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ANTIEMETIC POTENTIAL OF METHANOL ROOT BARK EXTRACT OF *TERMINALIA AVICENNIOIDES* (COMBRETACEAE) IN CHICKS

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ABSTRACT

Terminalia avicennioides (Combretaceae) is used to treat emesis and other gastrointestinal disorders in Northern Nigeria. The current study was designed to investigate *T. avicennioides* for potential antiemetic effect in copper sulphate and cisplatin-induced vomiting models in chicks. Phytochemical screening was conducted and acute oral toxicity test of the methanol root bark extract of *T. avicennioides* was carried out using OECD 425, 2001. Emesis was induced by oral administration of copper sulphate (60 mg/kg) and intraperitoneal cisplastin (10 mg/kg) to young chicks (150-170 g, 4-7 days old). The anti-emetic activity was studied on the extract at doses of 150, 300 and 600 mg/kg. The effect of the extract on apomorphine-induced pecking in chicks was also assayed to determine the probable pathway involved in the extract's antiemetic action. Preliminary phytochemical screening revealed the presence of alkaloids, saponins, glycosides, tannins, carbohydrates, cardiac glycosides, flavonoids, terpenes and triterpenes, while the oral median lethal dose (LD_{50}) of the extract was estimated to be greater than 2000 mg/kg in chicks. The extract produced a dose-dependent significant ($P < 0.05$) inhibition of retching (54.12, 59.70 and 73.78 % inhibition of retches) in the copper sulphate induced emesis, with the 600 mg/kg dose of extract inhibiting retches comparable to domperidon but better than metoclopramide. Cisplastin induced emesis was significantly ($P <0.05$) reduced by 84.52, 83.33 and 72.62 % respectively in inverse-dose dependent manner with the effect of the extract at150 and 300 mg/kg being comparable to metoclopramide but less than ondensetron (90.0 %). Extract of *T. avicennioides* significantly ($P < 0.05$) decreased apomorphine induced retches dose dependently in chicks. This study showed that methanol root bark extract of *T. avicennioides* possess antiemetic activity against copper sulphate and cisplastin induced emesis in chicks, which might be due to the presence of relevant phytochemical constituents.

KEYWORDS: Copper sulphate, Cisplatin, Emesis, Retches, *Terminalia avicennioides*, Chicks

INTRODUCTION

Emesis (vomiting) encompasses the forceful expulsion of stomach contents via the mouth or sometimes the nose [1]. Emesis is mediated through the coordinated actions of central and peripheral receptors of serotonin ($5HT_{1A}$, $5\text{-}HT_3$ and $5\text{-}HT_4$), dopamine (D_2), histamine (H_1), muscarinic cholinergic (ACh-M), cannabinoids (CB_1) and opioids (μ_2), neurokinin (NK_1) and Gamma-amino butyric acid ($GABAB_1$) [2]. Many commercially available allopathic drugs produce their antiemetic action by interacting with these receptors and also cause undesirable side effects like; dystonias and parkinsonism-like symptoms, often referred as

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extrapyramidal syndromes, severe sedation, restlessness, anxiety and occasional hypotension [3, 4]. These adverse effects heighten the need for natural product researchers to explore natural antiemetics with fewer side effects [5]. Antiemetics play important role in the treatment of cancer patients, on chemo- and radiotherapy, motion sickness, vomiting in pregnancy [6]. In Africa including Nigeria, medicinal plants used and investigated as antiemetics include *Afzelia africana* [7], *Anethum graveolens* and *Phragmite saustralis* [8], *Garcinia kola, Grewiala siodiscus, Nymphaea lotus,Solanum aethiopicum*, *Vitex iringensis* and *Acanthospernum hispida* [6].

Terminalia avicennioides (Combretaceae) hoshst is known by vernacular names of *Baushe* (Hausa), *Tsamiya jahmi* (Fulani), *Igiodan* (Yoruba), *Edo* (Igbo), *Kpace* (Nupe) and *Kpayi* (Gwari). Phytochemical investigation of whole plant reveals the presence of anthraquinones, saponins, steroids, tannins and terpenes [9]. The roots of *T. avicennioides* are often used in folk medicine for treating various ailments which include abdominal pains, nose bleeding, cancer, trypanosomiasis, peptic ulcer, skin rash, diarrhoea, malaria and vomiting [10]. Keeping in view these ethnomedicinal applications of *T. avicennioides*, this study intends to evaluate the antiemetic activity and possible mechanism of action of the crude extract of *T. avicennioides* using chick emesis models to verify the folkloric claim.

MATERIALS AND METHODS

Animals

Male chicks (150-170 g, 4-7 days old) kept at room temperature and fed with standard food and water *ad libitum* was used. All the experiments were performed in accordance to Institute of Laboratory Animal Resources, Commission on Life Sciences (National Research Council 1996), approved by the Ethical Committee of Ahmadu Bello University Zaria, Nigeria (ABUCAUC/2016/004).

Drugs and Chemicals

Drugs used were metoclopramide (Emcure pharmaceuticals, India), domperidone (Janssen, UK), ondensetron (GlaxoSmithKline, UK), chlorpromazine (AHPL, India), apormorphine (US World Meds, Llc), cisplastin (Cipla, India). Chemicals used include copper sulphate (Yogeshwar, India) and 70% methanol (AR JHD UN1230; Guangdong GuanghuaSci-Tech. Co., Ltd., China).

Collection and extraction of plant material

Terminalia avicennioides was collected from Samaru village in Zaria,Nigeria and identified by Mal. Namadi Sunusi, a botanist in the herbarium unit, Department of Biological Sciences, Ahmadu Bello University Zaria, Kaduna State where a voucher specimen (No.900239) was documented for future reference.

Root bark of *Terminalia avicennioides* were washed, peeled and sliced into smaller pieces and air dried, under the shade until a constant weight was obtained. The root bark was then reduced to powder using mechanical grinder and extracted with 70 % methanol in water using cold maceration method for 48 hours with occasional shaking and filtered. The filtrate was dried in flask evaporator under reduced pressure and controlled temperature (45- 50 °C) over a water bath followed by air drying of aliquots on a large surface plate. The residue obtained was stored in an air tight container and then placed in a desiccator until use. The percentage yield was then calculated.

Preliminary phytochemical screening

Methanol extract of *T. avicennnioides* was subjected to phytochemical screening according to the methods of [11, 12].

Acute toxicity test

Acute oral toxicity test of methanol root bark extract of *T. avicennnioides* was carried out using the revised method of [13]. Healthy four day old chicks were housed separately and allowed to acclimatize for a period of 24 hours in the laboratory, with free access to food and water. Any animal showing sluggish movement or any sign of illness was excluded.

Five chicks were fasted overnight and weighed. The first chick was orally administered a single dose 2000 mg/kg of the extract and food was withheld for4 hours. After 48 hours of observation without death, four (4) additional chicks were dosed 2000 mg/kg and observed for physical and behavioural changes as well as death in comparison to a control group of 5 chicks that were administered distilled water 10 ml/kg in a sequence usually at 48 hours intervals.

Antiemetic studies

Copper sulphate-induced emesis in chicks

The method of [14] was used. Four day old male chicks were divided into 6 groups comprising of six chicks each. Group-I was given 10 ml/kg distilled water as control, groups II, III and IV were pre-treated with methanol root bark extract of

Terminalia avicennioides at 150, 300 and 600 mg/kg doses respectively orally. Groups V and VI were given oral metoclopramide 10 mg/kg and domperidone 150 mg/kg as standard drugs respectively. The chicks were kept in large beakers at room temperature and were allowed to rest for ten minutes to stabilize. After 60 minutes, copper sulphate anhydride (60 mg/kg) was administered orally to each chick in all the groups. Immediately following copper sulphate administration, the number of retches [an emetic action without emptying gastric content (vomiting)] produced by each chick was recorded for ten minutes. The percentage retching inhibition was calculated as:

Retching inhibition (%) = [(A-B)/A] x 100

Where, A and B represent the frequency of retching in control and experimental groups respectively.

Cisplatin-induced emesis in chicks

Same process described above was repeated but cisplastin (10 mg/kg; intraperitoneally), instead of copper sulphate was used as emetic inducing agent and the number of retches for each chick in all the groups was counted for 10 minutes. Metoclopramide (3 mg/kg) and ondensetron (3 mg/kg) were used as standard drugs.

Apomorphine-induced pecking behaviour in chicks

The effect of the extract on apomorphine –induced pecking in chicks was assayed according to method described by [15]. Four day old male chicks were randomly divided into five groups of ten chicks per group and each chick was kept in a large propylene cage at 25°C for 30 min to stabilize. Group I served as the control and was treated with distilled water (10 ml/kg). Groups II, III and IV were treated with extract (150, 300 and 600 mg/kg) orally, while group V received chlorpromazine (2.0 mg/kg) intraperitoneally. Thirty minutes later, apomorphine (2.0 mg/kg) was injected intraperitoneally to each chick. Each chick was then placed in the testing cage (45×45×45) cm of three lateral walls covered with black dotted paper sheets. After one minute of apomorphine administration, each chick was observed directly for the number pecking activity/behaviour which was recorded singly for 10 minutes using hand tally counter.

Statistical analysis

Values for observations were expressed as mean + SEM. Data were analyzed statistically using SPSS" version 20. The significance of difference between means was determined by One Way ANOVA followed by Dunnett's post hoc test for multiple comparisons with *p* values considered significant at 0.05.

RESULTS

Preliminary phytochemical screening of the methanol root bark extract of *Terminalia avicennioides* revealed the presence of alkaloids, saponins, glycosides, tannins, carbohydrates, cardiac glycosides, flavonoids, terpenes and triterpenes.

Oral administration of the extract at the dose of 2000 mg/kg did not produce clinical symptoms of toxicity and mortality in the chicks. The oral median lethal dose (LD_{50}) of the extract was therefore estimated to be greater than 2000 mg/kg in chicks.

Effect of methanol root bark extract of *Terminalia avicennioides* on copper sulphate-induced emesis in chicks

Oral administration of anhydrous copper sulphate (60 mg/kg) produced significant number of retches in the control group. The extract produced a dose dependent and significant ($p \leq 0.05$) decrease in retching frequency when compared to the control group. The highest dose (600 mg/kg) of the extract inhibited 73.78% retch frequency comparable to domperidon150 mg/kg (73.78%) and exhibited better inhibition of retches than metoclopramide 10 mg/kg (50.00%) (Table1).

Effect of methanol root bark extract of *Terminalia avicennioides* on cisplastin-induced emesis in chicks

The retches induced by cisplastin (10 mg/kg) were significantly ($p \leq 0.05$) decreased by the extract. Percentage inhibition of 84.52, 83.33 and 72.62 were obtained at 150, 300 and 600 mg/kg doses respectively. The standard drugs metoclopramide and ondensetron inhibited retches by 85.71% and 90.47% respectively (Table 2).

Effect of methanol root bark extract of *Terminalia avicennioides* on apomorphine-induced pecking behaviour in chicks

The extract of *Terminalia avicennioides* significantly ($p< 0.05$) decreased number of pecks dose dependently in the treated chicks. The extract at the doses of 150, 300 and 600 mg produced 128.6, 115.5 and 100.8 pecks respectively while the standard drug chlorpromazine (2 mg/kg) produced

84.6 pecks against the control that produced 151.4 pecks (Table 3).

Table 1: Effect of methanol root bark extract of *Terminalia avicenioides* on copper sulphate induced retching in chicks

Treatment (mg/kg)	Mean Number of Retching	% Inhibition
Distilled water (10 ml/kg)	82.40±2.37	-
Extract TA (150)	37.80±2.81*	54.12
Extract TA (300)	33.20±2.53*	59.70
Extract TA (600)	21.60±2.08*	73.78
MCP (10)	41.20±2.22*	50.00
Domperidon(150)	21.60±1.77*	73.78

Values presented as mean ± SEM*Value significantly different compared to the distilled water group at p<0.05 (One Way ANOVA, Dunnett's test) TA =T. avicennioides, MCP = Metoclopramide

Table 2: Effect of methanol root bark extract of *Terminalia avicennioides* on cisplastin induced retching in chicks

Treatment (mg/kg)	Mean Number of Retching	% Inhibition
Distilled water (10ml/kg)	16.80±1.82	-
Extract TA (150)	2.60±0.50*	84.52
Extract TA (300)	2.80±0.37*	83.33
Extract TA (600)	4.60±0.67*	72.62
MCP (3)	2.40±0.60*	85.71
Ondensetron (3)	1.60±0.40*	90.47

Values presented as mean ± SEM. *Value significantly different compared to the distilled water group at p<0.001(One Way ANOVA, Dunnett's test). TA=*T. avicennioides,* MCP = Metoclopramide

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Table 3: Effect of methanol root bark extract of *Terminalia avicennioides* on apomorphine-induced pecking in chicks

Treatment (mg/kg)	Mean Number of Pecking
Distilled water (10ml/kg)	151.40±1.56
Extract TA (150)	128.60±1.20*
Extract TA (300)	115.50±2.39*
Extract TA (600)	100.80±1.49*
CPZ (2)	84.60±3.72*

Values presented as mean ± SEM. *value significantly different compared to distilled water at *p*<0.05(One Way ANOVA, Dunnett's test). TA=*T. avicennioides,* CPZ = Chlopromazine

DISCUSSION

Terminalia avicennioides has been reported to be one of the plants commonly used to treat vomiting [16, 17] and gastrointestinal disorders in rural areas of Northern Nigeria [18]. Preliminary phytochemical constituents of the methanol root bark extract identified in this study were similar to those reported in other studies carried out on the roots, bark and leaves which revealed the presence of tannins, anthraquinones, ellagic acid, saponins, flavonoids, phenols, steroids and glycosides [19, 9]. According to [20], secondary plant metabolites like saponins, glycosides, flavonoids and terpenes have been reported to possess antiemetic activity. Alkaloids are also reported to possess significant antiemetic potential [21]. These constituents could

be responsible for the antiemetic effect of methanol root bark extract of *Terminalia avicennioides*.

Emetic mechanisms of copper sulphate have been proposed to be by peripheral stimulation via direct stimulation of stomach wall [22, 23], 5-HT_{1A} receptor [24] and through effect on 5-HT_4 receptors [6]. Inhibitors of gastric irritation and 5-HT_4 receptor action and/or stimulation of 5-HT_{1A} receptor are therefore considered to decrease retching frequency induced by copper sulphate. In this study *T. avicennioides* extract produced a dose dependent and significant decrease in retching frequency induced by copper sulphate (60 mg/kg) in chicks. The retch frequency inhibition (73.78%) observed with the highest dose of the extract was comparable to domperidon (150 mg/kg) and higher than metoclopramide 10 mg/kg (50.00%). These observations suggest that the extract may be acting via inhibition of gastric stimulation, 5-HT_4receptor blockade and or 5-HT_{1A} receptor stimulation.

Cisplastin, an antineoplastic agent is reported to induce emesis via stimulation of serotonergic receptor (5-HT_3) of the vagus afferent neurons [25], and 5-HT_{1A} receptor stimulation [6]. The extract at the tested doses showed similar effectiveness in inhibiting frequency of retches as the standard drugs used (metoclopramide and ondensetron) suggesting that *Terminalia avicennioides* may interfere with 5-HT_3 receptors present in peripheral endings of afferent vagal nerves.

Apomorphine acts by activating dopamine D_2 and to lesser extent D_1-receptors at chemoreceptor trigger zone of the brain to induce emesis which is implicated in hyperactivity and stereotypic behaviors [26]. The study was carried out to ascertain dopamine receptor blocking effect of *Terminalia avicennioides* in apomorphine treated chicks. Dose dependent decrease in apomorphine induced pecking in chicks by the extract is suggestive of dopaminergic (D_2) receptor blockade at the chemoreceptor trigger zone.

CONCLUSION

The study has shown that methanol root bark extract of *T. avicennioides* possess antiemetic activity which may be mediated peripherally or centrally via blockade of serotonergic and dopaminergic receptors. The study also confirms the presence of potentially useful pharmacologically active principles and provided scientific credence for ethnomedicinal use of *T. avicennioides* root bark in the management of emesis.

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