Original Research Article

Evaluation of the anticonvulsant and antidepressant effects of the aqueous extract of the leaves of ascotheca paucinervia (t. anderson ex c.b. clarke) heine in mice

Abstract

The present study was undertaken to evaluate the anticonvulsant and antidepressant effects of *Ascotheca paucinervia* leaves by using strychnine at 2.5 mg/kg to induce convulsions and the forced swim test to create a stressful situation, respectively. Concerning convulsions, only the 500 mg/kg extract significantly increases ($p<0,001$) the time to onset of convulsion and it non-signifificantly reduces the duration of convulsions induced by strychnine. In addition, the extract very significantly reduces in a dose-dependent manner the time of immobility and it significantly increases the swimming time as well as the climbing time at both cases. In addition, the evaluation of the sedative effect of this extract shows that it produces a dose-dependent sedative effect and at doses of 250 mg/kg and 500 mg/kg, the extract significantly potentiates the sleep induced by phenobarbital. These results suggest that *Ascotheca paucinervia* leaves extract possess anticonvulsant and antidepressant effects.

Key words: Anticonvulsant activity, Antidepressant activity, Epilepsy, *Ascotheca paucinervia.*

1. Introduction

Convulsions are seizures, being the clinical expression of which results in more or less violent and involuntary muscular contractures of one or more muscles, of one or more limbs or even of the whole body, of cerebral or medullary origin, provoked by "the hyperexcitation of a neuronal group (Vidal, 2021). Unlike other seizures, epileptic seizures are characterized by the occurrence of two or more spontaneous seizures manifested by brief episodes of involuntary tremors affecting a part of the body (focal seizures) or the whole body (generalized seizures) and they result from excessive electrical discharges in a group of brain cells (Jost, 2018). Epilepsy suffers from a very negative brand image and is responsible for the suffering of approximately 50 million people worldwide, of whom 5 million are diagnosed each year, thus representing the second most common neurological disorder after migraine and with a mortality from 2 to 3 times higher than that of the normal population (WHO, 2019) whose most common cause is sudden unexpected death (Rasekhi et al., 2021). However, several psychiatric comorbidities are often associated with epilepsy, the most common of which is depression (Hingray et al, 2015). It is estimated that 6 to 30% of epileptics are affected by major depressive disorders (Viguera et al, 2018, Guekht et al, 2021). More than 80% of the African population uses traditional medicine and medicinal plants for their primary health care (WHO, 2020). Among the medicinal plants treating epilepsy, there is *Ascotheca Paucinervia*, a newly identified species in the Republic of Congo confirms the national herbarium, is a plant with multiple virtues, none of which would be scientifically tested. In African countries, 80% of the population uses traditional medicine and medicinal plants for their primary health care, because some of these plants contain secondary metabolites with little or no exploration of effective activities, little or non-toxic (Nesterkina et al. 2021) which can constitute original series leads for the development of new drugs (Kouga et al, 2010) and which remain an inexhaustible reservoir of new drugs. Indeed, numerous studies mention that approximately 400,000 plants species have been identified (Bachman, 2016) but only 2,000 to 3,000 of them have been the subject of scientific, chemical or pharmacological studies (VIDAL, 2012) including *Ascotheca paucinervia*. The present

work aims to evaluate the anticonvulsant and antidepressant effects of *Ascotheca paucinervia leaves* in mice.

2. Material and methods

This study was carried out in the laboratory of Pharmacodynamics and experimental physiopathology of the Faculty of Sciences and Techniques of Marien University - NGOUABI.

2.1. Plant material

The plant material consisted of the leaves of *Ascotheca paucinervia* harvested in January 2021 in the "Cuvette" department, in Makoua district precisely in the forest of the village of Feu (48 km) and dried at room temperature at the Laboratory of Pharmacodynamics and Experimental Pathophysiology (L2PE).

2.2. Animal material

The animal material was made up of mice of the Swiss albino strain with a body weight of between 20 and 25 g, of male and female sexes, provided by the IRSSA, reared at the animal facility of the Faculty of Science and Techniques under standard conditions (25±5°C, 40-70 HR), with a cycle of 12 hours of light and 12 hours of darkness. These mice had free access to tap water and standard food.

2.3. Preparation of the aqueous extract of *Ascotheca paucinervia* leaves

The aqueous extract of the leaves of *Ascotheca paucinervia* was prepared by decoction at 10%, 50 g of powder of *Ascotheca paucinervia* leaves and mixed in 500 ml of distilled water and boiled for 15 minutes at 75°C. After cooling, the decoction obtained was filtered with absorbent cotton. The filtrate collected was then evaporated at reduced temperature (50-60° C.) for 48 hours. The dry extract obtained was used to evaluate the acute toxicity and pharmacological tests.

2.4. Acute toxicity study

The acute toxicity of the aqueous extract of *Ascotheca Paucinervia* leaves was carried out according to the guideline N°425 of the OECD (OECD, 2022). It consists of testing the aqueous extract orally at a single dose of 5000 mg/kg. The test was carried out on 6 female mice divided into two groups of 3 mice each. The first group of which (negative control) received distilled water at 0.5ml/100g and the second one received the extract at 5000mg /kg. After administration of products, the mice were placed in individual cages for observations for 4 h. These observations were related to parameters such as tremors, alertness, vocalization, stool state, quantity of urine, reaction to stimuli, aggressiveness and sleep. The mortality rate of animals per group was evaluated for 48 hours after administration of products. Each animal's body weight, water intake and food consumption were measured daily for 14 days**.**

2.5. Pharmacological tests

2.5.1. Evaluation of the effects of *Ascotheca paucinervia* leaves against strychnine-induced seizures in mice (STR)

The method used was developed by Lehmann et al. in 1988 and taken up by Bassoueka (2016). It consists in inducing tonic convulsions within 10 minutes in mice by intraperitoneal administration of strychnine 2.5 mg/kg for one hour after all treatments. Four (4) groups of 5 mice each were formed and fasted for 18 hours before the experiment and treated as follows: Negative control group 1 received distilled water 0.5 mL/100 g, per-os. Positive control group 2 was treated with the reference molecule of diazepam 10 mg/kg, per os. Groups 3 and 4 were treated with the aqueous extract of *Ascotheca paucinervia* leaves at the respective doses of 250 and 500mg/Kg p.c per os. One hour after treatments, convulsions were induced by intraperitoneal injection of strychnine 2.5 mg/kg. The animals were observed for 10 minutes.

Those not presenting convulsions or presenting convulsions without dying during this period, were declared protected. The time to onset as well as the duration of seizures in each batch are determined (Bassoueka et al, 2016).

2.6. Evaluation of antidepressant effects of Ascotheca paucinervia leaves in mice

The forced swimming test was applied according to the protocol established by Porsolt et al. (1977), with some modifications. Four (4) groups of 4 mice were constituted and treated orally as follows: Group 1, negative control received distilled water 0.5 ml/100 g. Group 2, positive control, was treated with the reference molecule of Clomipramine at a dose of 15mg/kg. Groups 3 and 4 were treated with aqueous extract of *Ascotheca Paucinervia* leaves at doses of 250 mg/kg and 500 mg/kg respectively. One hour (1h) after the gavage, the mice were placed individually in a high glass cylinder 25cm with 20cm of diameter, containing 15cm of water, maintained at a temperature of ± 25°C for a period equivalent to 6 minutes. During this observation period, the durations of climbing, swimming and immobility are timed (chen et al, 2015, Khaladi et al, 2016, hajjaj et al, 2017, Ngannga et al, 2018).

2.7. Evaluation of sedative activity of aqueous extract of *Ascotheca paucinervia* leaves

2.7.1. Effect of aqueous extract of Ascotheca paucinervia leaves on motor activity

The method used was developed by Boissier and Simon in 1967 and taken up by Bassoueka (2016). It consists in assessing by using a cage with squared boards comprising 16 squares measuring 40×40 cm, based on the number of squares covered by a mouse in five (5) minutes. Four Groups (4) of 5 mice each were constituted and treated orally as follows: Group 1 of negative control received distilled water 0.5 mL/100 g. Group 2 of positive control was treated with the reference molecule of diazepam 10 mg/kg. Groups 3 and 4 were treated with the aqueous extract of *Ascotheca paucinervia* leaves at the respective doses of 250 and 500mg/Kg p.c. One hour after the administration of products, the animals were placed in turn in a squared cage, and the number of squares crossed by them after five (5) minutes is noted.

2.8. Effect of aqueous extract of *Ascotheca paucinervia* leaves on phenobarbital-induced sleep

The method used was developed by Lechat et al in 1964. Four (4) groups of 5 mice each were formed and fasted for 18 hours before the experiment and treated as follows. Negative control group 1 received distilled water 0.5 mL/100 g, per-os. Positive control group 2 was treated with the reference molecule of diazepam 10 mg/kg, per os. Groups 3 and 4 were treated with the aqueous extract of *Ascotheca paucinervia* leaves at the respective doses of 250 and 500mg/Kg p.c per os. One hour after the administration of various products, the animals received phenobarbital intraperitoneally at a dose of 10mg/kg and the time to onset and sleep duration were determined for each mouse. Sleep duration is considered as the time between when the mouse loses the righting reflex and when the righting reflex reappears. The loss and/or appearance of the reflex is assessed by tickling the mouse's ear. The awake mouse reacts by moving the front paw on the stimulated side (Bassoueka et al., 2015).

2.9. Statistical analyzes

Statistical analysis was done by using Excel software (Office 2010) and the results expressed as mean ± SEM were subjected to a one-way analysis of variance followed by the Student-Fischer t-test ($p < 0.05$, $p < 0.01$, $p < 0.001$). (Schwartz D.E., 1963).

3. Results

3.1. Assessment of acute toxicity

After administration of a single dose of 5000 mg/kg of the aqueous extract of *Ascotheca paucinervia* leaves orally and observation for four hours (04 h), the general behavior of the treated animals in comparison with that of the controls remains normal, except at the level of a few parameters where there were certain changes at a given moment of the observation. Thus, it is from the fourth hour of observation of the animals that it was noted a reduction in mobility, vigilance as well as an appearance of light sleep in the group treated with the aqueous extract of *Ascotheca paucinevia*. In the end, no death was recorded in 48 hours and the notation of the water consumption, food and the weight of the animals were carried out for 14 days.

3.2. Effect of the aqueous extract of *Ascotheca paucinervia* on weight change

Figure 1 shows the change in weight after single administration of the aqueous extract of *Ascotheca paucinevia* leaves orally at a dose of 5000 mg/kg of body weight for fourteen days (14 days). This presents three levels (03) of significance: a significant increase ($p<0.001$) in body mass on the second day (D2) of the weighing, as well as on the third day (D4), the fifth day (D8) and the eighth (D14) day ($p<0.01$) and fourth (D6), sixth (D10) and seventh (D12) day ($p<0.05$). In general, the extract significantly increases body mass compared to distilled water.

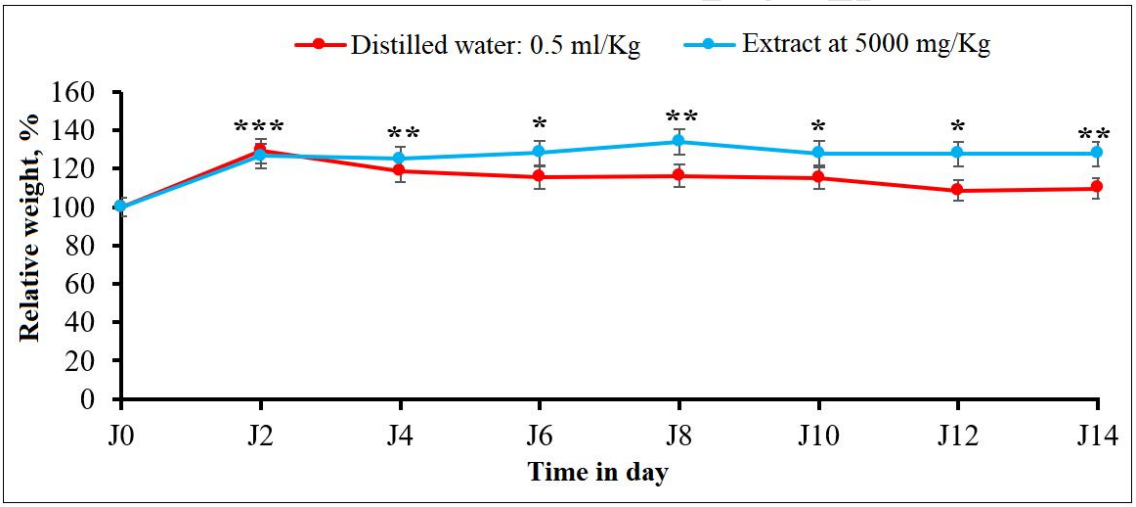

Figure 1. Effect of the aqueous extract of *Ascotheca pauinervia* leaves on the evolution of body weight. The results are expressed as mean ± ESM error, n=3, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

3.3. Effect of aqueous extract of *Ascotheca paucinervia* on food consumption

Figure 2 shows the effects of *Ascotheca paucinervia* leaves extract on food consumption after oral administration of the extract at a single dose of 5000 mg/kg body weight. The control and treated groups were fed with the standard food, i.e. 100 g for each group for fourteen (14) days. The amount of food remaining every two days was weighed and that consumed calculated. This figure shows an increase in the food consumption of the treated batch on the following days: D2, D4, D10 and D14 compared to the negative control.

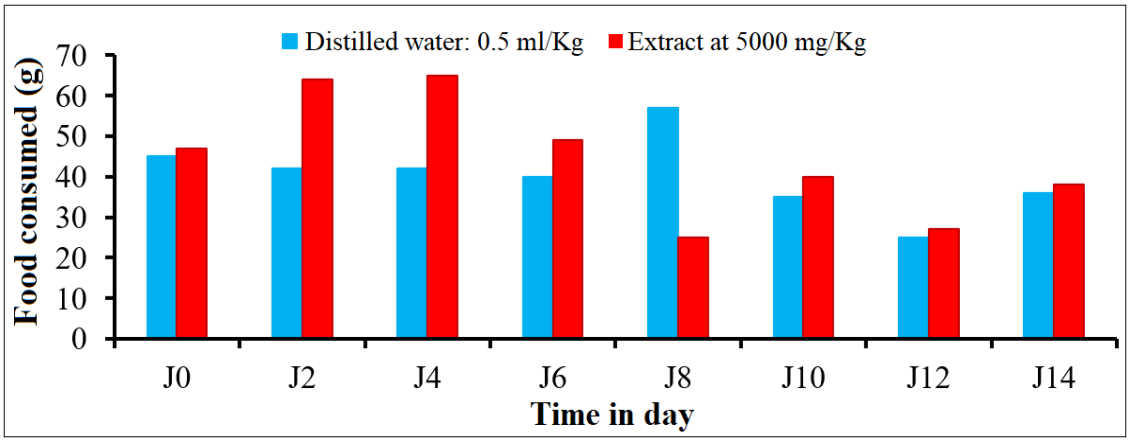

Figure 2. Effects of the aqueous extract of Ascotheca paucinervia leaves on food consumption

3.4. Effect of aqueous extract of Ascotheca paucinervia on water consumption

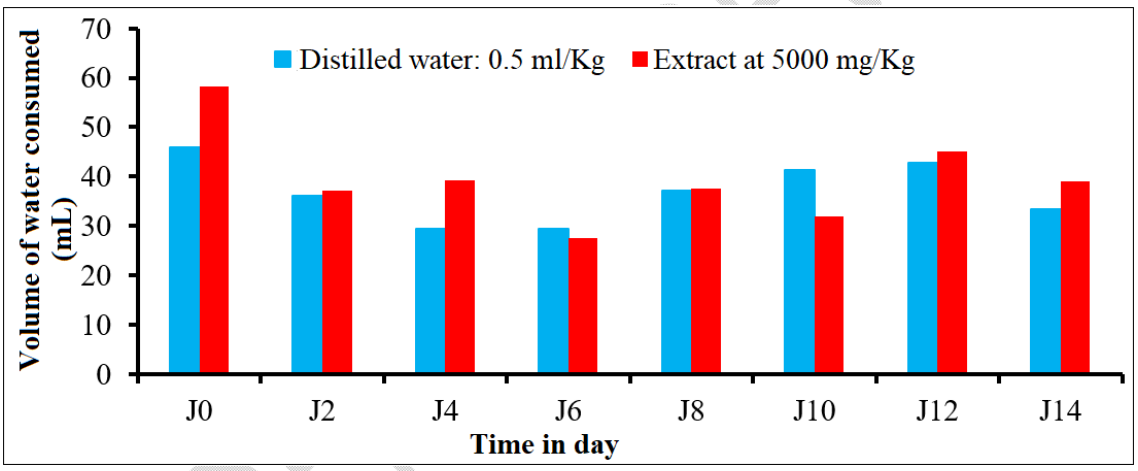

Figure 3. Effects of the aqueous extract of *Ascotheca paucinervia* leaves on water consumption

Figure 3 shows the effects of the aqueous extract of *Ascotheca paucinervia* leaves on water consumption after administration of aqueous extract of *Ascotheca paucinevia* leaves orally at a single dose of 5000 mg/kg. The control groups were treated and fed tap water for fourteen days. This shows an increase in water consumption on days: D0, D4, D12 and D14.

3.5. Effect of aqueous extract of *Ascotheca paucinervia* leaves against strychnine-induced seizures

Table 1 sqhows the effects of the aqueous extract of the leaves of *Ascotheca paucinervia* at doses of 250 and 500 mg/kg of body weight against convulsions induced by strychnine. Compared to distilled water, at a dose of 250 mg/kg, the extract non-significantly increases and decreases the time to onset of convulsions and the duration of convulsions respectively. At a dose of 500 mg/kg, the extract very significantly increases the delay as well as it

decreases the duration of convulsions in a non-significant way. Diazepam 10mg/kg used as a reference molecule led to a significant increase ($p<0.001$) in the time to onset of convulsions similar to that of the aqueous extract of *Ascotheca paucinervia* leaves at a dose of 500 mg/kg of body weight.

Table 1. Effect of A. *Paucinervia leaves* extract against STR-induced seizures

Products	Doses (mg/kg)	Time to onset of seizures (S)	Duration of seizures (S)
Distilled water + STR (b)	0,5 (a)	85,75 ± 10,19	20± 4,81
Diazepam + STR (b)	10	207 ± 10,40 ***	342,5 ± 15,96 ***
A.paucinervia + STR (b)	250	101 ± 9,66 NS	39,5± 15,51 NS
A.paucinervia + STR (b)	500	201,25± 85,36***	23± 2,67 NS
(a) (a): in ml/kg, (b): 2.5 mg/kg.i.p. The values are means ± SEM, with n = 4; *** p < 0.001 significant difference from and NS: non-significant difference from negative control.			

3.6. Antidepressant effect of aqueous extract of *Ascotheca Paucinervia* leaves in mice

Table 2 shows the effects of *Ascotheca paucinervia* leaves extract on antidepressant activity in the forced swimming model. Compared to distilled water, at a dose of 250 mg/kg, the extract significantly reduces and increases ($p<0.05$) the immobility time and the climbing time respectively, as well as it increases the time of swimming. At a dose of 500 mg/kg, the extract very significantly reduces and increases the time of immobility and the climbing time respectively, as well as it increases the swimming time in a non-significant way. Clomipramine used as a positive control, produced identical effects to that of the aqueous extract of *Ascotheca paucinervia* leaves.

Table 2. Antidepressant effect of aqueous extract of *Ascotheca Paucinervia* leaves in mice.

Treatments	Doses (mg/kg)	Immobility time	Climbing time	Swimming time
Distilled water	0,5(a)	170 ± 10,33	85,75±10,01	102,75 ± 21,11
Clomipramine	15	70,5 ± 11,89 ***	200,75±34,29 **	69 ± 21,74 **NS**
A.paucinervia	250	99,75 ± 21,10 *	134,4 ± 18,92 *	61 ± 5,93 **NS**
A.paucinervia	500	47 ± 25,31 ***	190,75 ± 25,91 **	134,25 ± 28,11**NS**
(a): in ml/kg. Values are means ± SEM, with n=4, *p<0.05; **p<0.01; *** p < 0.001 significant difference from and NS: non-significant difference from negative control.				

3.7. Evaluation of the sedative effect of the aqueous extract of *Ascotheca paucinervia* leaves in mice

3.7.1. Evaluation of the effect of the aqueous extract of *Ascotheca paucinervia* leaves on locomotor activity in mice

Table 3 shows the effects of aqueous extract of *Ascotheca paucinervia* leaves at doses of 250 and 500 mg/kg on locomotor activity. This shows that in comparison with distilled water, the aqueous extract of leaves of *Ascotheca paucinervia* significantly reduces the number of squares crossed at doses of 250 and 500 mg/kg and the effects are more pronounced at a dose of 500mg/kg. Diazepam 10 mg/kg used as a reference molecule caused a reduction in the number of squares crossed greater than that caused by the aqueous extract of *Ascotheca paucinervia* leaves at doses of 250 and 500 mg/kg of body weight.

Table 3. Effect of aqueous extract of *A. paucinervia* leaves on locomotor activity.

Products	Doses (mg/kg)	Number of squares crossed (5 min)
Distilled water	0,5 (a)	119,40 ± 9,38
Diazépam	10	23,66 ± 3,17 ***
Ascotheca paucineria	250	80 ± 11,23 *
	500	37,66 ± 1,76 **
(a): in ml/kg. Values are means ± SEM, with n=5, *p<0.05; **p<0.01; *** p < 0.001 significant difference from.		

3.8. Effect of aqueous extract of *Ascotheca paucinervia* leaves on barbiturate sleep in mice

Table 4 shows the effects of aqueous extract of *Ascotheca paucinervia* leaves at doses of 250 and 500 mg/kg on barbiturate sleep. Compared to distilled water; at a dose of 250 mg/kg of the aqueous extract, significantly decreases and increases respectively the time to onset and the duration of sleep. At a dose of 500 mg/kg of the aqueous extract, significantly decreases and increases respectively the time to onset and the duration of sleep. Diazepam 5 mg/kg, used as a reference molecule, produced a more significant effect than that produced by the extract of *Ascotheca paucinervia* leaves.

Table 4. Effects of aqueous extract of *A. paucinervia* leaves on barbiturate sleep

Products	Dosage (mg/kg)	Time to onset sleep time (min)	Duration of sleep (mins)
Distilled water + Ph (b)	0,5 (a)	38,33 ± 5,20	416,6 ± 22,82
Diazepam + Ph (b)	5	9,66 ± 0,31 ***	1360,2 ± 35,81 ***
A.paucineria + Ph (b)	250	18,66 ± 2,96 *	552,8 ± 14,04**
A.paucineria + Ph (b)	500	14,66 ± 1,20 *	501,4 ± 11,30*

4. DISCUSSION

This present study made it possible to evaluate the anticonvulsant and antidepressant effects of the aqueous extract of *Ascotheca paucinervia* leaves at the two doses of 250 and 500 mg/kg of body weight in mice. In order to establish the safety of the aqueous extract of *Ascotheca paucinervia* leaves, the estimation of acute oral toxicity was carried out in accordance with OECD guideline No. 425 (OECD, 2022). According to the latter, the level of overt toxicity is reached when at least one animal shows one of the following signs (from the day following the treatment): tremors, lethargy, irregular breathing or weight loss greater than 10% compared to the weight before treatment. However, the analyses of parameters highlighted to evaluate the acute toxicity of this extract at 5000 mg/kg in comparison with those of distilled water at 0.5ml/100g are globally identical during the four (04) hours of observation. Thus, this would suggest that the lethal dose 50 (LD50) of this extract would be greater than 5000 mg/kg because, no case of death was recorded within 48 hours as well as in the continuation of the observation (14 days) and according to the Globally Harmonized Classification System the latter could be classified in category 5 of LD50 between 2000 and 5000mg/Kg (OECD, 2022). In addition, it noticed a little later (from 4 a.m.) some changes, in particular the reduction in mobility, the reduction in alertness, the appearance of very light sleep. These results could probably be attributed to the sedative or hypnotic effects of this extract. In addition, the analysis of weight change shows a significant increase in the weight of animals in the treated group. In relation to the quantities of food and water consumed, this weight increase suggests that this extract would have virtues on digestion particularly, it would be an appetite stimulant (Ken, 2016). Our results are similar to those obtained by WOSSOLO et al. (2018) who worked on the aqueous extract of Cymbopogon densiflorus (Steud.). The anticonvulsant activity of the extract was studied using strychnine as a convulsinogenic agent, this substance produces spinal convulsions. The injection of strychnine into the animals first induces hyperexcitability, an increase in reflexes and then convulsions. Indeed, at doses of 250 and 500 mg/kg, the aqueous extract of the leaves of *Ascotheca paucinervia* increases respectively in a non-significant and very significant way ($p<0.001$) the time to onset of convulsions induced by strychnine and the significance of the extract at a dose of 500 mg/kg would appear to be equal to that of diazepam (Parampeep et al., 2014). Likewise, terpenoids have been shown to activate the enzyme glutamic decarboxylase, confirming the potential of terpenoids for the treatment of epileptic seizures (Mnayi et al., 2016). Concerning the duration of the convulsions, at doses of 250 mg/kg and 500 mg/kg the aqueous extract of the leaves of Ascotheca paucinervia insignificantly decreases the duration of the convulsions induced by strychnine. The inability of the aqueous leaf extract of *Ascotheca paucinervia* to significantly decrease the duration of strychnine-induced seizures suggests that the extract possesses a lower affinity than strychnine for glycine-mediated inhibitory neurotransmission receptors. These results differ from those obtained by Bassoueka et al., 2016 who worked on the anticonvulsant effect of the aqueous extract of the leaves of *Crossopterys febrifuga*. The forced swimming test (FST) was proposed by Porsolt et al. (1977). Thus, at doses of 250 and 500 mg/kg, the aqueous extract of the leaves of *Ascotheca paucinervia* leaves reduces respectively highly ($p<0.01$) and very highly significantly ($p<0.001$) the immobility time in mice. At a dose of 500 mg/kg, the effect of Ascotheca paucinervia leaf extract appears to be slightly greater than that of clomipramine, a molecule scientifically recognized as an antidepressant. In addition, the non-significant increase in swimming time and highly significant increase in climbing time of the treated batch suggests that the extract would act by using serotonergic and noradrenergic receptors (Cryan et al., 2010; Bandaruk et al., 2012; Gong et al, 2014). Effects could be attributed to tannins which are present since, tannic acid has been shown in many published papers to be a non-selective MAO inhibitor, which increases levels of monoaminergic neurotransmitters (Shankar et al, 2010 and Chandra et al. al., 2012; Mahendran et al., 2014 and Khalladi et al., 2016). It should be noted that the effects

are more accentuated at the higher dose, which would suggest that the effects could be dose-dependent. Results obtained are in agreement with those obtained by Nkundineza et al (2020) who worked on the aqueous extract of *cassia alata*.

5. Conclusion

In short, the aqueous extract of the leaves of *Ascotheca paucinervia* is weakly toxic up to 5000 mg/kg in a single dose and LD50 > 5000 mg/kg. It significantly increases the time to onset of seizures and non-significantly decreases the duration of seizures in mice. It very significantly reduces immobility time and increases swimming and climbing times in a non-significant and very significant way, respectively, in mice. The dose-dependently reduces the mobility of mice, and significantly decreases and increases respectively the time to onset and the duration of sleep;

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