticonvulsant activity against brucine-induced seizures by increasing the seizure threshold. Moreover, since the extract decreased the onset, duration and frequency of brucine-induced convulsion, this suggests that the extract might be acting via the glycinergic pathway.

Furthermore, the extract exhibited anticonvulsant activity by delaying the onset of Isoniazid-induced seizures and protected treated mice from mortality induced by seizures. The convulsant activity of INH involves the destruction of GABAergic neurotransmission in the central nervous system. It has been reported that INH inhibits GAD, an enzyme that catalyzes the synthesis of GABA from glutamic acid. Numerous anticonvulsant agents in current clinical use facilitate GABA neurotransmission by different mechanisms [31]. The effect of most anticonvulsant drugs is to enhance the GABA response, by improving the GABA-activated chloride channels opening. Therefore, the n-hexane fraction might be producing anticonvulsant action by increasing the concentration of GABA, an inhibitory transmitter in the CNS. The extract showed a significant delay in the onset of convulsion and decreased duration of the seizure when compared with the non-drug treated group. The results suggest that the possible mechanism of hexane fraction of the *D. senegalense* effect was either prevention of the decrease in GABA or modification of the rate of GABA depletion produced by INH [32].

The abdominal constriction response induced by acetic acid is a sensitive procedure to establish peripherally acting analgesics. This response is thought to involve local peritoneal receptors. This suggests that the n-hexane fraction of *D. senegalense* extract possesses analgesia for pain produced by peripheral action. Acetic acid mice writhing is widely used in the animal models for screening compounds with peripheral analgesic activity [33, 34]. The writhing response is considered to be a visceral inflammatory pain [35]. Acetic acid is a chemical irritant that produces tissue necrosis of the peritoneal region accompanied by the release of chemical mediators such as bradykinin, prostaglandin, histamine, substance P, vasoactive polypeptide, which cause pain either by activation or sensitization of nociceptors that encode tissue injury [36]. The extract fraction significantly reduced the number of writhes at the doses used in the study. Indications suggesting peripheral action. The mechanism of analgesic effect of the fraction in acetic acid-induced writhing could be due to the blockade of the effect or the release of endogenous substances that excites pain nerve endings similar to that of acetylsalicylic acid and other NSAIDs [37].

To confirm the analgesic activity of the extract fraction, a centrally acting model of analgesia was also assessed. This method which is used to indicate the involvement of the central analgesic mechanism is believed to involve spinal reflex [38]. It has been reported that centrally acting agents such as morphine, possess this activity in both types of study, whereas peripherally acting agents like acetylsalicylic acid have been reported to exert anti-nociceptive action only in the writhing test [39]. In the tail immersion test, the extract fraction caused a prolonged latency period, indicating an increase in the nociceptive threshold. The response to the tail-immersion test is a spinal reflex with the involvement of higher neural structures and is used to evaluate central analgesic activity [40]. There is, therefore, the possibility that the analgesic effect of the extract may be associated with spinal or supraspinal pathways. The plant extract fraction in our study inhibited both types of pain. The analgesic effect in both models suggests that it has been acting through peripheral as well as central mechanisms.

The occurrence of several biologically active phytochemicals in various plant extracts such as flavonoids, triterpenes, alkaloids, steroids, tannins, and glycosides can be responsible for their respective pharmacological properties. The observed pharmacological activities of the extract in the various animal models used could be attributed to the presence of these phytochemicals [41]. The high LD50 value from acute toxicity studies showed that constituents from fraction leaf extract may be generally regarded as safe. This high degree of relative safety is consistent with the use of the plant in traditional medicine.

5. Conclusion

Our results suggest that n-hexane fraction from *Detarium senegalense* possesses anticonvulsant as well as central and peripheral analgesic properties. Therefore, further studies need to be carried out to identify the specific phytomolecules and their particular mechanism(s) of action.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest is associated with this study.

Statement of ethical approval

The study was conducted according to the Animal Ethical Committee Guidelines of Nnamdi Azikiwe University Teaching Hospital, Nnewi Campus, Anambra State (NAUTH/CS/66/VOL.14/VER.3/291/2022/060) and every effort was made to minimize animal suffering.

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