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(RESEARCH ARTICLE)

Anxiolytic and antipyretic effects of the aqueous extract of the leaves of *Solanum aethiopicum* (Solanaceae) in the white mouse *Mus musculus* Swiss (Muridae)

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Abstract

The anxiolytic and antipyretic effects of the aqueous extract of the leaves of *Solanum aethiopicum* (plant used in traditional medicine in Africa) were evaluated by oral administration of doses 17.5; 43.75; 87.5 and 175 mg/kg to mice of the *Mus musculus* Swiss strain. Four psychopharmacological tests were performed: the stress-induced hyperthermia test; the elevated plus maze test; the open arena test and the hole board test. A significant decrease in stress-induced hyperthermia was observed in mice receiving the 175 mg/kg dose (1°C) unlike those treated with distilled water (3°C). The 175 mg/kg dose of *S. aethiopicum* extract and diazepam significantly increase the number of entries and the percentage of time spent in the open arms of the maze. Diazepam and doses of *S. aethiopicum* significantly decrease the number of uprights and the number of head tilts. *Solanum aethiopicum* significantly increases the number of lines crossed and the time spent in the center of the open arena. On the hole board, there was a significant increase in the number of head tilts (11.2±1,64) in the mice that received the 175 mg/kg dose of *S. aethiopicum* and in the number of lines crossed in the mice treated with all doses of the extract. This shows that the extract of *S. aethiopicum* would contain compounds with antipyretic and anxiolytic properties.

Keywords: *Solanum aethiopicum*; Aqueous extract; Raised plus maze; Open arena; Hole board; Anxiolytic

1. Introduction

Mental health disorders constitute one of the threats to public health as well as the lives of populations and the stability of a country [11]. The consequences of such disorders represent a significant health and social burden, including in terms of discrimination, marginalization, social cohesion and impact on the economy [11]. One of these disorders, anxiety, affects 18% of the total population worldwide and mainly affects the population group aged 18 and over [2, 12]. Therefore, anxiety disorders represent the category of the most prevalent mental disorders in the population [11].

Different medications are used to treat anxiety disorders, including antidepressants and anxiolytics such as benzodiazepines. Nevertheless, the use of benzodiazepines in the treatment of anxiety disorders is problematic due to the onset of habituation, tolerance and dependence, both physical and psychological, and a withdrawal syndrome upon cessation. consumption with the risk of the appearance of a rebound phenomenon. Plants are increasingly being tested. In Africa, herbal medicine plays an important role in the treatment of various diseases, especially among the low-income

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population [9]. because imported drugs are beyond the reach of a large majority of populations. because of their very high costs [18].

Studies have revealed that alkaloid-rich plants such as Solanaceae, Apocynaceae and Rubiaceae are used to treat states of anxiety and mental disturbances [17] in the city of Douala in Cameroon. However, there are very few data on the pharmacological effects of *S. aethiopicum* leaves on diseases of the central nervous system, particularly anxiety disorders. The purpose of this study was to verify the hypothesis that *S. aethiopicum* possesses anxiolytic and antipyretic properties in order to justify its use in traditional medicine in Cameroon. These properties were evaluated using different tests.

2. Material and methods

2.1. Plant material

The leaves of *S. aethiopicum* were harvested in Ngaoundere, a locality located in the Adamaoua region (Cameroon). *S. aethiopicum* was identified at the National Herbarium of Yaoundé (Cameroon) by comparison with a sample under the number N43013/HN.

2.2. Animal material

White mice, *Mus musculus* swiss, of both sexes weighing between 18 and 30 g, provided by the National Veterinary Laboratory (LANAVET) of Garoua (North – Cameroon) were acclimatized for five days in the laboratory of medicinal plants, health and galenic formulation of the University of Ngaoundere before the start of each experiment. They had free access to food and drinking water. They were divided into 6 groups including a negative control group receiving distilled water, a positive control group receiving diazepam or phenobarbital depending on the tests and 4 groups receiving doses of the extract.

2.3. Chemical substances

Diazepam sold in 10 mg/2 ml ampoule under the trade name Valium® (La Roche Laboratory) and phenobarbital in 100 mg/ml ampoule under the name Gardénal® (Novartis Laboratory) were used.

2.4. Methods

2.4.1. Preparation of the decoction

5 g of dry powder from the leaves of *S. aethiopicum* were introduced into a beaker containing 50 ml of distilled water. The whole was boiled for 20 minutes on a hot plate set at 100°C. After cooling, the mixture was filtered using Wattman number 1 paper. The filtrate obtained (stock solution) was diluted with distilled water by 1/2, 1/4 and 1/10 and administered to mice in a volume of 10 ml/kg.

2.5. Pharmacological tests

2.5.1. Phytochemical screening

Preliminary tests of phytochemical characterization of the extract of *S. aethiopicum* were carried out by qualitative colorimetric methods [19], for the determination of the main chemical groups involved in the treatment of diseases of the central nervous system.

2.6. Stress-induced hyperthermia test

The Hugo Sachs model H11 thermometer was used to measure the rectal temperature of animals.

The method used is that described by [20]. The animals were marked and evenly divided into six groups of ten animals each. The animals were treated with distilled water (negative control batch) and Phenobarbital (20 mg/kg) intraperitoneally, thus constituting the positive control. The other groups were treated with doses of the extract (test batches). Within the same group, the time separating the treatments from one mouse to another was one minute. One hour later, the mice were consecutively removed from the cages at one-minute intervals and their body temperature was measured through the anal orifice at the rectum. Before each temperature measurement, the probe was immersed in a 9‰ concentrated sodium chloride solution. This experiment was based on the fact that among animals in the same cage, mice removed later had a higher temperature than those removed earlier [6]. Stress-induced hyperthermia is

defined as the difference between the average temperature of the last three mice and the average temperature of the first three mice [7].

2.7. Elevated Plus Maze Test

The elevated plus maze test was performed according to the method described by [21]. It is a device made up of two open arms (35 cm x 5 cm) and two closed arms (35 x 5 x 15 cm) and a central platform (5 x 5 cm). The device is usually raised one meter above the ground (Ngo Bum et al., 2009). The one we used to have a height of 70 cm. The animals were divided into six groups of five animals each. The first batch had received distilled water, the second batch had received Diazepam (3 mg/kg) and the other four batches received the doses of the decoction. One hour after the treatment, the mice were individually placed in the device in the center of the platform, starting point for the exploration of the open arms and the closed arms. After five minutes of observation, the mouse was returned to its original cage and the experimental device was cleaned with ethyl alcohol (70°C). The number of entries and exit of each animal in the closed arms and in the open arms as well as the time taken were recorded and considered as the conventional parameters of the experiment. The number of straightening, head tilting, grooming was recorded.

2.8. Open Arena Test

The open arena used to measure animal locomotion is a lighted open space, made of wood, consisting of four sides of 45 cm × 45 cm with a height of 30 centimeters. The platform is divided into 16 small squares of equal dimensions (15 cm × 15 cm) [3]. For the experiment, thirty mice were divided into six groups. Two control batches including the positive control which had received Diazepam at a dose of 0.3 mg/kg intraperitoneal [8] and the negative control which had received distilled water by gavage as well that, four lots corresponding to the doses of the extract administered by gavage. One hour after the treatment, the mice were placed one by one in the device for a five-minute observation per mouse. Parameters such as the time spent in the center, the number of straightening, the number of lines crossed and the number of grooming were evaluated.

2.9. Hole board test

The hole board test was performed according to the method described by [15]. The perforated board is a device consisting of a floor with a surface area of 40 cm2 and a wall 1.8 cm high. The floor being dotted with 16 holes of 3 cm in diameter each. Four feet 25 cm high from the ground served as support for the device. The six groups of five animals were treated as follows: distilled water for the negative control, Diazepam (0.5 mg/kg) for the positive control and doses of the extract for the other four batches. One hour after the treatment, the mice were individually placed in the center of the platform, the starting point of the perforated board. The observation was made for five minutes. The following parameters were recorded: the number of head tilts, the number of lines crossed, the number of groomings, the latency of the first head tilt.

2.10. Statistical analysis of data

Data were compared using the analysis of variance test (ANOVA) and Tukey's multiple comparison test (HSD). From $p \leq 0.05$, the values were considered significant. Statistical analyzes of the results were performed using Graphpad Prism 8.0.

3. Results

3.1. Phytochemical screening

The phytochemical characterization test of the extract from the leaves of *S. aethiopicum* revealed the presence of alkaloids, flavonoids, sterols, terpenes and tannins.

Anxiolytic activity of *Solanum aethiopicum*

3.2. Antipyretic activity

The doses of the extract and phenobarbital had resulted in a significant decrease in stress-induced hyperthermia compared to distilled water (3°C). These values were 1.8±0,47; 1.8±0,49; 1±0,54 and 0.9± 0,42°C respectively for the 43.75; 87.5; 175 mg/kg doses and phenobarbital (Figure 1).

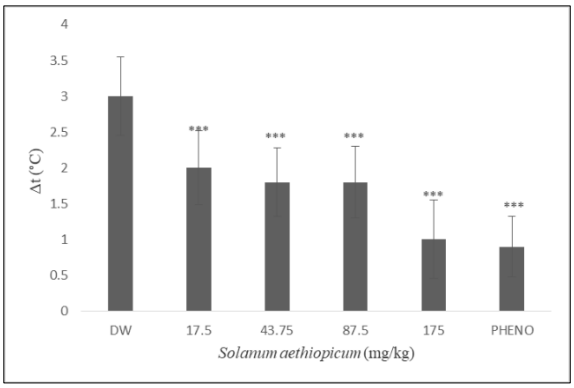

Figure 1 Anti hyperthermia effect of *Solanum aethiopicum*

Each bar represents the mean ± the standard deviation. n=number of mice (5), ***P ≤ 0,001 significant difference from negative control. DW= negative control made up of mice having received distilled water, DZP= positive control made up of mice having received phenobarbital

3.3. Locomotor activity

3.3.1. Effect of Solanum aethiopicum on mouse exploration in the elevated plus-maze

The extract had significantly increased parameters such as the number of entries into the open arms from 0.2 ±0,44 in the negative control group to 3.4±1,67 in the mice having received the 175 mg/kg dose of the aqueous extract (A) this value was 3.6±1,51 in mice given diazepam; the percentage of the number of entries into the open arms of 4.34% in the negative control batch and 72.27% in the batch that received the 175 mg/kg dose of the extract; the percentage of time spent in the open arms was 39.8% in the mice of the negative control batch while it was 90.53%, 90.6%, 89.93%, 89.66% respectively in the mice having received doses of 175, 87.5, 43.75 and 17.5 mg/kg of the extract. The percentages of the number of entries and the time spent in the closed arms were respectively 95.65% and 66.6% for the negative control group, 22.72% and 6.6% for the 175 mg/kg dose; these values were 21.73% and 6.66% in the mice having received diazepam (3 mg/kg). The number of straightening and tilting of the head were significantly reduced by diazepam and the doses of the decoction (B) and (C) while the number of grooming was increased (D) (Figure 2).

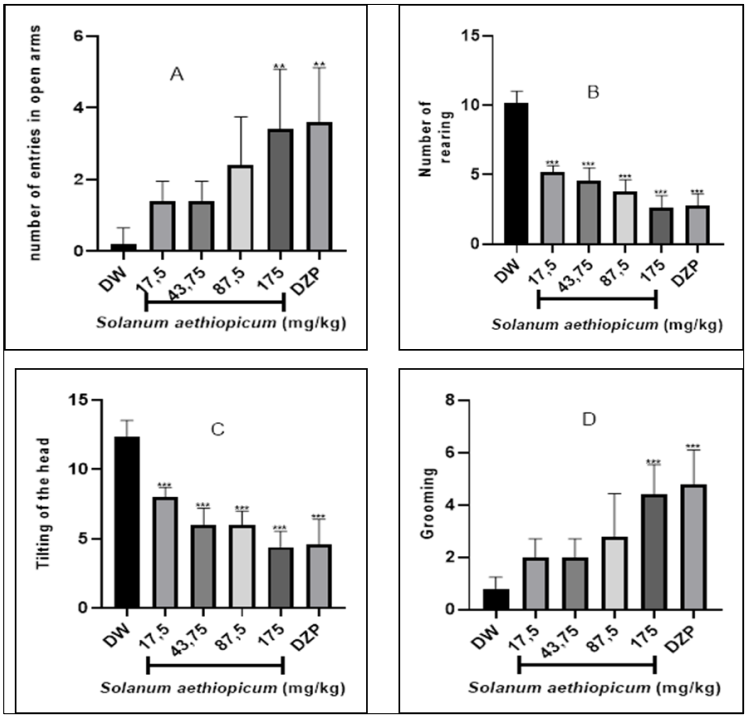

Figure 2 Effects of *Solanum aethiopicum* on open arm entry count (A), rearing count (B), head tilt count (C), and grooming count (D).

Each bar represents the mean ± the standard deviation. n=number of mice (5), **P ≤ 0,01, ***P ≤ 0,001 significant difference from negative control. DW= negative control made up of mice having received distilled water, DZP= positive control made up of mice having received diazepam

3.4. Effect of *Solanum aethiopicum* on habituation of mice in the open arena

Diazepam and extract significantly increased the number of grooming, lines crossed and time spent in the center in mice given the extract doses (A), (B) and (C) while, the number righting was significantly reduced in mice from the same batches (D). (Figure 3).

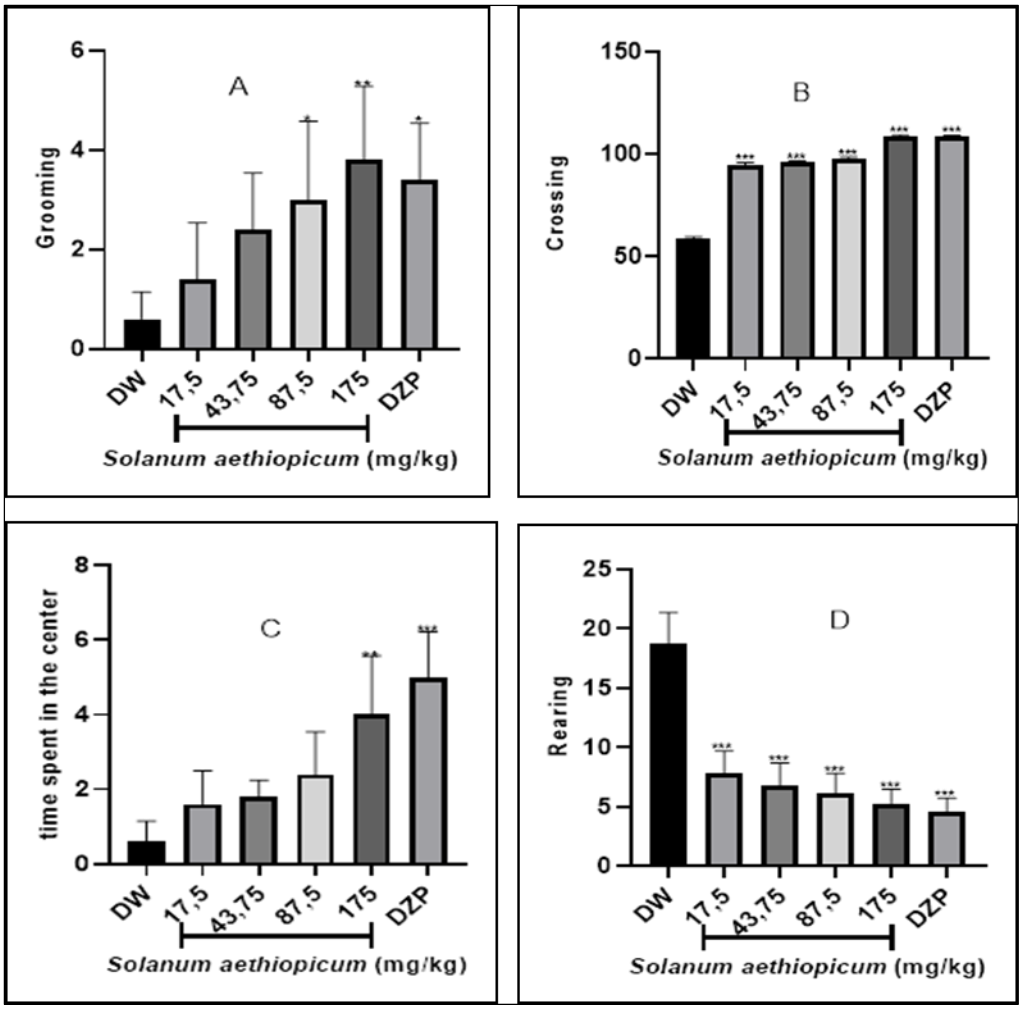

Figure 3 Effects of *Solanum aethiopicum* on number of grooming (A), number of lines crossed (B), time spent in the center (C) and number of rearing (D).

Each bar represents the mean ± the standard deviation. n=number of mice (5), **P ≤ 0,01, ***P ≤ 0,001 significant difference from negative control. DW= negative control made up of mice having received distilled water, DZP= positive control made up of mice having received diazepam

3.5. Effects of *Solanum aethiopicum* on the coordination of mice on the hole board

The number of lines crossed was 22±1.41 in the mice having received distilled water (DW) while it was 69.4±1.14 in those having received the 175 mg/kg dose of the extract, this value was 69.8±1.30 in the batch having received diazepam (figure 10). The latency time before the first tilt of the head was 13.4±2.07 in the negative control batch while it was 4.6±1.14 in the mice having received the 175 mg/kg dose of the extract. On the contrary, the number of head tilts had increased significantly in mice having received the 175 mg/kg dose of the extract (11.2±1.64) as well as diazepam (12.2±1.92) compared to the negative control group. (figure 4). The number of grooming also increased significantly in mice that received the doses of the extract and diazepam (Figure 4).

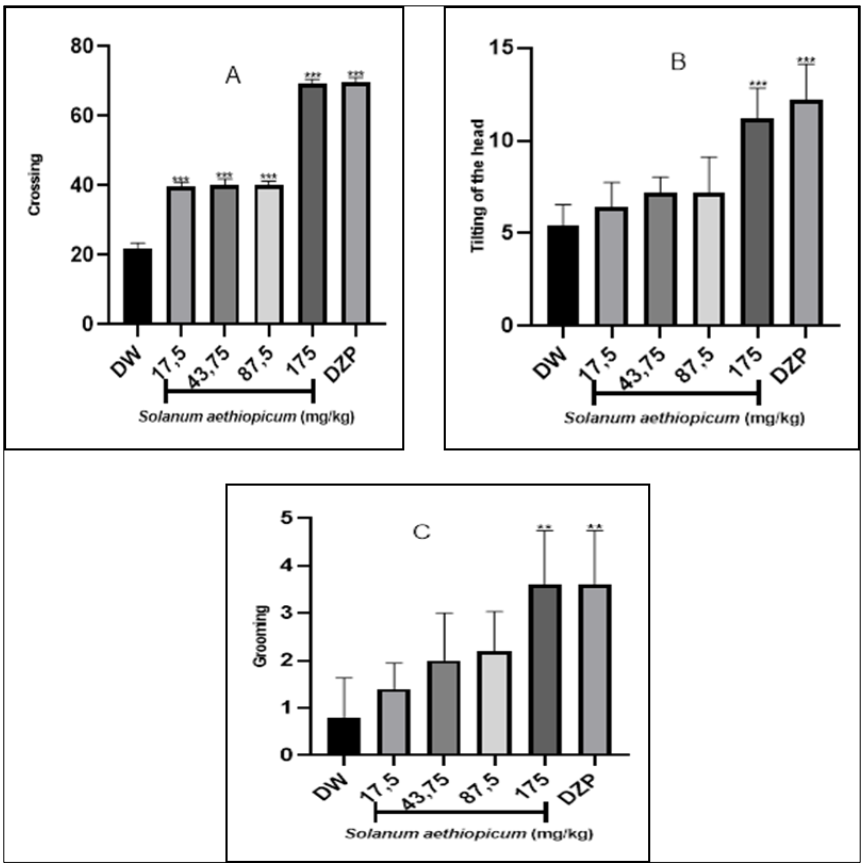

Figure 4 Effects of *Solanum aethiopicum* on number of lines crossed (A), number of head tilts (B), and number of grooms (C).

Each bar represents the mean ± the standard deviation. n=number of mice (5), **P ≤ 0,01, ***P ≤ 0,001 significant difference from negative control. DW= negative control made up of mice having received distilled water, DZP= positive control made up of mice having received diazepam

4. Discussion

Solanum aethiopicum extract appears to significantly reduce the average rectal temperature of mice by reducing the production of prostaglandins in the hypothalamus, the body temperature thermostat. If therefore we must admit that drugs that lower body temperature are antipyretics, the extract of *S. aethiopicum* would have antipyretic properties, that is to say that it inhibits the synthesis of prostaglandins E14 and E2 which act on the hypothalamus and are thought to be involved in raising body temperature. These properties could be explained by the presence of alkaloids and terpenes [4, 10]. Similar results were obtained by [14] with the leaves of *Piliostigma reticulatum* and [8] with the leaves of *Mimosa pudica*, *Afrormosia laxiflara*, *Microglossa pyrifolia* and the bark of *Chenopodium ambrosioides*. *S. aethiopicum* extract would reduce stress-induced hyperthermia. Given that stress-induced hyperthermia is antagonized by anxiolytics [5], the extract of *S. aethiopicum* would possess anxiolytic properties.

S. aethiopicum extract significantly increases the number of entries and the percentage of time spent in the open arms and decreases the number of entries and the percentage of time spent in the closed arms of the maze. According to [12], the increase in the number of entries and the percentage of time spent in open arms and the decrease in the number of entries and the percentage of time spent in closed arms indicate the increase in exploration and the decrease in the animal's aversion to the open arms of the labyrinth. These results suggest the presence of anxiolytic properties [12,14]. Anxiolytics exert an inhibitory action on GABA which is the main inhibitory neurotransmitter (soothing action on the brain) of the brain. The extract of the leaves of *S. aethiopicum* has a strong presence of alkaloids which are according to [17] anxiolytic compounds. It was also found that *S. aethiopicum* extract significantly reduced the frequency of righting in the closed arms of the elevated plus-maze. The number of head tilts decreased significantly in mice dosed with *S. aethiopicum*. These results support the observations of [1] that a reduction in the frequency of raising and tilting the head in the closed arms and open arms of the elevated plus-maze, respectively, indicates a decrease in anxiety in

children. rodents. Thus, the results suggest that the extract of *S. aethiopicum* would possess anxiolytic properties which are explained by the presence of alkaloids and terpenes.

Rodents tend to avoid lighted and open spaces. Data obtained during the open arena test showed a significant increase in the number of rightings in mice treated with *S. aethiopicum* extract. The extract significantly increases the time spent in the center in the open arena. Since the increase in the number of rearings and the time spent in the center in the open arena indicates the increase in the locomotor activity and the level of exploration in rodents this shows a reduction in anxiety [1, 14]. Exploration behavior and locomotor activity of mice evidenced by the use of the pegboard showed a significant increase in the number of lines crossed and head tilt in mice treated with the extract of *S. aethiopicum* and Diazepam. The increase in locomotor and exploration activity in rodents treated with Diazepam is an intrinsic manifestation of the reduction in anxiety [1, 6]. Since an increase in the number of head tilts and the number of lines crossed in the hole board test is indicative of anxiolysis [22], the extract of *S. aethiopicum* would possess anxiolytic properties; properties that would be mediated by GABAergic neurotransmission in the cerebral cortex and hippocampus [23]. The reduction in the latency of the first tilt of the head indicates a decrease in anxiety in mice [1].

5. Conclusion

The anxiolytic and antipyretic effects of *Solanum aethiopicum* were evaluated in white mice. It appears that the extract significantly inhibits the increase in body temperature suggesting that it would have antipyretic properties. On the one hand, the extract of *S. aethiopicum* significantly increases the number of entries and the time spent in the open arms of the maze and on the other hand, it significantly decreases the number of entries, the percentage of time spent and the frequency of righting in the closed arms of the maze. It has been noted that the *S. aethiopicum* extract significantly increases the number of lines crossed and the time spent in the center while the frequency of rectification is reduced significantly. All of these observations suggest that *S. aethiopicum* may have anxiolytic properties. The 175 mg/kg dose of the extract is the most effective.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interests.

Statement of ethical approval

The experiment was carried out at the Laboratory of Medicinal plants, Health and Galenic formulation, Faculty of Sciences, University of Ngaoundere in accordance with approval by the National Ethics Committee of Cameroon (Ref. No. FW-IRB00001954).

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