INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

(p-ISSN: 2348-5213: e-ISSN: 2348-5221)

www.ijcrcps.com

DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 8, Issue 1 - 2021

Research Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2021.08.01.002

Sedative and Anticonvulsant Activities of Hydroalcoholic Extract of *Borreria stachydea* Leaves in Mice

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Abstract

The use of herbal drugs in the treatment of many neurological disorders is gaining popularity in developing countries due to their fewer unwanted side effects, affordability and cultural acceptability. This study was undertaken to investigate the sedative and anti-convulsant activities of the hydromethanolic extract of *Borreria stachydea* leaves (HEBS). We evaluated the acute toxicity of HEBS using the standard method of OECD. The sedative activity was evaluated using thiopental sodium (TS) sleeping time test while the anticonvulsant activity was evaluated using strychnine, pentylenetetrazole (PTZ) and picrotoxin- induced seizures in mice. The doses of HEBS used were 100, 200 and 400 mg/kg and administered (i.p.) once during the experiment. Results of acute toxicity study showed that HEBS produced no signs of toxicity or mortality up to a dose of 3200mg/kg. In the TS sleeping time test, HEBS significantly ($p< 0.001$) decreased onset of sleep and increased duration of total sleeping time. Against strychnine-induced seizures, HEBS offered 16.67- 66.67% protection. HEBS also protected the mice by 16.67- 33.33% against PTZ- induced seizures. While against picrotoxin- induced seizures, HEBS offered 16.67 protection only at 400 mg/kg. It was concluded that the hydromethanolic extract of *B. stachydea* leaves possess sedative and anticonvulsant activities. The findings therefore provide some scientific rationale for the traditional use of the extract in the management of epilepsy.

Keywords: Sedative, Anti-convulsant, *Borreria stachydea*, Hydroalcoholic

1.0 Introduction

Epilepsy is the most prevalent neurological disorder affecting nearly fifty (50) million people worldwide. Epilepsy is characterized by uncontrolled discharge of neurons in the brain (Venkateshwarlu *et al.*, 2013). Children under the age of seven (7) and adults above fifty five (55) years are at the highest risk to have epilepsy. Approximately 5% of the world population does experience epilepsy in their lifetime (Gupta & Babar, 2012). Seizure is a characteristic feature in epilepsy and is associated with disordered and rhythmic high frequency discharge of impulses by a group of neurons in the brain (Landrigan *et al.*, 2005). Seizures are fundamentally divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or electrographic evidence exists to suggest that the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking (CCTILE, 2003).

Antiepileptic drugs are those agents that effectively control seizures in nearly 70% to 80% of subjects, but their use is largely affected due to the serious side effects such as trauma, tumors and cerebral infarction (Venkateshwarlu *et al.*, 2013). The development of new pharmacological agents that can overcome these barriers has become a major goal in epilepsy research. The plant kingdom is a major target in the search of new drugs of natural origin to be used for protection against this debilitating neurological disorder.

Borreria stachydea (DC) commonly known in English language as ant's wheat is an erect, hairy and weedy herb, about 30-60 cm high with mauve flowers. It belongs to Rubiaceae family (Dalziel, 1937). Through personal communication, we found out that this plant is used in traditional medicine to treat venereal diseases, inflammations, epilepsy and gonorrhea. To the best of our knowledge, no scientific investigation has been carried out to support the claim of the neurological benefits of *B. stachydea.* Hence, this study investigated the sedative and anti-convulsant potentials of the hydromethanolic extract of the leaves of *B. stachydea*. Thiopental sodium- induced sleeping test was employed to investigate the sedative effect while strychnine, pentylenetetrazole and picrotoxin- induced seizures models were used to evaluate the anti-convulsant potentials of the plant in mice.

2.0 Materials and Methods

2.1 Materials

2.1.1Chemicals and drugs

All experimental drugs and chemicals (analytical grade) used were purchased from Sigma Chemical Co. Ltd (USA).

2.1.2 Animals

Healthy adult mice (18- 30 g) were used for this study. They were maintained at 23.0 ± 2.0 ^{o}C, 12 h light and dark cycle, fed with standard animal feed (Feeds Masters, Ilorin, Nigeria) and water was provided ad libitum. The animals were used in compliance with the National Institute of Health Guide for the Care and use of Laboratory Animals (Publication nos. 85-23, revised 1985).

2.2 Methods

2.2.1 Plant collection and identification

The leaves of *Borreria stachydea* were collected from a natural habitat in Nsukka area of Enugu State, Nigeria. The plants were identified at the Department of Pharmacognosy, University of Nigeria, Nsukka.

Figure 1: Picture of *Borreria stachydea* in its natural habitat

2.2.2 Preparation of extract

The leaves of *Borreria stachydea* were dried under shade for five (5) days and pulverized using a manual blender. One thousand- five hundred (1500) gram of the pulverized leaves was macerated in 5000 ml of methanol: Water (70:30) for 72 hours. The resulting mixture was filtered using Whatmann filter paper (Size No1) and dried in an oven at 45ºC. The Hydroalcoholic extract of *Borreria stachydea* was labelled 'HEBS' and stored in the refrigerator till required.

2.2.3 Acute toxicity study

The acute toxicity of HEBS was evaluated in mice. After single dose of treatment animal was observed for 14 days. The study was conducted in accordance with OECD Guideline 423 (Organization for Economic Cooperation and Development) for the testing of chemical solutions described by (Ondele *et al.,* 2015; Boumba *et al.*, 2018*)*. It allows to determine the lethal dose (LD_{50}) and the therapeutic dose of the extracts to be used.

2.2.4 Evaluation of sedative activity

Thiopental sodium-induced sleeping time test

The method described by Williamson *et al.* (1996) was adopted in this study with slight modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline 10 ml/kg, while groups 2, 3 and 4 received 100, 200 and 400 mg/kg, p. o. of HEBS respectively. Group 5 received diazepam (1 mg/kg). 30 min post-treatment, thiopental sodium (40 mg/kg, i.p.) was administered to mice in all the groups to induce sleep. The animals were observed for the latent period (time between Thiopental sodium administrations to loss of righting reflex) and duration of sleep (the time between the loss and recovery of righting reflex).

2.1.6 Evaluation of anti-convulsant activity

Strychnine-induced seizure in mice

The method described by Porter *et al.* (1984) was adopted in this study with slight modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 received normal saline 10 ml/kg, while groups 2, 3 and 4 received 100, 200 and 400 mg/kg p.o. of HEBS respectively. The fifth group was given Phenobarbital 30 mg/kg i.p. Thirty minutes post-treatment, mice in all the groups received 1.5 mg/kg of strychnine (s.c). The proportions of mice presenting convulsions as well as the onset of tonic convulsions were recorded. Abolition of tonic extension of the hind limbs within 30 min after strychnine administration was considered as an indicator for anticonvulsant effects (Porter *et al.*, 1984).

Pentylenetetrazole induced-seizure test in mice

The method of Swinyard *et al.* (1989) was employed to induce convulsion in mice using PTZ. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline 10 ml/kg b. w, groups 2, 3 and 4 received 100, 200, and 400 mg/kg i.p. of HEBS respectively, while the fifth group was injected with valproate 200 mg/kg. Thirty minutes after pre-treatment, the animals received PTZ (85 mg/kg s.c.). Mice were observed over a period of 30 min. The absence of an episode of clonic spasm of at least 5 s duration indicated an extract's or a compound's ability to abolish the effect of PTZ-induced seizure threshold (Swinyard *et al.*, 1989).

Picrotoxin- induced seizures in mice

The method described by Salih and Mustafa, (2008) was adopted for this study with slight modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline (10 ml/kg) intraperitoneally. Groups 2, 3 and 4 received 100, 200 and 400 mg/kg i.p. of HEBS respectively, while group 5 received diazepam 10 mg/ kg. Thirty minutes after pretreatment, 10 mg/kg of Picrotoxin was administered to each mouse s.c. They were then observed for tonic hind limb seizures for 30 min period. The absence of tonic hind limb extension (THLE) or prolongation of the onset of THLE was considered as an indication of anticonvulsant activity (Navarro-Ruiz *et al.*, 1995).

2.3 Statistical Analysis

Results were presented in tables and expressed as mean ± SEM. The level of significance was tested using One-way ANOVA followed by Duncan Multiple Range Test (DMRT). Results were regarded as significant when $p<0.05$. All statistical analyses were performed using SPSS software, version.

3.0 Results

3.1 Acute Toxicity

In the acute toxicity studies (**Table 1**), the aqueous leaf extract of *Borreria stachydea* produced no signs of toxicity and zero mortality up to a dose of 3200 mg/kg. According to the globally harmonized classification system of the OECD (2001), this extract can be classified in category 5 with the LD_{50} higher than 3200 mg / kg.

Table 1: General State of Animals after Administration of Hydroalcoholic Extract of *Borreria stachydea* Leaves (HEBS)

	Treatment					
Parameters	**10 ml/kg NS**	**200 mg/kg HEBS**	**400 mg/kg HEBS**	**800 mg/kg HEBS**	**1600 mg/kg HEBS**	**3200 mg/kg HEBS**
Mobility	N	N	N	N	N	N
Aggressiveness	N	N	N	N	N	N
Salt state	N	N	N	N	N	N
Pain sensitivity	N	N	N	N	N	N
Vomiting	A	A	A	A	A	A
Vocalization	A	A	A	A	A	A
Erection pilot	A	A	A	A	A	A
Tail state	N	N	N	N	N	N
Ptosis	A	A	A	A	A	A
Falling asleep	A	A	A	A	A	A
Vigilance	+	+	+	+	+	+
Mortality	A	A	A	A	A	A

Key: NS: Normal saline; A: Absent; N: Normal; +: yes; -very weak; --: no reaction; D: decrease; n=6

3.2 Thiopental Sodium-induced Sleeping Time Test

The result of thiopental sodium-induced sleeping time test is presented in **Table 2**. The extract significantly ($p< 0.001$) decreased the onset of sleep observed in a dose- dependent manner. Additionally, there was a significant ($p< 0.001$) increase in duration of total sleeping time observed in mice treated with HEBS at 100, 200, and 400 mg/kg when compared with the control. The highest dose (400 mg/kg) of the extract used produced a similar effect to that of the positive control (diazepam 1 mg/kg).

Table 2: Effect of Hydroalcoholic Extract of *Borreria stachydea* Leaves (HEBS) on Thiopental Sodium-induced Sleeping Time in Mice

Treatment	Onset of action (min)	Duration of sleep (min)
Control (10ml/kg NS)	15.82 ± 0.41	80.22 ± 1.23
HEBS (100 mg/kg)	13.32± 0.28**	101.78± 1.46**
HEBS (200 mg/kg)	10.11± 0.13***	141.44± 1.11***
HEBS (400 mg/kg)	8.29 ± 0.09***	162.33 ± 1.28***
Diazepam (1 mg/kg)	8.23 ± 0.11***	173.45 ± 1.26***

Normal saline (NS), HEBS, Diazepam were administered 30 min intraperitoneally before the injection of Thiopental sodium (40 mg/kg i.p). Values are the mean ± SEM, n=6. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

3.3 Strychnine-induced Seizures in Mice

The extract produced protection against strychnine-induced seizures in mice. HEBS at 100, 200 and 400 mg/kg gave 16.67, 33.33 and 66.67% protection against strychnine-induced hind limb extension and death respectively. The standard drug used, Phenobarbital (30 mg/ kg), offered 100% seizure protection. There was no significant difference between the control and the test groups in the mean onset of seizures/mortality (**Table 3**).

Table 3: Effect of Hydroalcoholic Extract of *Borreria stachydea* Leaves (HEBS) on Strychnine-induced Seizures in Mice

Treatment	Onset of seizure/mortality (min)	% Seizure/mortality protection
Control (10ml/kg NS)	5.61 ± 0.29	0.00
HEBS (100 mg/kg)	5.28± 0.40	16.67
HEBS (200 mg/kg)	7.34± 0.32	33.33
HEBS (400 mg/kg)	8.11 ± 0.23	66.67
Phenobarbital (30 mg/kg)	0.00	100.00

Normal saline (NS), HEBS and Phenobarbital were administered 30 min intraperitoneally before the injection of strychnine (2.5 mg/kg) subcutaneously. Values are the mean ± SEM, n=6.

3.4 Pentylenetetrazole (PTZ) - induced Seizures in Mice

Table 4 shows the result of PTZ- induced seizures in mice. The extract at the highest dose (400 mg/kg) protected 33.33 % of the mice against PTZ- induced seizures while both 100 and 200 mg/kg offered only 16.67% protection.

The standard antiepileptic drugs used valproate 200 mg/kg gave 100% protection. A significant ($p< 0.001$) differences in the mean onset of seizures was also observed between the test groups and the control. The extract at doses 400 mg/kg offered the highest protection (33.33%) against mortality while HEBS at 100 and 200 mg/kg offered 16.67% protection against mortality. There was no significant difference on the mean onset of mortality.

Table 4: Effect of Hydroalcoholic Extract of *Borreria stachydea* Leaves (HEBS) on Pentylenetetrazole (PTZ) - induced Seizures in Mice

Treatment	Mean onset of seizure (min)	% seizure protection	Mean onset of mortality (min)	% mortality protection
Control (10ml/kg NS)	5.77 ± 0.71	0.00	6.23± 0.94	0.00
HEBS (100 mg/kg)	11.32± 1.81***	16.67	13.26± 1.23***	16.67
HEBS (200 mg/kg)	15.48± 1.57***	16.67	15.50± 1.61***	33.33
HEBS (400 mg/kg)	12.33 ± 1.23***	33.33	13.14± 1.29***	33.33
Valproate (200 mg/kg)	0.00	100.00	0.00	100.00

Normal saline (NS), HEBS, sodium valproate were administered 30 min intraperitoneally before the injection of PTZ (85 mg/kg) subcutaneously. Values are the mean ± SEM, n=6. One way ANOVA, ***p<0.001 Dunnett post hoc test

3.5 Picrotoxin- induced Seizures in Mice

Result shows that HEBS only at the highest dose (400 mg/kg) used protected mice (16.67%) against THLE and death induced by picrotoxin. Phenobarbital (30 mg/kg) offered 33.33% seizure protection. HEBS at doses of 200 and 400 mg/kg and the standard drug, Phenobarbital, increased the mean onset of seizures/mortality significantly at $p< 0.05$ and $p< 0.01$ respectively (**Table 5**).

Table 5: Effect of Hydroalcoholic Extract of *Borreria stachydea* Leaves (HEBS) on Picrotoxin-induced Seizures in Mice

Treatment	Onset of seizure (min)	% Seizure protection	% Mortality protection
Control (10ml/kg NS)	5.32 ± 0.45	0.00	0.00
HEBS (100 mg/kg)	6.45± 0.16	0.00	0.00
HEBS (200 mg/kg)	9.72± 0.63*	0.00	0.00
HEBS (400 mg/kg)	9.34 ± 0.77*	16.67	16.67
Phenobarbital (30 mg/kg)	10.32 ± 0.98**	33.33	33.33

Normal saline (NS), HEBS, Phenobarbital were administered 30 min intraperitoneally before the injection of picrotoxin (10 mg/kg) subcutaneously. Values are the mean ± SEM, n= 6, one-way ANOVA, *p< 0.05 Dunnett's post hoc multiple comparison.

4.0 Discussion

In screening natural products for pharmacological activity, assessment and evaluation of the toxic characteristics of a natural product extract, fraction, or compound are usually initial steps taken. In this study, *B. Stachydea* extract at doses up to 5000 mg/kg had no treatment-related signs of toxicity or mortality in any of the animals tested during the period of observation. Therefore, according to the globally harmonized classification system of the OECD (2001), the extract can be classified in category 5 with the LD_{50} higher than 3200 mg / kg. With oral LD_{50} of this value, the extract can be regarded as being safe or practically nontoxic.

In our study, the thiopental sodium injection significantly modified the latency to reduce sleep as well as increasing the duration of sleeping time. Substantial evidence revealed that the CNS depressant such as thiopental sodium bind to the gamma amino butyric acid type A ($GABA_A$) receptor complex and potential gamma aminobutyric acid (GABA) mediated hyperpolarization of postsynaptic neurons. The potentiation of barbiturate sleep is thought to be due to the presence of alkaloids and flavonoids in medicinal plants (Silva *et al.*, 2011). These observations suggest that the extract has some sedative properties of tranquilizers and hypnotics, which may be involved in the anticonvulsant activity described below (Geoffrey *et al.*, 1995).

The convulsing action of strychnine 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. Strychnine- sensitive postsynaptic inhibition in higher centers of the CNS is also mediated by glycine. Strychnine acts as a selective, competitive antagonist at all glycine receptors (Larson, 1969; Rajendra *et al.*, 1997). The extract significantly protected the animals against strychnine- induced seizures. The ability to prevent the strychnine-induced seizures by the extract demonstrates additional anticonvulsant effects mediated via glycine receptors (Ogbonnia *et al.*, 2003).

PTZ is a well-known convulsant, and the chemically induced seizure using PTZ test usually identifies compounds that raise seizure threshold in the brain. PTZ has been shown to interact with GABA neurotransmitter and GABA receptor complex (De Deyn *et al.*, 1992). The extract of *B. stachydea* protected the animals against the chemically induced convulsion of PTZ. This finding indicates that the extract may contain compounds that can raises seizure threshold in the brain (White *et al.*, 1998). The ability of the extract to increase the latency time to onset of a seizure in the PTZ test suggested a possible interaction of the extract with GABA-ergic neurotransmission and anticonvulsant activity against *petit mal* epilepsy (Vida, 1995).

Picrotoxin is a non-competitive antagonist of $GABA_A$ receptor chloride channels (Leonard, 2003) and its GABA inhibitory actions affect different areas of the central nervous system, thus picrotoxin produces generalized tonic- clonic seizures, which lead to death in most of the cases (Abdul- Ghani *et al.*, 1980). Only at the highest dose of the extract of *B. stachydea* did it protect the animals against picrotoxin-induced THLE and death. Also, the extract extended the mean onset of seizures, which indicates mild anticonvulsant activity against picrotoxin.

5.0 Conclusion

The present study showed that the hydromethanolic extract of *B. stachydea* leaves possesses sedative and anticonvulsant activities principally mediated by the $GABA_A$ receptor complex in the CNS, which is also involved in other physiological functions related to behavior, and in several psychological and neurological disorders. The findings therefore provide some scientific rationale for the traditional use of the extract in the management of epilepsy.

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Website: www.ijcrcps.com

Subject: Pharmacology

Quick Response Code

DOI: 10.22192/ijcrcps.2021.08.01.002

How to cite this article:

AKO Alwell Chinonso, IDAKWOJI Precious Adejoh, NWEJE- ANYALOWU Paul Chukwuemeka, AGBANA Busayo Emmanuel, OLUBIYO Gloria Taye. (2021). Sedative and Anticonvulsant Activities of Hydroalcoholic Extract of *Borreria stachydea* Leaves in Mice. Int. J. Curr. Res. Chem. Pharm. Sci. 8(1): 15-23.

DOI: http://dx.doi.org/10.22192/ijcrcps.2021.08.01.002

