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EFFECTS OF ETHANOL LEAF EXTRACT OF *TERMINALIA AVICENNOIDES* GUILL & PERR ON THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

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ABSTRACT

The search for plant drugs for the treatment of various ailments has been a major preoccupation of man since the stone age.This study is designed to evaluate the effects of the ethanolic leaf extract on the central and peripheral nervous systems. The central action was determined as the effects of the leaf extract on pentobarbitone sleep, its anticonvulsant activities, its analgesic and it muscle relaxant activities using various experimental animals. The peripheral action was determined by the local anaesthetic activity. The results show that the ethanol leaf extract had intraperitoneal LD50 > 2150mg/Kg b.w. and an oral LD_{50} of >5000mg/Kg b.w. which indicates that the extract is relatively safe according to the literature. The extract at concentration of 50 and 100mg/ml produced 61.1 and 72.2% local anesthesia compared with xylocaine (0.3 and 1mg/ml) which exerted 58.3 and 66.6%. The analgesic effect of the leaf extract was evaluated with acetic acid induced writhing and nociception with heat. It was observed that the extract conferred 34.5 and 53.75% protection from writhes induced by acetic acid on mice. Similarly there was a significant ($p<0.5$) dose dependent protection conferred on mice when pain was induced by heat. In the muscle relaxation evaluation the leaf extract showed also dose dependent muscle relaxant properties on the inclined board. The ethanol extract significantly increased the sleeping time of pentobarbitone dose dependently in rats. In the anticonvulsant using pentylenetetrazole (PTZ), the extract was able to confer protection to rats treated with convulsive dose of PTZ. Thus the ethanol leaf extract of *Terminalia avicennoides* was able to produce substantial depressant effects on both the peripheral and central nervous system. These are seen in its potentiation of barbiturate sleep, induced local anesthesia, analgesia, and anticonvulsant and muscle relaxant activities. Therefore the ethanol leaf extract of this plant could be a good source of chemotherapeutic agent(s).

Keywords: Terminalia avicennoides, Local anesthesia, Analgesia, Anticonvulsant, Muscle Relaxant, Sleeping time.

INTRODUCTION

Traditional plant- based medicine that has been historically used in different parts of the world or different cultural systems are considered in western medicine as "alternative medicine [1]. They are referred to as herbal medicine or botanical medicine being that herbs are plants or plant parts valued for medicinal, aromatic or savory qualities used for therapeutic or medicinal purposes [2]. .The use of herbs is the oldest form of health care known to mankind; it is the integral part of development and modern civilization. The use of herbs to treat diseases is almost universal among the non-industrialized societies [3]. in many village market places, medicinal herbs are sold alongside with vegetables and other wares. The Peoples Republic of China is the leading country for incorporating traditional herbal medicine into modern health care system and thousands of species are thus available for the Chinese herbalist. Plantations exist in China for the cultivation of medicinal plants and prescriptions are filled with measured amounts of specific herbs rather than pills or ointments [4]. Indeed, about 25% of the prescription drugs dispensed in the United State contain at least one active ingredient derived from plant material, some are made from plant extract, others are synthesized to mimic a natural plant compound [2].

Undisputedly the history of the use of medicinal plants is inseperably intertwined with that of modern medicine, many drugs listed as conventional medications were originally derived from plants. All over the world, herbal medicine is representative of the most important field of medicine. The study on the medicinal plant

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is essential to promote the proper use of herbal medicine in order to determine their potentials as source of new drugs.

MATERIAL AND METHODS

Experimental Animals

All the laboratory animals used in this study followed the standard procedure for the handling of animals. The animals were handled according to the International Guiding Principles for Biomedical Research involving animals as certified by the Ethic Board of the Faculty of Veterinary Medicine [5].

One hundred and fourteen (114) albino rats (weighing between 100-180 g), twenty five (25) mice (weighing between 20-34 g) of both sexes and two (2) normal male rabbits were kept in well ventilated cages under standard conditions of temperature, light and humidity in the Department of Pharmacology, Physiology and Biochemistry laboratory, Faculty of Veterinary Medicine, University of Maiduguri. They were given grower's mash, water ad libitum and allowed to acclimatized to the laboratory conditions for two weeks prior to the experiments.

Extract Preparation

Two grams of the ethanol extract was dissolved in 10 ml of distilled water, which served as the stock solution having concentration of 200 mg/ml.

Acute Toxicity Evaluation (LD_{50})

The acute toxicity (LD_{50}) of the crude ethanol extract of *Terminalia Avicennioides* was determined using standard conventional procedures as described by Lorke (1983).[6]. In this study, two different routes of administration were considered, the oral and intra-peritoneal.

In phase I, the rats were divided into 3 groups of three rats each for each route (a total of nine rats) and then treated with the crude ethanol extract at doses of 10, 100 and 1000 mg/Kg body weight intraperitoneally(i.p.) and orally and observed for 24 hours for mortality.

In the phase II, the animals in each group (for each route) were divided into 3 groups of one animal each and the ethanol extract was administered at doses of 1600, 2900 and 5000 mg/Kg body weight and were observed for mortality over 24 hours. The LD_{50} value was calculated as the geometric mean of the surviving group and the dead group in the second phase.

Local Anesthetic Evaluation

The method described by Shetty and Anika (1982) [7]. was used as adopted by Abdulrahman, (2004). Four identical, symmetrical and circular regions were shaved on the dorsum of a male rabbit with the 2-shaved circles on the thoracic regions and 2 others on the lumber regions 24 hours before the commencement of the experiment. Two concentrations (1.0 and 0.3 mg/ml) of xylocaine and the extract (50 mg/ml and 100 mg/ml) were prepared. Then 0.2 ml each of 0.3 mg/ml and 1.0 mg/ml were injected intradermally in the right thoracic and left lumbar shaved regions respectively to form wheals, which were encircled with a marker. Likewise 0.2 ml each of the two extract concentrations was injected intradermally in the shaved right lumbar and left thoracic regions respectively to form wheals, which were also encircled with a marker. The encircled regions were each pricked with a needle 10 times at 5 minutes interval for 30 minutes starting with zero time. The number of responses to pain by the rabbit when pricked with a needle was recorded.

Analgesic Evaluation

Effect of Extract on Acetic Acid-Induced Writhing in Mice

The abdominal constriction resulting from i.p. injection of acetic acid (0.6%) consisting of a contraction of abdominal muscles, together with a stretching of hind limbs, was carried out according to the procedure described by Abdulrahman (2004); Correa *et al.*(1996); Santos *et al. (*1994).[8-10]. The animals were divided into 5 groups of 5 mice each. Groups 1 and 5 were labeled as the negative and positive controls respectively, while groups 2-4 were pretreated with graded doses (mg/kg) of *T. avicennioides* extract (i.p.). Acetic acid was administered thirty (30) minutes later. The number of writhes was counted for 30 minutes. Anti-nociception was expressed as the reduction of the number of abdominal constrictions between the negative control mice (water treated mice), mice pretreated with the extract and the positive control (Pentozocine treated mice).

$$\textbf{\% protection} = \frac{(\text{Mean control} - \text{mean test}) \times 100}{\text{Mean control}}$$

Effect of Extract on Thermally-Induced Pain in Rat

The effect of the extract on hot plate-induced paw was investigated in adult rats. The hot plate test was used to measure the response latencies according to the method of Vaz *et al*. (1996) [11]. In these experiments, the electric hot plate was maintained at 45 ± 1°C (as it was connected to a thermostatically controlled water bath). Animals were placed into a glass beaker on the heated surface and the time(s) between placement and the shaking or licking of the paws or jumping was recorded as the index of response latency. An automatic 30 sec cut-off was used to prevent tissue damage. The animals were divided into 5 groups of 5 rats per cage. Group I served as the negative control and received only distilled water. Groups 2-4 were pretreated with graded doses (mg/kg) (i.p.) of *T. avicennioides* leaf extract, 30 minutes prior to their being placed on the hot plate and group 5 served as a positive control. The number of jumps per minute was used as a criterion of discomfort.

Muscle Relaxant Activity Evaluation

Twenty rats of both sexes were divided into four (4) equal groups. The method of Kitano *et al.*, (1983), used by Abdulrahman (2004) [8, 12] was adopted. The rats were placed one after the other on the smooth surface of a board inclined at 35° to the horizontal before and 30 minutes after treatment with varying doses of the extract intraperitoneal (i.p). Each rat was allowed a minimum of 10 seconds to remain on the board. The rats that slipped

down the board before 10 seconds were counted as positive for muscle relaxation.

Effect of Ethanolic Leaf Extract of *Terminalia avicennioides* on Pentobarbitone Sleeping Time Effect

Twenty five rats of both sexes were randomly divided into four groups of five rats each. Group 1 (control) was treated with pentobarbitone (35 mg/kg) only, while groups 2-4 were treated respectively with graded doses of the ethanolic extract plus pentobarbitone (35 mg/kg). All treatments were done intraperitoneally (i.p) and pentobarbitone was given 30 minutes before extract administration. The time of pentobarbitone administration, the onset of sleep and the time of awakening were recorded.

Anticonvulsant Evaluation

Adult rat of both sex were used for this experiment. 12 hours before the experiment, food was withdrawn, but water remained available *ad libitum* until the start of the experiment. The animals were randomly divided into four groups of 5 rat each and be treated as follows: Group 1 was given a convulsive dose of Pentylenetetrazole PTZ (60 mg/kg S.C.). Groups 2-4 received graded doses (mg/kg) of the ethanolic extract (i.p.), 30 minutes later, pentylene tetrazole (60 mg/kg) was injected subcutaneously (S.C) on the back of the neck of the animals. Seizures were manifested as tonic convulsions (tonic hind limb extension). The ability to prevent this feature or prolong the latency or onset of the tonic hind-limb extension over a 24 hour period was taken as indication of anticonvulsant activity. The onset of tonic convulsions and the number of rats presenting convulsions per minute and the duration of convulsions were recorded. Animal that does not show tonic hind limb extension during this period of observation was considered as not haven convulsed. The rat was monitored for instances of death up to 24 hours after the experiment [13, 8].

$$\textbf{\% survival} = \frac{\text{Survive animal X 100}}{\text{Total animal}}$$

STATISTICAL ANALYSIS

Data were presented as mean ± standard deviation (S.D). One way Analysis of variance using SPSS 16.0 for windows was used to test between the means, with P<0.05 considered significant [14] using DUNCAN ALPHA for statistics descriptive homogeneity.

RESULTS

Acute Toxicity Studies (LD_{50})

The acute toxicity value of the crude ethanolic leaf extract of *Terminalia avicennioides* in rat was found to be 2154 mg/Kg. No death was recorded on administration of up to 5000 mg/Kg dose of the extract via the oral route which made it impossible to estimate the LD_{50} via oral route using Lorke's method. For the intraperitoneal route no death was in the first phase of extract administration (10 mg/Kg, 100 mg/Kg and 1000 mg/Kg), using Lorke's table but in the second phase using the extract of dose of 1600 mg/Kg, 2900 mg/Kg and 5000 mg/Kg, dead were recorded on administration of 2900 mg/Kg and 5000 mg/Kg of the ethanolic extract as shown on Table 1

Analgesic Effect of Ethanolic Leaf Extract of *Terminalia avicennioides.*

The ethanolic extract showed that the acetic acid induced writhes observed was dose dependent. At the dose of 200 mg/Kg the extract conferred 34.5% protection from the writhes induced by acetic acid on mice, while 53.7% and 64.6% protections were also observed on administration of 600 mg/Kg of the ethanolic extract and 20 mg/Kg Pentazocine (positive control) with no significance difference at 95% confidence level for mean ($p<0.05$) as shown in Table 2.

The time for pad licking increased dose dependently. At the dose of 200 mg/Kg and 400 mg/Kg of the extract prolonged the time of pad licking from 4.6±0.57 to 5.8±0.44. While a maximum pad licking time of 7.8±0.44 was observed on administration of 600 mg/Kg compared to the positive and negative controls that had pad licking time of 13±1.58 and 2.4±0.54 respectively which were significantly different at ($p<0.05$) as shown in Figure 1.

Effect of Ethanol Extract of *Terminalia avicennioides* Leaf on Muscle Relaxation (Inclined Board Method)

Forty percent of the rats treated with 200 mg/Kg and sixty percent of the rats treated with 400 mg/Kg of the extract slid down the board while a maximum percentage relaxation of 80% was produced on administration of 600 mg/Kg of the extract. The extract's muscle relaxation activity was also dose dependent as shown on Figure 2.

Local Anaesthetic Effect of Ethanolic Leaf Extract of *Terminalia avicennioides.*

The ethanolic extract of *T. avicennioides* leaf also exhibited a local anesthetics effect compared to Xylocaine. The extract produced 61.1 % and 72.2 % local anaesthesia at 50 and 100 mg/ml concentrations respectively on the rabbit. Xylocaine exerted a local anaesthetic effect of 58.3 % and 66.6 % at 0.3 and 1.0 mg/ml concentrations respectively as shown in Table 3.

Effect of Ethanolic Leaf Extract of *Terminalia avicennnioides* on Pentobarbitone Sleeping Time Effect

The ethanolic extract of *Terminalia avicennioides* significantly increased ($p<0.05$) the sleeping time of pentobarbital dose dependently in rats (Table 4). At a dose of 200 mg/Kg the duration was 107.80±7.56 min compared to the control which was pentobarbitone alone (60.40±3.64 min). An increase of the extract dose to 400 mg/Kg resulted in duration of the sleep to 157.8±6.34 min while at a dose of 600 mg/Kg the duration of the sleep rose to 167.40±4.21 min and they are statistically not different at $p<0.05$, unlike onset of sleep of group C which was significantly different from the control group at $p<0.05$.

Effect of ethanolic extract of *Terminalia avicennioides* leaf on pentylenetetrazole (PTZ) induced convulsion

The ethanolic extract of *Terminalia avicennioides* at doses of 200,400 and 600 mg/Kg exerted 40%, 60% and 80% protection to rat against PTZ induced convulsion respectively. It was observed that the mean number of spasm of group B and D were significantly ($p<0.05$)different from the control group. Meanwhile the mean time of onset of convulsion increase with increasing extract dose from 6.2±1.30min to 23.2±2.16min for 200 mg/Kg to 600 mg/Kg of the extract as compared to negative control that had 2.6±0.54min. There is no significance difference between group B and C. However the mean onset of death was dose dependent for the rats treated with 200 mg/Kg and 600 mg/Kg of the ethanolic extract. The mean onset of deaths were significantly different from the control group at $p<0.05$ as presented in Table 5.

Table 1. Mortality rate in rats on administration of various doses of ethanolic leaf extract of *Terminalia avicennioides*

Phase	Dose (mg/Kg)	No of rat	Mortality rate	
			Oral route	IP route
I	10	3	0/3	0/3
	100	3	0/3	0/3
	1000	3	0/3	0/3
II	1600	1	0/1	0/1
	2900	1	0/1	1/1
	5000	1	0/1	1/1

$LD_{50} = \sqrt{a \times b} = 2154$ mg/kg

Table 2. Effect of ethanolic leaf extract of *Terminalia avicennioides* on acetic acid (0.6%) induced writhing on mice

Treatment	Dose (mg/Kg)	No of writhes per 10 min (mean±SD)	% Protection
Control (AA)	-	71.2±5.63	0.00
Extract + AA	200	46.60±1.51	34.50
Extract + AA	400	40.80±0.83	42.70
Extract + AA	600	33.00±2.91	53.70
Pentozocine + AA	20	25.20±3.34	64.60

AA = Acetic acid

Table 3. Local anaesthetic effect of ethanolic leaf extract of *Terminalia avicennioidses* on rabbit

Drug	Conc. (mg/ml)	No of responses over time (min)							Total out of 36	% Anesthesia
		0	5	10	15	20	25	30		
Xylocaine	0.30	0	2	3	3	4	4	5	21	58.3
	1.00	0	3	3	3	4	5	6	24	66.6
Extract	50.00	0	3	3	4	4	4	4	22	51.1
	100.00	0	3	4	4	5	5	5	26	72.2

Table 4. Effect of ethanolic leaf extract of *Terminalia avicennioides* on pentobarbitone sleeping time effect

Group	Extract treatment	Onset of sleep (min)±SD	Sleeping time (min)±SD
A	Pentobarbitone (35mg/Kg)	10.80±0.83*	60.40±3.64
B	200 mg/Kg + Pentobarbitone (35mg/Kg)	13.40±1.94	107.80±7.56
C	400 mg/Kg + Pentobarbitone (35mg/Kg)	14.20±0.83*	157.40±6.34
D	600 mg/Kg + Pentobarbitone (35mg/Kg)	17.60±1.14	167.40±4.21

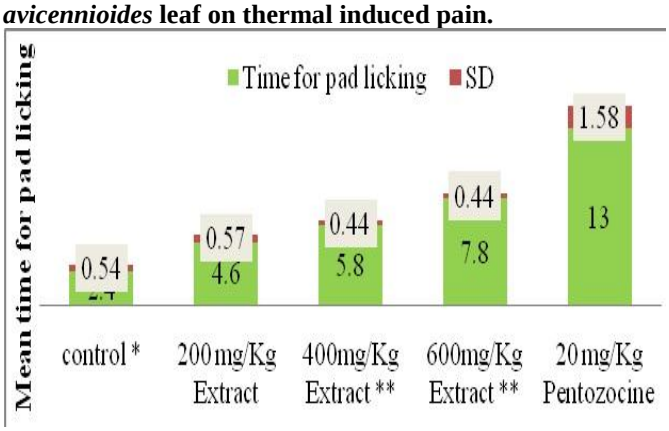
(*) means no significant difference at $P<0.05$

Table 5. The effect of ethanolic extract of *Terminalia avicennioides* leaf on pentylenetetrazole (PTZ) induced convulsion

Extract pretreatment	Mean no of spasm per min.	Mean onset of convulsion (min.)	Mean onset of death (min)	Quantal death	% Survival
Control + 60 mg/Kg PTZ	6.0±0.54	2.6±0.54	7.5±1.29	4/5	20
200 mg/Kg + 60 mg/Kg PTZ	9.2±1.30*	16.2±1.30*	12.0±2.00	3/5	40
400 mg/Kg + 60 mg/Kg PTZ	15.6±0.89	20.8±0.83*	35.5±4.94	2/5	60
600 mg/Kg + 60 mg/Kg PTZ	16.8±0.83*	23.2±2.16**	43.0±0.00	1/5	80

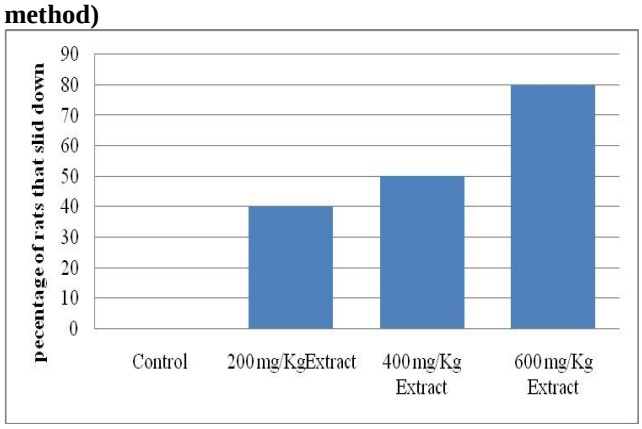
Star (*) means no significant difference at $P<0.05$; ** means there is significance difference at $P<0.05$

Figure 1. Effect of ethanolic extract of *Terminalia avicennioides* leaf on thermal induced pain.



Control * = distilled water, ** = significantly related, $p<0.05$

Figure 2. Effect of ethanol extract of *Terminalia avicennioides* leaf on muscle relaxation (inclined board method)



DISCUSSION

The acute toxicity study of the ethanolic leaf extract of *T. avicennioides* showed intraperitoneal LD_{50} of 2154 mg/Kg body weight. There has been a report that plants with LD_{50} of 1500 mg/Kg body weight and above are not toxicity [15].

Anesthetics are used as an adjunct to surgical procedures in order to render the patient unaware of, and unresponsive to, painful stimulations. The plant showed some peripheral nerve actions as it was observed to possess local anesthetic properties [15]. The local anesthesia was similar to that observed with xylocaine. The local anesthetic effect was observed to yield 61.10 % anesthesia at 50 mg/ml of the extract compared to 0.30 mg/ml of xylocaine (58.50%). The increase in anesthetic effect of the extract at 100 mg/ml was found to produce 72.20% anesthesia against 66.60 % produced by 1.00 mg/ml xylocaine.

The result also showed that the leaf extract of *T. avicennioides* induced some analgesic activity in rats. The extract at 600 mg/Kg conferred 53.65% protection from writhes or stretches induced by acetic acid on rats. This was found to be significantly lower than the effect of pentazocine (20 mg/Kg) in the extent to which the writhing or stretching induced by acetic acid was reduced (64.60%). Acetic acid is believed to trigger the production of noxious substances within the peritoneum which causes the writhing responses. The analgesic efficacy of the leaf extract of *T. avicennioides* was an indication of the analgesic activity of the extracts. The result of the finding supported that of Abdulrahman (2005) [8]. The leaf extract produced analgesia (antinociception) when pain was induced using heat (Eddy's hot plate). The analgesic activity may be due to the presence of bioactive substances present in the extract. The leaf extract also possessed muscle relaxant activity as shown by its effect on the inclined board test that evaluated muscle relaxant activity. The extract induced sleep on its own and appeared to potentiate barbiturate sleeping time in a dose dependent manner indicating a pharmacological action. The increase in dose of the extract in treated rats resulted in the increase in duration of sleep. The extract may have acted synergistically with barbiturates which are known CNS depressants. Extract from other plants were reported to also potentiate the sleeping time of barbiturates [8]. The extract's ability to increase the time of sleep is a clear indication of its sedative and depressant action on CNS and agrees with similar experiments in both mice and rats using other plants [8, 16,17].

Certain centrally acting drugs are available which have the effect of reducing the background tone of the muscle without seriously affecting its ability to contract transiently under voluntary control, another central nervous action of the ethanolic extract was observed by its effect on pentylenetetrazole (PTZ) induced convulsion on rats. The extract appeared to reduce the convulsant effect in a dose dependent pattern. It depressed the central nervous system stimulation from convulsing [16], the ability of the extract to protect rat stimulated with PTZ may be an indication of its pharmacological depressant activity on both the spinal cord and brain stem. Many diseases of the brain and spinal cord produce an increase in muscle tone which can be painful and disabling, chronic pain is also associated with local muscle spasm[18]. The leaf extract also possessed muscle relaxant activity as shown by its effect on the inclined board test that evaluated muscle relaxant activity [19,16].

CONCLUSION

From the results it may be said that the extract possesses some psychoactive components and had appreciable depressant effects on the animals under study.

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