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The Anticonvulsant and analgesic activities of *Alysicarpus vaginalis* ethanol leaf extract in experimental animals

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Abstract

Epilepsy and pain-related disorders constitute a major global health burden, particularly in low- and middle-income countries where access to effective and affordable therapies remains limited. Medicinal plants continue to provide valuable sources of bioactive compounds with potential therapeutic relevance.This study evaluated the anticonvulsant and analgesic activities of the ethanol leaf extract of *A. vaginalis* using established animal models. Fresh leaves of *A. vaginalis* were extracted with ethanol and subjected to phytochemical screening and acute toxicity testing. 30 mice were randomized and separated into 5 groups of 6 mice each. Group 1 representing the negative control group and was pre-treated with of distilled water, while group 2, 3 and 4 were pre-treated with graded doses of the ethanol leaf extract of *A. vaginalis*. All administrations were given per-oral. The 5th group of mice (positive control group) was pre-treated with Sodium valproate. Anticonvulsant activity was assessed using pentylenetetrazole- and isoniazid-induced seizure models in mice, while analgesic activity was also evaluated using acetic acid-induced writhing and formalin-induced nociception models in rats. Phytochemical analysis revealed the presence of alkaloids, flavonoids, saponins, tannins, triterpenoids, steroids, and glycosides. The extract significantly delayed seizure onset and reduced seizure duration in a dose-dependent manner. Significant inhibition of nociceptive responses was observed in both peripheral and central pain models. Acute toxicity studies indicated safety at 5000 mg/kg in mice. The findings demonstrate that *A. vaginalis* possesses significant anticonvulsant and analgesic activities, supporting its traditional use and warranting further pharmacological and clinical investigations.

Keywords: *Alysicarpus vaginalis*; Leaf extract; Convulsion; Analgesic; Mice; Rats

1. Introduction

The majority of people on the planet rely on traditional medicine, which uses herbs to cure a variety of illnesses. Herbal traditions served as a source for modern medicine [1]. The use of plants or other natural substances to treat a wide range of illnesses has been made possible by herbal medicine, a respectable kind of alternative medicine that has become increasingly popular in both wealthy and developing countries [2,3]. Because the secondary metabolites of plant extracts arise as complexes of naturally occurring, structurally related analogues, their use is less harmful to

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human health and the environment [4]. Years of fighting diseases with crippling effects have led to an awareness of the medicinal potential of plants. This has prompted the search for drugs from unusual sources, particularly natural products from plant parts like bark, seeds, fruits, roots, leaves, and wood [5]. Furthermore, utilizing herbal medicines in folk medicine offers an intriguing and mainly unexplored avenue for developing novel potential pharmacological effects [6]. Modern science has recognized their potency and included a variety of medications derived from plants in contemporary pharmacology. Numerous investigations have been conducted to substantiate the application of these herbs against pathogenic microorganisms and illnesses associated with oxidative stress.

It is believed that phytoconstituents are good alternatives to conventional drugs used in the treatment of diseases because they are inexpensive and may have less adverse effects [7] Despite the growing concern about these plant products due to their lack of standardization, they are in high demand by traditional care givers for the treatment of various diseases including cancer. Thus, there are growing research interests geared towards natural products for finding new drug entities from among the myriads of plant species in African forests that are largely untapped. These efforts have often been successful since many plant materials have been found to have numerous and diverse pharmacological activities [8].

2. Materials and Method

2.1. Plant collection and authentication

The fresh leaves of *Alyscarpus vaginalis* were sourced from along the vast areas of Umudim Community Amichi, Nnewi South Local Government bushes, where it is commonly found in Anambra State, Nigeria

2.2. Preparation of plant and extraction procedure

The fresh leaves of *A. vaginalis* 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 three (103) mature Swiss mice and thirty (30) Adult Wistar rats, both male and female gender weighing between 18-25 g and 200 - 220 g were used for the study. They were sourced from the Animal House of Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus. The animals were kept in plastic cages and allowed to acclimatize in a laboratory environment for 14 days. During the period of study, they were given pellets (Guinea Feeds, Plc Nigeria) and provided with clean water *ad libitum*. The National Institute of Health [9] Guide for the Care and Use of Laboratory Animals was applied.

2.4. Phytochemical analysis

The method as described by Inyang-Agha, [10], Aziz, [11] was adopted for the phytochemical analysis of the ethanol extract of *A. vaginalis* 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 *A. vaginalis* was evaluated using the method of Nagaraja et al. [13];

Yakubu et al., (14), 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 *A. vaginalis* 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. 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.

2.8. Acetic acid-induced abdominal writhing in mice

Ant-nociceptive activity of hexane fraction from *A. vaginalis* 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.

2.9. 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

It is important to know the chemical nature of plant products when their pharmacological responses are determined. Phytochemical evaluation of *A. vaginalis* leaf extract showed the presence of the following secondary metabolites; alkaloids, saponins, tannins, flavonoids, triterpenoids, steroids, reducing sugars and glycosides, while phlobatannins and anthraquinones were not detected

3.2. Acute toxicity test

The ethanol leaf extract of *A. vaginalis* did not produce any lethality or significant signs of toxicity in rats up to 5000 mg/kg body weight after 24 and 72 hours.

3.2.1. Effect of ethanol leaf extract of A. vaginalis on pentylenetetrazole-induced convulsion in mice

It was observed that in the control group, the mean onset of convulsion and death was reduced in comparison with the groups that received the ethanol leaf extract and Sodium Valproate. The mean onset of convulsion and mean duration of convulsion progressively increased with increase in the dosage of the extract administered to the mice. Those that received 400 mg/kg of the extract had the longest mean time of onset of convulsion, while in those that received 200 mg/kg of Sodium Valproate, no convulsion and no mortality was observed. The difference in the mean onset of convulsion, mean duration of convulsion, mortality and % protection among the groups was significant ($p<0.05$). A greater degree of significance ($p<0.01$) was seen in the standard drug, Sodium Valproate (Table 3).

3.2.2. Effect of ethanol leaf extract of A. vaginalis INH-induced convulsion in mice.

In the control group, there was a very short mean onset of convulsion and mean duration of convulsion when compared to the other groups, and there was 100% mortality. A dose-dependent increase was observed in the mean onset of convulsion and duration of convulsion. While percentage protection among the groups that received 100 mg/kg, 200 mg/kg and 400 mg/kg of the extract were low, the highest percentage protection was seen in the group that received 200 mg of Sodium Valproate. The difference between the groups was also statistically significant ($p<0.05$), that of standard drug (Sodium valproate) was significant ($p <0.01$) (Table 4).

3.2.3. Effect of A. vaginalis ethanol leaf extract on acetic acid-induce writhing in mice

The administration of the 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 ($p<0.01$) comparable to the standard acetylsalicylic acid at 150 mg/kg (Table 5).

3.2.4. Effect of A. vaginalis ethanol leaf extract on formalin -induced pain in Wistar rats

In the formalin test, *A. vaginali* (100 mg/kg, 200 mg/kg, 400 mg/kg) significantly ($p< 0.05$ and $p< 0.01$) dose dependent inhibition of pains in both early phase and late phase of formalin-induced nociception in rats. In the both phase, aspirin (150 mg/kg) significantly reduced the nociception ($P < 0.01$). The result is comparable to that exhibited by aspirin (Table 6).

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

Drug	Dose (mg/kg)	Mean onset of seizure(min)	Mean Duration of seizure (min)	Quantel Protection	Mortality	% Protection
Control	20 mL/kg	5.44±0.30	7.00±0.59	0/6	6	0.00
A. vaginalis	100	10.52±0.71	17.84±0.14	1/6	5	17a
A. vaginalis	200	15.12±0.39	25.15±1.20	2/6	4	33a
A. vaginalis	400	20.45±0.30	30.38±1.54	3/6	3	50a
Sodium Valproate	200	-	-	-	-	100 b

Results represent the mean ± SEM (n=6) a $p < 0.05$; bp < 0.01 compared to the control group

One-way ANOVA + Dunnett's post hoc test

Table 2 Effect of ethanol leaf extract of *A. vaginalis* INH-induced convulsion in mice

Drug	Dose (mL/kg)	Mean onset of Seizures (min)	Mean duration of Seizures (min)	Quantal protection	Mortality	%Protection
Distilled water	20 mL/kg	4.15±0.20	5.56±0.28	0/6	6	0.00
A. vaginalis	100 mg/kg	14.35±0.38	25.16±0.35	1/6	5	17a
A. vaginalis	200 mg/kg	14.56±0.43	29.02±1.60	2/6	4	33a
A. vaginalis	400 mg/kg	16.12±0.28	34.07±0.18	2/6	4	33a
SodiumValproate	200 mg	-	-	-	-	100b

Results represent the mean ± SEM (n=6) a $p < 0.05$; bp < 0.01 compared to the control group

One-way ANOVA + Dunnett's post hoc test

Table 3 Effects of *A. vaginalis* ethanol leaf extract in acetic acid-induced Writhing in mice

Treatment	Dose (mg kg)	Mean number of writhes	% Inhibition
Distilled water	20 mL kg	19.53± 1.35	-
A. vaginalis	100	8.40± 1.46	57a
A. vaginalis	200	4.85±0.88	75b
A. vaginalis	400	2. 48±0.72	87b
Aspirin	150	1.55±0.60	92b

Results represent the mean ± SEM (n=6) a $p < 0.05$; bp < 0.01 compared to the control group

One-way ANOVA + Dunnett's post hoc test

Table 4 Effect of *A. vaginalis* ethanol leaf extract in formalin-induced pain in rats

Treatment	Dose (mg/kg)	Early phase score of pain (0-15 min)	% Inhibition	Late phase score of pain (25-60 min)	% Inhibition
Distilled water	20 mL/kg	2.81±0.10	-	2.65±0.08	-
A. vaginalis	100	1.40±0.11	50a	1..18±0.10	55a
A. vaginalis	200	1.15±0.09	59a	1.00±0.02	62a
A. vaginalis	400	0.97±0.62	65a	0.79±0.10	70b
Aspirin	150	0.92±0.08	67a	0.72±0.05	73b

Results represent the mean ± SEM (n=6) [a] $p < 0.05$; [b]p < 0.01 compared to the control group

One-way ANOVA + Dunnett's post hoc test

4. Discussion

The antiseizure and antinociceptive activities of ethanol leaf extract from *A. vaginalis* were studied in two experimental models of PTZ and INH-induced convulsions in mice. The effects of the extract were also observed on analgesic activity using the acetic acid-induced writhing and formalin induced pain in rats, 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 [17]. 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 [18]. 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 [19]. The mechanism by which PTZ is believed to exert its action is by acting as an antagonist at the GABAA receptor complex [20]. PTZ prevents GABA mediated Cl− influx in the Cl− channel via an allosteric interaction, leading to convulsions in animals [21]. Deficiencies in GABA neurotransmission in both experimental animal models and human syndromes are associated with epilepsy [22]. Agents protecting against tonic-clonic seizures induced by PTZ are considered to be useful to control myoclonic and absence seizures in humans [23, 24]. 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 [225]. 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 [26], which makes the receptor a prospective target for anticonvulsant drugs [27]. 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 [28, 29]. The effect of most anticonvulsant drugs is to enhance the GABA response, by improving the GABA-activated chloride channels opening. Therefore, the extract 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 *A. vaginalis* effect was either prevention of the decrease in GABA or modification of the rate of GABA depletion produced by INH [30].

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 *A. vaginalis* 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 [31, 32]. The writhing response is considered to be a visceral inflammatory pain [33]. 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 [34]. 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 [35, 36].

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 [37]. 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 [38]. 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 [39]. 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 [40]. 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 ethanol stem bark extract from *A. vaginalis* 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

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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, Awka, Anambra State (NAU/AREC/2025/0190), as well the National Institute of Health Guide for the care and use of Laboratory Animals.

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