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Anxiolytic-like effects of the decoction of *Psorospermum febrifugum* in mice

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ABSTRACT

In Cameroon, leaves of *Psorospermum febrifugum* Spach (Hypericaceae) (*P. febrifugum*) are used in traditional medicine to treat anxiety, agitation and fever. Stress induced hyperthermia, elevated plus maze, open field and hole board tests were used to evaluate the anxiolytic properties of the plant in mice. The doses of the decoction used were 25, 50, 100 and 200 mg/kg. The decoction of *P. febrifugum* showed antipyretic properties by reducing in a dose dependent manner the body temperature that changed from 36.70 ± 0.62°C to 32.82 ± 1.26°C at the dose of 200 mg/kg. The decoction of *P. febrifugum* showed also anxiolytic activities in the four tests. In the hole board, *P. febrifugum* decreased the latency of the first head dip and increased the number of head dips. In the elevated plus maze, *P. febrifugum* increased the number of entries into open arms, the percentage of entries and time into open arms and reduced rearing, head dipping and the percentage of entries and time into closed arms. In the open field, *P. febrifugum* like diazepam produced an increase in crossing, grooming and in time spent in the center and reduced the number of rearing. In stress-induced hyperthermia test, *P. febrifugum* antagonised dose dependently the increase of temperature. ΔT° decrease from 1.87°C in the control group to 0.70°C at the dose of 200 mg/kg. This finding could justify the use of *P. febrifugum* in traditional medicine in Cameroon in treatment of anxiety and fever.

INTRODUCTION

According to WHO 2001 [1], approximately 450 million people suffer from a mental or behavioral disorder; and only a small minority of them receive the most basic treatment. Anxiety is among the most common psychiatric disorders [2-3]. Its estimated prevalence is high [4-5]. Approximately two-thirds of the anxious patients respond to currently available treatments, but the magnitude of improvement is still disappointing [6], therefore the need for better-tolerated and more efficient treatments is remaining high. It is becoming very useful considering and looking for alternative and low cost effective herbal therapy, especially in low income countries, where the majority of the population relies on herbs remedies [7]. The broad use of medicinal plants is often attributable to its efficiency, accessibility and affordability. Moreover, Traditional medicine is sometimes the only affordable source of health care in developing countries. Thus, *Psorospermum febrifugum* Spach, like *Acanthus montanus*, *Bridelia micrantha*, *Croton macrostachyus, Cyperus articulatus, Microglossa pyrifolia, Mimosa pudica, Nauclea latifolia* and *Piliostigma reticulatum* is one of the medicinal plants used in the treatment of brain diseases in Cameroon [8-13]. *P. febrifugum* grows in Savannah areas and tropical West Africa [14]. Earlier pharmacological studies have shown that *P. febrifugum* posses anticonvulsant, antimicrobial and sedative properties [15-16]. Chemical studies revealed the presence of xanthones in *P. febrifugum* [17-18]. Very few pharmacological studies are done with this plant. In addition there is no scientific evidence about the anxiolytic effects of *P. febrifugum*. The present work is aimed to assess the effect of *P. febrifugum* on anxiety using mice models.

MATERIALS AND METHOD

Plant material

Leaves of *P. febrifugum* were collected in rainy season (October 2010), from Ngaoundere-Dang locality, Cameroon. A Voucher specimen was deposited at the National Herbarium of Cameroon in Yaoundé and identify under the number 74108/SRF/CAM.

Preparation of decoction

The preparation of the decoction was done according to the traditional Healers. Fresh leaves were dried in the shade and ground. 10 grams of leaves powder were macerated in 35 ml of distilled water for 1 h. The mixture was boiled for 20 min. After cooling, the supernatant was collected and filtered with Whatman N° 1 filter paper. 24 ml of the decoction were obtained. Part of the decoction was diluted to less concentrated solution by adding distilled water. The initial decoction and the diluted solution were then ready to be used. In another experiment, after filtration, the decoction was evaporated in a drying oven at 45°C and 480 mg of a dark brown solid was obtained. The yield of the extraction was 4.8 %. The decoction was administered orally (p.o.) 1 h before pharmacological tests in a volume of 10 ml/kg of mice body weight. The following doses were used: 25, 50, 100 and 200 mg/kg.

Animals

Adult *Mus musculus* Swiss mice (20-25 g) were obtained from the Veterinary National Laboratory of Garoua (Cameroon). They were housed ten animals per cage at a room temperature of 25°C in a 12h light/12h dark cycle. Food and water were available ad libitum. For experiments, animals were randomly assigned to control or treatment groups. The study was done in accordance with the national (reg. N° FWA-IRB00001954) and international (EEC, 1987; USNRC, 1996) ethical committee guidelines for the care and used of laboratory animals. All efforts were made to minimize both the suffering and number of animals used.

Chemicals

Diazepam (Valium®, Roche, France) and phenobarbital (Sigma Chemical, USA). Chemicals were diluted in distilled water and were administered in a volume of 10 ml/kg of mice body weight.

Phytochemical screening

Preliminary phytochemical screening of the decoction of the leaves of *P. febrifugum* was done using methods already described for the determination of flavonoids, alkaloids, saponins, tannins, anthraquinons, polyphenols [19].

Pharmacological tests

Stress-induced hyperthermia (SIH) test

Animals were marked and housed 10 per cage. Naïve mice were removed from the cage one after the other in a precise order and treated with NaCl 0.9% (negative control group), phenobarbital 20 mg/kg ip (positive control group), or one of the four doses of the decoction of *P. febrifugum* (test groups). All animals within a given cage were consecutively treated at 1-minute intervals. After 60 minutes, mice were again consecutively removed from the cage (1-minute intervals) and their body (rectal) temperature was recorded. This experiment is based on the fact that among animals in the same cage, mice removed later have a higher body temperature than those removed earlier [11, 20-21]. Stress-induced hyperthermia (SIH) was defined as the difference between the mean temperature of the first three mice and the mean temperature of the last three mice.

Open field (OF) test

The OF used was a wooden square box 40 x 40 x 45 cm; the floor was divided into 16 smaller squares of equal dimensions (10 x 10 cm). One hour after appropriate treatment, naive mice were placed in the center of the OF and were observed for 5 minutes to evaluate the effects of the plant on both exploratory activity and anxiety [22-24]. Hand-operated counters and stopwatches were used to score crossing (number of square floor units entered), rearing (number of times the animal stood on its hind legs), grooming, and defecation. The positive control group received diazepam 0.3 mg/kg.

Hole-board (HB) test

The HB apparatus consisted of a gray wooden box (40 x 40 cm, 2.2 cm thick) with 16 equidistant holes of 3 cm in diameter. Mice were treated 1 h prior to testing with NaCl 0.9% (10 ml/kg, p.o.) for the negative control group, *P. febrifugum* decoction for the four test groups and Diazepam (0.5 mg/kg, i.p.) for the positive control group. Each animal was placed singly in the center of the board facing away from the observer and its behavior was recorded for 5 min. The behavior recorded was: the number of head-dips and rearing, the number of crossing (the number of squares crossed with all four paws) and the latency to the first head-dip using stopwatches [25-27].

Elevated plus maze (EPM) test

This apparatus comprised two open arms (16 x 5 cm) and two closed arms (16 cm x 5 cm x 10 cm) that extended from a common central platform (5 x 5 cm). The entire maze was elevated to a height of 50 cm above floor level. The negative control group received distilled water, the positive control group received diazepam (3 mg/kg), and the four test groups received four different doses of *P. febrifugum*. One hour after treatment, mice were individually placed on the EPM center platform facing an open arm and observed for 5 minutes [11, 28-30]. The number of entries into open or closed arms, the time spent in open or closed arms, rearing and head dipping were recorded with stopwatches.

Statistical analysis

Data expressed as mean ± SEM were analyzed with ANOVA two-way, followed by Tukey (HSD) as the post-hoc test. Some other data expressed as percentage were analyzed using the Fischer exact test, two tails. Data of negative control groups were compared to data of positive control groups and groups that were treated with the decoction. The differences were considered significant from $p<0.05$. The statistical package used for the analysis was XLSTAT 2007.

Results

Phytochemical characterization

The decoction of *P. febrifugum* contains alkaloids, flavonoids, saponins, tannins, anthraquinons and polyphenols.

Anxiolytic-like effects of *P. febrifugum* on the HB test

P. febrifugum and diazepam treated mice showed a strong decrease in the latency time of first head dipping, from 153.7 ± 23.0 s in the control group to 48.5 ± 6.1 s at the dose of 200 mg/kg [$F(6,29) = 24$; $p < 0.001$]. *P. febrifugum* like diazepam also significantly increased the number of head dips from 17.2 ± 1.2 in

Table 1: Effect of *P. febrifugum* in HB test: Latency to the first head dipping, Head dipping, Crossing, Rearing and Fecal boli

Treatments	Dose (mg/kg)	Latency to first head dipping (s)	Head dipping	Crossing	Rearing	Fecal boli (g)
NaCl	---	153.7 ± 23.0	17.2 ± 1.2	16.2 ± 5.4	29.2 ± 4.2	0.01 ± 0.02
P. febrifugum	25	72.3 ± 17.1^{c}	28.8 ± 18^{c}	20.2 ± 5.5	29. 2 ± 7.1	0.05 ± 0.02
P. febrifugum	50	69.0 ± 16.3^{c}	32.0 ± 4.0^{c}	11.2 ± 1.4	23.7 ± 3.9	0.05 ± 0.02
P. febrifugum	100	63.5 ± 24.0^{c}	35.2 ± 3.5^{c}	16.2 ± 1.2	21.8 ± 2.5	0.04 ± 0.01
P. febrifugum	200	48.5 ± 6.1^{c}	38.8 ± 5.5^{c}	17.8 ± 1.4	16.2 ± 1.8^{b}	0.02 ± 0.03
DIAZ	0.5	34.5 ± 7.1^{c}	48.0 ± 2.7^{c}	15.8 ± 1.9	14.0 ± 2.0^{b}	0.01 ± 0.01

Treatments were administered 1 hour before the test. DIAZ = diazepam 0.5 mg/kg, NaCl = NaCl (0.9%). Data are mean ± SEM, N = 5, bp<0.01, cp<0.001, compared to CON, ANOVA followed by Tukey (HSD).

Table 2: Effect of *P. febrifugum* in OF test: Rearing, Crossing, Grooming, Center time and quantity of Fecal boli

Treatments	Dose (mg/kg)	Rearing	Crossing	Grooming	Fecal boli (g)	Center time (s)
NaCl	----	23.0 ± 2.6	13.0 ± 0.7	10.3 ± 1.3	0.05 ± 0.02	37.5 ± 4.3
P. febrifugum	25	15.7 ± 3.0^{b}	17.5 ± 1.7^{c}	12.3 ± 15	0.02 ± 0.02	52.5 ± 11.7^{a}
P. febrifugum	50	14.2 ± 1.5^{c}	18.0 ± 2.0^{c}	18.0 ± 1.7^{c}	0.02 ± 0.01	61.2 ± 12.5^{b}
P. febrifugum	100	15.2 ± 3.2^{b}	18.0 ± 1.0^{c}	19.3 ± 1.5^{c}	0.01 ± 0.01^{a}	62.5 ± 7.8^{b}
P. febrifugum	200	10.3 ± 2.7^{c}	19.8 ± 0.5^{c}	18.8 ± 3.2^{c}	0.00 ± 0.00^{b}	79.0 ± 16.7^{c}
DIAZ	0.3	5.2 ± 0.9^{c}	20.8 ± 0.9^{c}	20.8 ± 3.5^{c}	0.00 ± 0.00^{b}	98.5 ± 21.5^{c}

Treatments were administered 1 hour before the test. DIAZ = diazepam 0.3 mg/kg, NaCl = NaCl (0.9%). Data are mean ± SEM, N = 5, ap<0.05, bp<0.01, cp<0.001, compared to CON, ANOVA followed by Tukey (HSD).

Table 3: Effect of *P. febrifugum* in EPM test: Closed arm entries, Total arms entries, Ratio OE/TE vs CE/TE, Rearing and Head dipping

Treatments	Dose (mg/kg)	Closed arm entries	Total arms entries	Ratio OE/TE vs CE/TE	Rearing	Head dipping
NaCl	---	6.7±1.0	8.3±1.4	25.0±0.4	14.3±0.9	5.5±0.8
P. febrifugum	25	3.0±1.0^{c}	5.0±1.3	66.7±0.3^{b}	9.3±1.2^{b}	4.7±1.4
P. febrifugum	50	2.9±0.6^{c}	6.2±1.0	113.8±0.7^{c}	7.3±0.8^{c}	2.5±1.7
P. febrifugum	100	2.2±0.9^{c}	6.5±1.7	195.4±0.8^{c}	7.2±0.6^{c}	4.2±0.9
P. febrifugum	200	2.0±1.7^{c}	8.3±2.8	315±0.6^{c}	5.8±0.8^{c}	3.8±2.2
DIAZ	3	1.5±0.7^{c}	11.3±1.9	653.3±1.7^{c}	3.5±0.5^{c}	3.7±1.1

Treatments were administered 1 hour before the test. DIAZ = diazepam 3 mg/kg, NaCl = NaCl (0.9%). Data are mean ± SEM, N = 5, ap<0.05, bp<0.01, cp<0.001, compared to CON, ANOVA followed by Tukey (HSD).

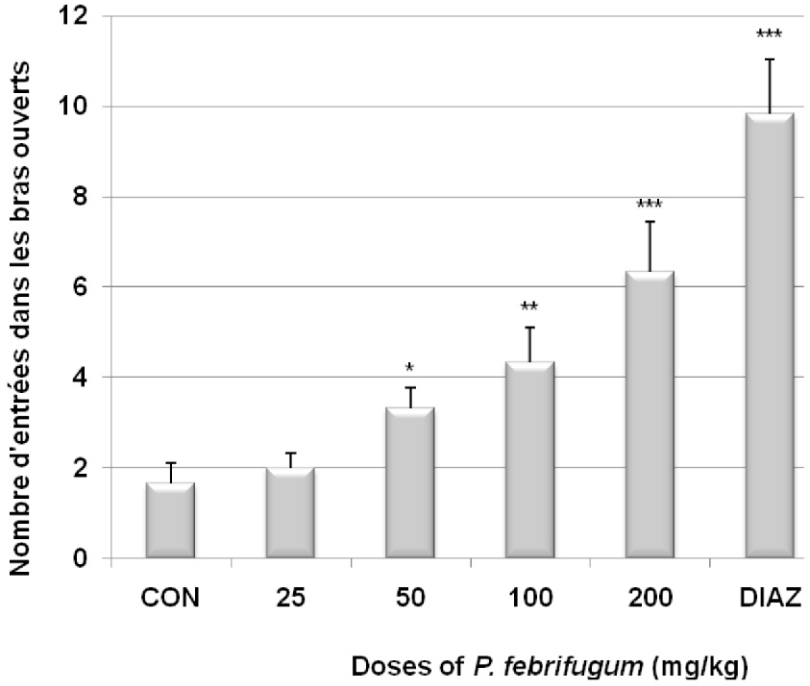

Figure 1: Effect of *P. febrifugum* on open arms entries.
The figure represents the number of open arms/session time (5min). Treatments were administered 1 hour before the test. CON = NaCl 0.9%, DIAZ = diazepam 3 mg/kg, N = 5 per dose, *p<0.05, **p<0.01, ***p<0.001, when compared to NaCl (ANOVA two-way, followed by Tukey (HSD)).

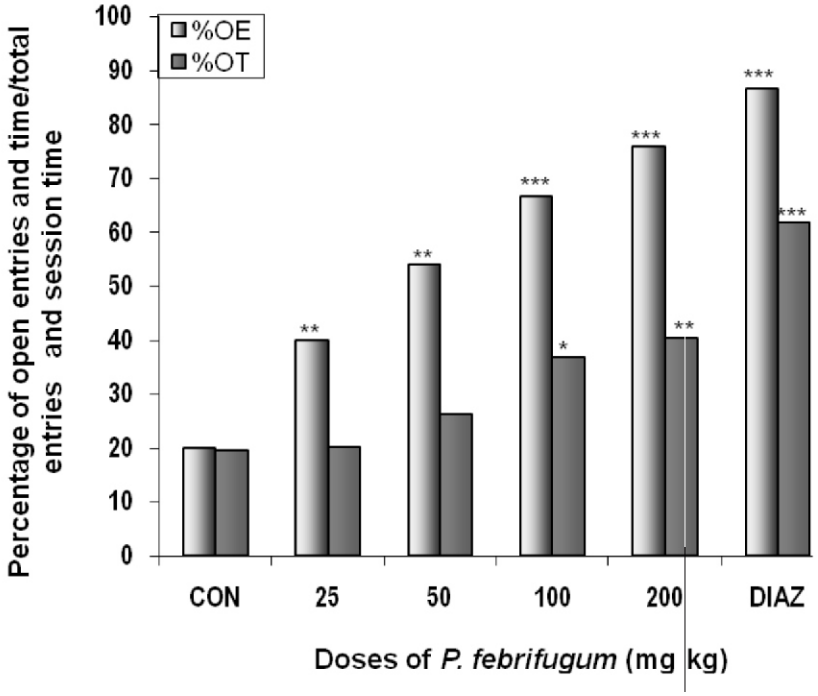

Figure 2: Effect of *P. febrifugum* on open arms entries and time in EPM.
The figure represents the percentage of open arms entries/total arms entries and the percentage of open arms time/session time (5min). Treatments were administered 1 hour before the test. CON = NaCl 0.9%, DIAZ = diazepam 3 mg/kg, N = 5 per dose, *p<0.05, **p<0.01, ***p<0.001, when compared to NaCl (Fischer exact test, two tails).

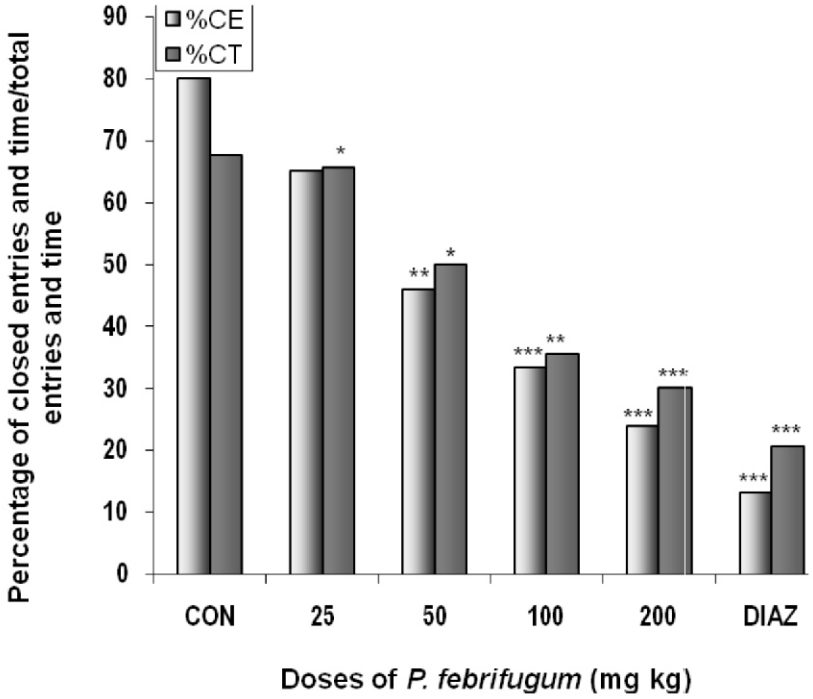

Figure 3: Effect of *P. febrifugum* on closed arms entries and time in EPM.
The figure represents the percentage of closed arms entries/total arms entries and the percentage of closed arms time/session time (5min). Treatments were administered 1 hour before the test. CON = NaCl 0.9%, DIAZ = diazepam 3 mg/kg, N = 5 per dose, *p<0.05, **p<0.01, ***p<0.001, when compared to NaCl (Fischer exact test, two tails).

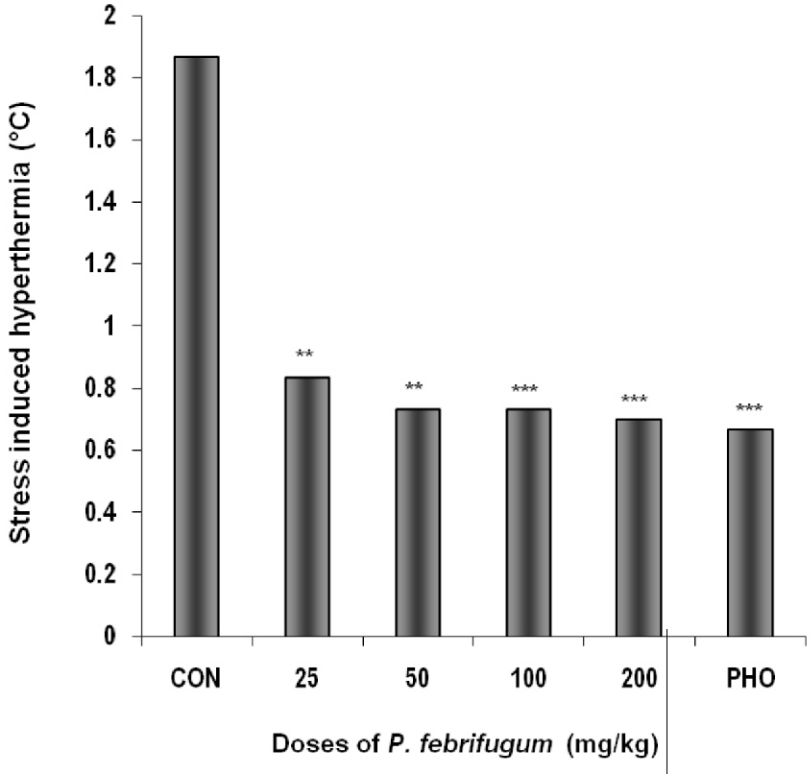

Figure 4: Effect of *P. febrifugum* on SIH in mice.
The figure represents the difference of the temperature (ΔT°C) between the first three mice and the last three mice. Treatments were administered 1 hour before the test. CON = NaCl 0.9%, PHO = phenobarbital 20 mg/kg. N = 10 per dose, **p<0.01, ***p<0.001, when compared to NaCl (Fischer exact test, two tails).

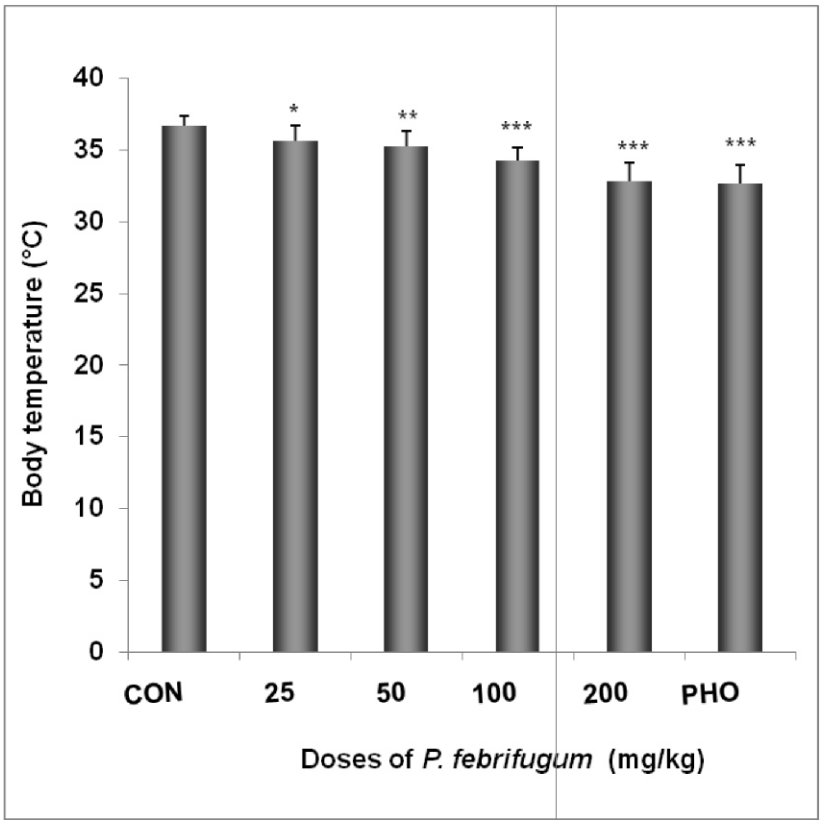

Figure 5: Effect of *P. febrifugum* on the body temperature in mice.
The figure represents the body temperature. Histograms are expressed as mean + S.E.M., n = 10 per dose, *p < 0.05, **p < 0.01, ***p < 0.001, ANOVA two-way, followed by Tukey (HSD). CON = NaCl 0.9%. Pheno = Phenobarbital 20 mg/kg.

the control group to 38.8 ± 5.5 at the dose of 200 mg/kg [F(6,29) = 14; p < 0.001]. By contrast, both *P. febrifugum* and diazepam decreased the number of rears and did affect neither the mass of fecal boli nor the number of crossing (Table 1).

Anxiolytic-like effects of *P. febrifugum* on the OF test

The OF test revealed that *P. febrifugum* increased in dose dependant manner, the number of crossing and grooming from 13.0 ± 0.7 and 10.3 ± 1.3 in the control groups to 19.8 ± 0.5 and 18.8 ± 3.2 at the dose of 200 mg/kg [F(6,29) = 16; p < 0.001] and [F(6,29) = 11; p < 0.001] respectively. The increase was also observed in the time spent by mice in the centre from 37.5 ± 4.3 s in the control group to 79.0 ± 16.7 s at the dose of 200 mg/kg [F(6,29) = 47; p < 0.001]. Controversially, *P. febrifugum* decreased the number of rears and the mass of fecal boli (P<0.01) and (P<0.01) respectively. The effect was the same with diazepam (0.3 mg/kg) (Table 2).

Anxiolytic-like effects of *P. febrifugum* on elevated plus maze test

Diazepam strongly increased the number of open arm entries and the percentage of entries and time spent in the open arms compared with the negative control (P<0.001). Mice treated with the decoction also had a significant increase in the number of entries into open arms from 1.7±0.4 in the control group to 6.3±1.1 at the dose of 200 mg/kg [F(5,31) = 3.94, P<0.01] (Figure 1), as well as in the percentage of entries into open arms (from 20% in the control group to 76% at the dose of 200 mg/kg) (p < 0.001), and in the percentage of time spent in open arms (from 19.6% in the control group to 40.4% at the dose of 200 mg/kg) (p < 0.01) (Figures 2). Like diazepam, *P. febrifugum* reduced the number of closed arm entries [F(6,29) = 8.9, P<0.001] (Table 3) and the percentage of entries and time in closed arms (P<0.001) (Figure 3). In addition, the ratio of open entries/total entries versus closed entries/total entries was strongly increased by *P. febrifugum* (P<0.001). The number of rears was reduced both by diazepam and *P. febrifugum* [F (6, 29) = 17, P<0.001] (Table 3).

Anxiolytic-like effects of *P. febrifugum* on SIH test

As expected, phenobarbital decreased the difference of the temperature (T°) between the first three mice and the last three mice. *P. febrifugum* produced the same effect at all doses [F (6, 29) = F18.5, P<0.001] (Figure. 4). SIH was 0.67 for phenobarbital and 0.7 for *P. febrifugum* (200 mg/kg).

In addition, the extract decreased the body temperature of mice from 30.73°C in the control group to 28.28°C at the dose of 200 mg/kg [F(6,53) = 27; p < 0.001] (Figure 5).

DISCUSSION

In stress-induced hyperthermia test, *P. febrifugum* antagonized the hyperthermia induced by stress. This antagonism, close to the effect of phenobarbital, suggested the presence of anxiolytic-like activity in *P. febrifugum* [20, 31]. The decrease of the latency to the first head dipping and the increase of the number of head dipping in HB also suggested the presence of anxiolytic-like effects [27, 32]. The presence of anxiolytic properties was confirmed in EPM where *P. febrifugum* increased the number of entries, the percentage of entries and time into the open arms, and reduced the percentage of closed arms entries and

time [30, 33]. The correlation of the increase in time spent in open arms with the increase in the number of entries in open arms accorded the presence of anxiolytic-like activity of *P. febrifugum*. Even the slight increase of crossing in OF that showed the increase of the exploratory activity revealed by the increase of the ratio OE/TE vs CE/TE when compared with the negative control, since closed arms entries, rearing and head dipping in EPM were reduced, confirmed the presence of anxiolytic-like properties [34-36]. These anxiolytic properties could be mediated by some components in the extract interacting with the benzodiazepine/ $GABA_A$ receptors as agonists, with the $5\text{-}HT_{1A}$ receptors as agonists, with the NMDA receptors as antagonists, or with any other mechanisms [31, 37-38]. The phytochemical characterization of *P. febrifugum* revealed the presence of alkaloids, flavonoids, saponins, tannins, anthraquinons and polyphenols. The anxiolytic activity could be related to the presence of some of these chemical families in the decoction [7, 39].

CONCLUSION

The decoction of *P. febrifugum* possesses anxiolytic-like effects mediated at least by the benzodiazepine and GABA sites of the receptor complex $GABA_A$. This finding could justify the use of *P. febrifugum* in traditional medicine in Cameroon. However, further studies are ongoing in other to clarify the mechanisms of action of *P. febrifugum* and its active components.

List of abbreviations:

Closed arms entries (CE), Negative control (CON), closed arms time (CT), diazepam (DIAZ), Elevated plus maze (EPM), open arms entries (OE), open arms time (OT), phenobarbital (Pheno), stress-induced hyperthermia (SIH), total arms entries (TE).

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