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Research Article

EVALUATION OF ANTINOCICEPTIVE ACTIVITY OF ETHANOL WHOLE PLANT EXTRACT OF *Viscum album* L. IN RATS

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ABSTRACT

Viscum album L is widely distributed in tropical and subtropical Africa, Asia and Europe. They are used in the treatment of nervous complaints, bleeding, tumours, diabetes mellitus and arthritis. The study was conducted to evaluate the antinociceptive activitiy of the ethanol whole plant extract. The Preliminary phytochemical screening and acute toxicity study on the plant extract was carried out based on the outlined standard procedures, whereas the antinociceptive activity was evaluated using acetic acid-induced writhing and tail immersion test. The Preliminary phytochemical screening of the extract revealed the presence of flavonoids, alkaloids, glycosides, tannins, saponins, steriods and triterpenes. The intraperitoneal and oral LD_{50} was found to be greater than 2000 and 5000 mg/kg respectively. The ethanol extract of the plant produced significant ($p<0.05$) and dose-dependent antinociceptive activity in both methods used. The peak antinociceptive effect occurred at 1000 mg/kg with a percentage inhibition of 88.3% in acetic acid-induced writhing test. Similarly 1000 mg/kg produced maximum increase in pain threshold by 1.91 fold in the tail immersion test at 90 minutes. The results demonstrate that the ethanol whole plant extract of *Viscum album* was found to be relatively less-toxic and contain some pharmacologically active constituents which might be responsible for the observed antinociceptive activity of the plant extract. These amply justify the traditional use of this plant as an analgesic.

Keywords: *Viscum album*, Ethanol, antinociceptive

INTRODUCTION

Inflammation is the local response of living mammalian tissues to injury due to any agent. It is the body's defense reaction in order to eliminate or limit the spread of injurious agents as well as to remove the consequent necrosed cells and tissue [1]. The body responds to inflammation using different mechanisms that enables it to adequately fight injurious or infectious agents. Cells of different types are involved in bringing about inflammation processes [2]. Following an injury or infection, white blood cells (leukocytes) are mobilized to aid in phagocytosis and destruction of pathogens for systemic repair. Though inflammation is important in the body, it could be deleterious if the stimulus persists for longer periods as it can cause certain painful inflammatory diseases such as arthritis or gastritis [3]. Pain on the other hand is a sensory modality which in many cases represents the only symptom for the diagnosis of several diseases. It often has a protective function [4]. In spite of the effectiveness of non steroidal anti-inflammatory drugs (NSAIDs) they have associated toxic effects on the gastro-intestinal tract and renal system [5]. Conversely, selective cyclooxygenase -2 (COX-2) inhibitors with little toxic effect on the gastro-intestinal tract have been associated with toxic cardiovascular effects [6]. Research to explore safer and more efficacious alternative treatments is therefore necessary. Man has been using plants primarily as source of food and medicines for centuries. Of recent, there is a renewed interest in the study of plants because of their potential to yield drugs of novel activity [7]. Majority of the users rely on herbal medicines for health care because the other treatment options available are more expensive and they are often thought to be associated with serious side effects such as upper gastrointestinal complications, organ damages and blood cancer. Research by scientists all over the globe suggests that plant based drugs and additives are better and safer in addressing ever-growing health problems in man and that no plant is entirely useless. *Viscum album* L. has been used in the indigenous systems of medicine for treatment of headache and some inflammatory diseases. The plant has been used for various medicinal purposes from ancient times, it has been reported to possess a number of therapeutic applications in folk medicine in curing or managing of a wide range of diseases such as diabetes mellitus, chronic cramps, stroke, stomach problems, heart palpitation, to lower blood pressure, difficulties in breathing and hot flushing in menopause [8]. Therefore, this study was embarked upon purposely to evaluate the phytochemistry, acute toxicity and analgesic activity of *Viscum album* L as acclaimed by traditional healers here in Maiduguri, Nigeria.

MATERIALS AND METHODS

Collection and preparation of plant materials

The *Viscum album* were freshly collected from Hawul local Government area of Borno state, Nigeria in December 2014, and was identified by Professor S.S Sanusi in the Department of Biological Science, University of Maiduguri. The whole plant was collected and dried at room temperature for one week, then the dried plants were grounded using wooden pestle and mortar at which the powdered material was weighed several times until constant weight was obtained and was extracted in the Pharmacognosy laboratory.

Extraction of the plant material

Three hundred grams of the powder was weighed and was subjected to maceration using 400 ml of 95% ethanol. The mixture was stirred and kept for 24 hours and then filtered. The filtrate was evaporated under reduced pressure using rotary vacuum evaporator at a 40ºC and the content was air dried and the dried ethanol extract was obtained and coded VAEE (*viscum album* ethanol extract). The Percentage (%) yield was calculated as = x/y multiply by100 (where x = weight of dried concentrated extract and y = weight of the dried powdered plant.

Phytochemical Analysis

The VAEE was screened for presence of phytochemicals using standard methods described by Brain and Tuner [9], Trease and Evans [10] and Sofowora [11].

Acute Toxicity Studies *(*LD_{50} **Determination*)*

The acute toxicity of VAEE was determined using modified Lorke's method as described by Lorke [12]. The experiment was performed using the intraperitoneal and oral route of administration.

Intraperitonial (ip) LD_{50}

Nine (9) healthy Wistar strain albino rats of both sexes weighing 103-168 g were randomly selected and divided into three groups (labelled A, B and C) of three animals each. The animals in each group were weighed and labelled with picric acid on either the head, back or tail (as required), as a mark of identification. The groups were then treated respectively with the extract at incremental doses of 100 mg/kg, 1000 mg/kg and 2000 mg/kg intraperitoneally (modified lorke's method). The animals were then observed for 24 hours for signs of toxicity and mortality.

Oral LD_{50}

The study was conducted in two phases. In the first phase, three groups of three rats each were administered with the extract at respective oral doses of 10mg, 100mg, 1000mg and 2000 mg/kg. The rats were observed for signs of toxicity and possible deaths for 24 h and 72 h. In the second phase, another three groups of three rats each were administered respective doses of 2900, 3500 and 5000 mg/kg body weight of the extract. They were equally monitored as in phase one for signs of toxicity and deaths.

Animal Model

Swiss-Albino rat of either sex (120-170 g body weight) were collected from Faculty of Pharmacy, University of Maiduguri animal house. They were housed in standard wire meshed plastic cages, allowed access to food (Vital® Feed) and water *ad libitum*. All the animals were handled according to the international guiding principles for biomedical research involving animals (CIOMS) as certified by the animal Ethics Committee of the Faculty of Veterinary Medicine, University of Maiduguri.

Analgesic activity test of the VAEE

The study of analgesic activity of the VAEE was performed in animal models. For the screening of analgesic activity against peripheral mechanism of pain, acetic acid induced writhing test was considered.

Acetic acid induced writhing test

This was carried out according to the method described by Koster *et al* [13] and Singh & Majundar [14]. Five groups (A, B, C, D and E) of five rats each were used. They were deprived of food for 24 hr before the commencement of the experiment. Those in group A received distilled water (2 ml/kg) to serve as negative control group, while those in groups B, C and D received 250, 500 and 1000 mg/kg respectively of the VAEE; while those in group E received pentazocine (30 mg/kg) to serve as the positive control group. The drug and extract administration were carried out intraperitoneally (i.p). Sixty minutes later, 2 ml/kg of 0.8% acetic acid solution (in 0.9% w /v normal saline) were administered to all groups to induce writhing. Writhing response was observed as described by Tuner [15]. The number of writhes was counted from five minutes after acetic acid administration for thirty minutes. A reduction in the number of writhing as compared with the negative control group was considered as evidence of analgesia. The percentage protection was obtained using the formula described by Hernandez-Perez *et al* [16] as shown below;

$$\% \text{ inhibition} = \frac{\text{Mean number of writhes in negative control} - \text{Mean number of writhes in test group}}{\text{Mean number of writhes in negative control group}} \times 100$$

Tail immersion test

The tail immersion method was used to evaluate the central mechanism of analgesic activity [17]. This was based on the method described by Singh and Majundar [14]. Twenty five rats of both sexes (weighing between 120-170 g) were randomly divided into five groups (A, B, C, D and E) of five rats each. They were deprived of food for 24 hr before the commencement of the experiment. Those in group A (negative control) received distilled water (2 ml/kg), while those in groups B, C and D received 250, 500 and 1000 mg/kg respectively of the VAEE. Group E (positive control) received pentazocine (30 mg/kg). All treatments were by i.p route. Sixty minutes later, the tail (up to 10 cm) was dipped into a water bath maintained at 55 ± 0.5 °C. The time (in seconds) to withdraw the tail clearly out of the water was taken as the reaction time. The latent period of the tail response was determined at 30, 60, 90 and 120 min after the administration of drugs and extract. The percentage (%) increase in pain threshold (latency) was calculated as below; % increase in pain threshold =

$$\% \text{ inhibition} = \frac{\text{Mean reaction time in test control} - \text{Mean reaction time in negative control group}}{\text{Mean reaction time in negative control group}} \times 100$$

Statistical Analysis

The results were analysed for statistical significance using student's t-test followed by post Bonferroni test. A p value of less than 0.05 was considered significant. The statistical analysis was performed for all experimental animal models by using one way ANOVA followed by post test Bonferroni (SPSS, 2007: version 16). The mean value ± SEM was calculated for each parameter. All the test samples and standard drug's parameter were compared with control group at respective time. Finally, the test drugs were compared with standard drug to know the statistical significant difference between two groups at respective time.

Table 1 Qualitative phytochemistry of ethanol whole plant extract of *Viscum album*

	Phyto constituents	Results
	Alkaloids	
(a)	Dragendroff's Reagent	–
(b)	Mayer's Reagent	+
	Carbohydrates	
(a)	Molish's Test	+
(b)	Fehling's Test	+
	Flavonoids	
(a)	Shinoda's Test	+
(b)	$FeCl_3$ Test	+
(c)	Pb acetate Test	+
	Glycosides	
(a)	Free anthraquinones	+
(b)	Combined anthraquinones	+
	Saponins	
(a)	Frothing Test	+
(b)	Fehling's Test	+
	Steroids	+
	Tannins	
(a)	$FeCl_3$	+
(b)	Pb acetate	+
	Triterpenes	+

– = not detected; + = present

Table 2 Acute toxicity study of ethanol whole plant extract of *Viscum album*

Phases	Dose (mg/kg)	
	IP	Oral
Phase 1	10	10
	100	100
	1000	1000
	2000	2000
Phase 2		
	-	2900
	-	3500
	-	5000
LD_{50}	**>2000 mg/kg**	**>5000 mg/kg**

IP = Intraperitoneal route, LD_{50} = Lethal Dose that can kills 50% of rats

Table 3 Effect of ethanol whole plant extract of *Viscum album* in acetic acid- induced Writhing Test

Group	Dose (mg/kg)	No. of Writhes (Mean ± S.E.M)	% Inhibition
Distilled Water	10ml/kg	60.60 ± 3.37	-
Extract	250	34.60 ± 2.29*	42.90
Extract	500	23.00 ± 1.14*	62.05
Extract	1000	7.10 ± 0.86*#	88.30
Pentazocine	30	6.40 ± 0.58*	89.44

Results were expressed as mean ± standard error of the mean, n = 5, *= p<0.05 was considered significant and '#'- indicates there is no significant difference between standard and test drug at p<0.05 significant level

Table 4 Effect of ethanol whole plant extract of *Viscum album* on tail immersion method in albino rats

Treatment	Dose	Response Time in seconds (mean ± SD)							
	(mg/kg)	30 min(sec)	% increase in pain threshold	60 min (sec)	% increase in pain threshold	90 min (sec)	% increase in pain threshold	120 min(sec)	% increase in pain threshold
Distilled Water	10ml/kg	2.26 ± 0.05	0.00	2.30 ± 0.07	0.00	2.46 ± 0.05	0.00	2.44 ± 0.05	0.00
Extract	250	4.64± 0.14*	105.31	4.66 ± 0.14*	102.61	5.14 ± 0.05*	108.94	4.96 ± 0.05*	103.27
Extract	500	5.28± 0.04*	133.62	5.53 ± 0.05*	140.43	5.96 ± 0.06*	142.27	5.52 ± 0.05*	126.23
Extract	1000	5.54± 0.05*	145.13	6.02 ± 0.06*	161.74	7.18± 0.07*#	191.86	6.02 ± 0.06*	146.72
Pentazocine	30	6.44± 0.07*	185.00	7.00 ± 0.10*	204.35	7.53 ± 0.15*	206.10	9.42 ± 0.23*	286.10

Results were expressed as mean ± SEM. n = 5, * = P<0.05 was considered significant and '#'- indicates there is no significant difference between standard and test drug at p<0.05 significant level

RESULTS ANALYSIS

Preliminary phytochemical screening
The preliminary phytochemical screening of the ethanol plant extract of *Viscum album* showed the presence of alkaloids, carbohydrates, flavonoids, glycosides, saponins, tannins, steriods and triterpenes (Table 1).

Acute toxicity
The acute toxicity of ethanol plant extract of *Viscum album* in albino rats was found to be greater than 2000 mg/kg and 5000 mg/kg intraperitoneally and orally respectively (Table 2).

Effect of ethanol whole plant extract of *Viscum album* in acetic acid induced writhing
The analgesic activity of ethanol whole plant extract of *Viscum album* in acetic acid induced pain in albino rats was found to be dose dependent. The activity of the extract was found to be significantly lower than the activity of the standard drug used in this study (pentazocine) ($p<0.05$). The highest dose (1000 mg/kg) produced a significant ($p<0.05$) percentage inhibition of 88.30 % which was found to be statistically not significant ($p>0.05$) when compared with the standard drug with percentage inhibition of 89.44 % (Table 3).

Analgesic effect of ethanol whole plant extract of *Viscum album* in tail immersion test
The analgesic activity of ethanol whole plant extract of *Viscum album* in tail immersion test in albino rats was found to be dose dependent. The peak antinociceptive effect of the extract occurred at 90 minutes for all the dose levels. The activity of the extract was found to be significantly ($p<0.05$) lower than the activity of the standard drug (pentazocine). However the extract at 1000 mg/kg produced a significant ($p<0.05$) inhibition of 191.86 % which was found to be statistically not significant ($p>0.05$) when compared with the standard drug (pentazocine) with percentage inhibition 206.10% (Table 4)

DISCUSSION

The phytochemical analysis of the whole plant of *Viscum album* ethanol extract (VAEE) revealed the presence of some bioactive constituents which agreed with several literature reports in which similar compounds were reported [18-20]. However, Oguntoye and his colleagues [19] did not detect saponins in both aqueous and ethanol extracts. The source of the *Viscum album* in the present study was obtained from the tree *Gardenia erubescens* which may account for the variation in the phytochemical constituents among several possibilities. The usefulness of these metabolites in phytomedicines or treatment of ailments has been documented [21-22]. Flavonoids are free radical scavengers and therefore useful in management of inflammatory diseases e.g. tumour and oxidative stress related diseases [22]. Other related studies also supported the activities of flavonoids and tannins as antinociceptive and /or anti-inflammatory agents [22]. There are also reports on the role of flavonoid in analgesic activity primarily by targeting prostaglandins [23]. Tannins detected in the present study are also claimed to possess analgesic activity [24]. Therefore, the presence of these metabolites in these plants supports their uses in treatment of various ailments traditionally especially in the treatment of pains [25].

The result of acute toxicity (LD_{50}) is greater than 2000 mg/kg intraperitoneally which shows that the extract is relatively less-toxic. According to Clarke and Clarke [26] any substance who's LD_{50} in rats falls between 50 and 500 mg/kg is toxic, between 500 mg/kg but less than 1000 mg/kg is moderately toxic and greater than 1000 mg/kg is non-toxic.

The antinociceptive activity of the VAEE produced significant graded dose effects in all the two models employed viz; acetic acid-induced writhing and tail immersion. These finding are in agreement with the reports of several literatures in which *Viscum album* was found to exhibits antinociceptive and antiinflammatory activities [20, 27, 28]. Intraperitoneal injection of acetic acid in this experiment produced abdominal contorsions by activating the chemosensitive nociceptors in the animals as reported by Onasanwo and Elegbe [29]. The percentage reduction in the number of abdominal contorsions indicates the level of analgesia in the acetic acid induced writhing reflex model [30]. The inhibition of writhing in rats by the ethanol extract may suggest a peripheral mechanism of action possibly via inhibition of prostaglandins among several possibilities. The acetic-acid induced writhing test is widely used to study the peripheral analgesic effects of drugs [31]. This was supported by several studies that the acetic acid induced writhing response is a sensitive procedure to evaluate peripherally acting analgesics. The response is thought to be mediated by peritoneal mast cells [32], acid sensing ion channels [33] and the prostaglandin pathways [34]. A narcotic analgesic was used as a positive control in this study because it inhibits both peripheral and central pain [35]. Acetic acid-induced writhing model represents pain sensation by triggering localized inflammatory response. Such pain stimulus leads to the release of free arachidonic acid from tissue phospholipids [36], via cyclooxygenase (COX), and prostaglandin biosynthesis [37]. The extract significantly ($p<0.05$) reduced the number of acetic acid-induced writhes in rats. The analgesic effect of the extract could be due to either its action on visceral receptors sensitive to acetic acid, to the inhibition of the synthesis of algogenic substances or the inhibition at the central level of the transmission of painful stimuli as postulated by Franzotti *et al* [38]. Tail immersion test are considered to be selective to examine compounds acting through opioid receptor; the extract increased mean basal latency which indicates that it may act via centrally mediated analgesic mechanism. The extract showed significant ($p < 0.05$) dose dependent analgesic effect in the tail immersion test, which involves higher brain functions and consists of responses to nociceptive stimuli organized at a supraspinal level [39]. Orhan and his colleagues [20] evaluated the anti-inflammatory and anti-nociceptive effect of the ethyl acetate fraction of *Viscum album* in experimental mice in which the extract posses a remarkable and dose-dependent anti-inflammatory activity which is as potent as indomethacine. The ethanol extract of *Viscum album* inhibited both mechanisms of pain, suggesting that the plant extract may act as a narcotic analgesic. Such a mode of action is proposed for opioid analgesic such as morphine. It is also reported that the inhibition of pain could arise not only from the presence of opioids and/or opiodiomimetics but could also arise from the presence of phenolic constituents [40] and also steroidal constituents [41]. So, it may be due to the similar type of constituents present in the extract. Perhaps the presence of one of more of these secondary metabolites may be responsible for the analgesic effect of the extract.

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CONCLUSION

The ethanol whole plant extract of *Viscum album* L is relatively safe, contains some pharmacologically active constituents which may be responsible for the observed anti-nociceptive activity. The results support the traditional use of this plant in some painful and inflammatory conditions.

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