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Acute Toxicity and Aphrodisiac Activity of the Aqueous Extract of the *Panax ginseng* C.A. Meyer Rhizomes (Zngiberaceae) In Albino and Normal Male Rats of the Wistar Strain

Etame Loe Gisèle[1*], Dibong Siegfried Didier[1,2], Amougou Mackenzie Bénédicte Aimée[2], Sikadeu Sandrine[2], Talla Clovis[1], Tankeu Séverin Elisée[2], Yinyang Jacques[1], Ngene Jean Pierre[1], Ngoule Charles Christian[1], Kidik Pouka Cathérine[1], Nnanga Nga Emmanuel[1]

[1]Department of Pharmaceutical sciences, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, P.O. Box 2701Douala, Cameroon

[2]Laboratory of Biology and Physiology Organisms, Faculty of Science, University of Douala, P.O. Box 24157 Douala, Cameroon

Original Research Article

***Corresponding author**
Etame Loe Gisèle

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Abstract: The objective of the study was to evaluate the aphrodisiac property of the aqueous extract of *Panax ginseng* C.A. Meyer rhizomes (Zngiberaceae) in albino and normal male rats of the Wistar strain. Colorimetric and precipitation methods were used to highlight secondary metabolites of the plant. The acute toxicity test was conducted according to OCDE guideline 423. Four lots of 6 animals were used to evaluate the aphrodisiac property of *P. africana*. The positive control received sildenafil citrate (5 mg/Kg) and the negative control, distilled water. The test lots received the extract at 500 and 2000 mg/Kg for 8 days. The copulatory parameters were observed on days 1, 4 and 8. The phytochemical screening revealed the presence of ginsenosids, alkaloids, tannins, saponosides and tri terpenes in the extract. No changes in the general appearance of the rats and no mortality were recorded during the toxicity test, highlighting that *P. africana* is non-toxic. The extract significantly increased the sex parameters of the tested rats. This aphrodisiac effect of *P. africana* attributed to identify secondary metabolites justifies its use in traditional medicine as a sexual stimulant.

Keywords: Panax ginseng, rhizomes, extrait aqueux, toxicité aiguë, potentiel aphrodisiaque.

INTRODUCTION

Many diseases cause a high number of deaths each year all over the world. However, good nutrition and regular physical activities would reduce a significant number of deaths [1]. Unfortunately, the continental imbalance at all scales prevents the respect of the latter, which is why people have been exploiting medicinal plants since ancient times.

According to WHO [2], traditional medicine is the body of knowledge and practices that can or cannot be explained, used to diagnose, prevent or eliminate a physical, mental or social illness based on practical and transmitted experiences generation to generation orally or in writing [3]. Medicinal plants are widely used in developed countries where they are widely available and offer an alternative to pharmaceutical products. These plants are valuable resources for the vast majority of rural people in Africa, where more than 80% use their primary health care [4-8]. Several treatments based on the same plant have incredible results, such as ginseng. Recently, large numbers of interest have been brought to study the health benefits of ginseng as well as its constituents using modern techniques. Many studies have reported that ginseng functions as a free radical scavenger and immunomodulator, help to maintain optimal health against aging and certain chronic conditions such as erectile dysfunction [9-11].

Erectile dysfunction is a public health problem that affects the quality of life of patients and their partners [12]. It often reflects the absence of a man's sexual performance to cope with his own expectations, which in turn are influenced by cultural and social factors [13]. The definition revisited in 2004 by the Second International Consultation on Sexual Dysfunction, considers erectile dysfunction as the persistent or recurrent disability for a man to obtain or maintain a penile erection sufficient to allow sexual activity [14]. Fortunately, the treatment of erectile dysfunction has made remarkable progress in recent

decades, especially with the arrival of the new class of inhibitors, phosphodiesterase type 5 (PDE5). Among these, Viagra (Sildenafil Citrate) modifies the hemodynamics in the penis. Nevertheless, this drug, in addition to its high cost, has several undesirable side effects such as headache, reddening, hypertension, nasal congestion and dyspepsia [15]. The aim of the work was to evaluate the aphrodisiac activity of the aqueous extract of *Panax ginseng* rhizomes in male albino and normal rats of Wistar strain. The specific objectives were to: identify the secondary metabolites present in the aqueous extract; study the acute toxicity of the aqueous extract; test the properties of the aqueous extract on the sexual behavior of albino and normal male rats of Wistar strain.

MATERIALS AND METHODS

Plant material

The rhizomes of *Panax ginseng* (Zingiberaceae) were collected at Foumbot, Noun Department, Western Region (Cameroon). The botanical identification of the species was carried out at the Laboratory of Biology and Physiology of Plant Organisms of the Faculty of Science, the University of Douala.

Animal material

Normal and albino rats of Wistar strain at least 3 months old and weighing between 180 and 240 g were used. Similarly, adult female rats (minimum 3 months of age), weighing between 120 and 170 g, were used for the copulation tests. These rats were raised at the Laboratory of Animal Physiology of the Faculty of Science of the University of Douala. The rats were raised to room temperature, under a natural nycthemeral cycle and received throughout the duration of the experiment water at will, and a standard diet during the tests.

METHODOLOGY

Preparation of aqueous extract

Freshly harvested rhizomes were cleaned and dried in the sun (25 °C) for 15 days. Seven kilograms of fresh rhizomes were washed, cut into thin strips and dried. The mass of dry matter obtained (2 Kg) was pulverized with the aid of an electric grinder to obtain 1.5 Kg of brown powder. This powder obtained was used for the preparation of the aqueous extract. Thus, 400 g of powder were taken and then mixed with 2 L of distilled water. The mixture obtained was homogenized and macerated for 48 H. The macerate was sieved and the filtrate collected with Wattman N° 1 paper, followed

Phytochemical Screening

The study has highlighted the presence of some chemical groups in the plant. The pulverized plant material is used up successively by maceration in solvents of increasing polarity (chloroform, methanol, water). Phytochemical tests for tannins, alkaloids, saponins, steroids, flavonoids, saponosides have been carried out by different methods [16-20].

Acute toxicity

The experimental protocol used was that of OCDE Guideline 423 [21]. The young female rats (18 rats distributed in 6 lots of 3 rats) were randomly selected and submitted to fasting for 12 H before the test, but receiving distilled water at will. These lots were treated as follows: the control group received distilled water at 10 mL/Kg. Lots 1, 2, 3, 4 and 5 were treated with the aqueous *P. ginseng* extract at doses of 5 mg/Kg, 50 mg/Kg, 300 mg/Kg, 2000 mg/Kg and 5000 mg/Kg. After oral administration to the different lots, young female rats were observed individually for the first 24 H after treatment. The observation then continued for fourteen days following the administration of the substance. These observations concerned the behavior and the general state of these rats. The batch mortality was evaluated for 48 H, after administration, moreover these rats underwent during the study period weighings respectively every 2 days (D0, D2, D4, D6, D8, D10, D12, D14) to evaluate the weight variation.

Evaluation of aphrodisiac properties

Evaluation of the properties of the aqueous *P. ginseng* extract on the sexual behavior of albino and normal male rats was conducted according to the Mbongue protocol [22]. Four lots of 6 rats each fasted for 24 H were distributed as follows: the negative control group received distilled water at 5 mL/ Kg, the positive control group was treated with sildenafil citrate at a dose of 5 mg/Kg; the other 2 lots received the extract respectively at doses of 500 and 2000 mg/Kg.

The study took place in 8 days. The rats of the different batches received administration of the different products by means of a feeding tube, every day. One hour after the gavages on days 1, 4 and 8, the rats were placed in a cage each for 10 min for acclimatation. A female ovariectomized and made receptive by injection of a subcutaneous dose of 15 µg/Kg of estradiol benzoate 48 H before the experiment, followed by injection of a dose of 60 µg/Kg of progesterone H before the experiment. Then, each lot was introduced into a cage for a period of 30 min, during which the copulatory parameters were observed: latency of sexual uprisings, frequency of sexual uprisings, number of intromissions, number of erections and number of ejaculations meticulously observed for 30 min.

STATISTICAL ANALYSIS OF THE DATA

Data was entered into an Excel sheet (Microsoft Office, USA) and then exported to GraphPadPrism version 5.0 for Windows analysis

software (San Diego, California, USA) set Statview version 5.0 (SAS Institute, Inc., Illinois, USA)). The data were presented as mean ± error standard on mean (ESM) in histograms. The one-way order of variance (ANOVA) was used to compare the mean values of reproductive parameters between the different groups of animals in the experiment. Subsequently, the Dunnett test was used to make even comparisons between the test groups and the control groups (negative and positive). The Barlett sphericity test was used previously to ensure that the study data adhered to the ANOVA utilization hypotheses (for example, equality of the variances of the lots to be compared). The repeated measures in ANOVA was used to study the weight change of each lot during the follow-up time, while the non-parametric Kruskal-Wallis test was used to compare the average weight of the different lots according to each day of followed. The threshold of significance was set at p-value <0.05.

RESULTS AND DISCUSSION

Results

Phytochemical screening of rhizome extracts

The phytochemical screening of *Panax ginseng* rhizome extracts, by qualitative characterization reactions, made it possible to detect several families of compounds in the plant: tannins, sterols, saponosides, flavonoids and alkaloids (Table 1).

Table-1: Phytochemical screening tests on *P.ginseng*

Secondary metabolites	Observations	Résults
Saponins	Abundant foam	+++
Catholic tannins	Appearance of a green blue color	+++
Alkaloïds	Appearance of a white precipitate	+++
Sterols	Formation of a red ring	++
Flavonoïds	Absence of a redcolor	-

-: Negative; +:Lowly positive; ++: Positive; +++: Strongly positive

Evaluation of the acute toxicities parameters of the aqueous extract of *Panax ginseng* rhizomes

Fifteen minutes after gavage, for doses ranging from 5 to 5000 mg/Kg, no motor difficulties were observed. No changes in the overall appearance of young female rats (hair, eye, ear, and mouth conditions) were observed for 2 weeks. In other words, the different doses of the extract did not cause any deaths in the 6 lots of 3 female rats: The LD_{50} was greater than 5000 mg/Kg (Table 2).

Table-2: General condition of young female after administration of rhizome aqueous extract of *P. Ginseng*

Lots parameters	lot T(-)	Group 1 5mg/Kg	Group 2 50mg/Kg	Group 3 300mg/Kg	Group 4 2000 mg/Kg	Group 5 5000 mg/Kg
Number of female rats	3	3	3	3	3	3
Mobility	N	N	N	N	N	N
Aggressiveness	N	N	N	N	N	N
Stool condition	N	N	N	N	N	N
Sensitivity to pain	N	N	N	N	N	N
Vomiting	A	A	A	A	A	A
Vocalization	N	N	N	N	N	N
Pilot erection	N	N	N	N	N	N
Tail condition	N	N	N	N	N	N
Vigilance	N	N	N	N	N	N
Number of deaths	0	0	0	0	0	0

N : Normal ; A : Absent

Effect of aqueous extract on the weight change of young female rats

Female rats showed no significant decrease in body mass regardless of the dose of aqueous extract administered to animals (Fig. 1).

Effects of the aqueous extract of *Panax ginseng* rhizome on copulatory parameters

Effect of the aqueous extract on the latency of sexual uprisings

The effect of the extract showed no significant evolution ($p > 0.05$) of the latency of sexual uprisings between the different days of treatment (Fig. 2).

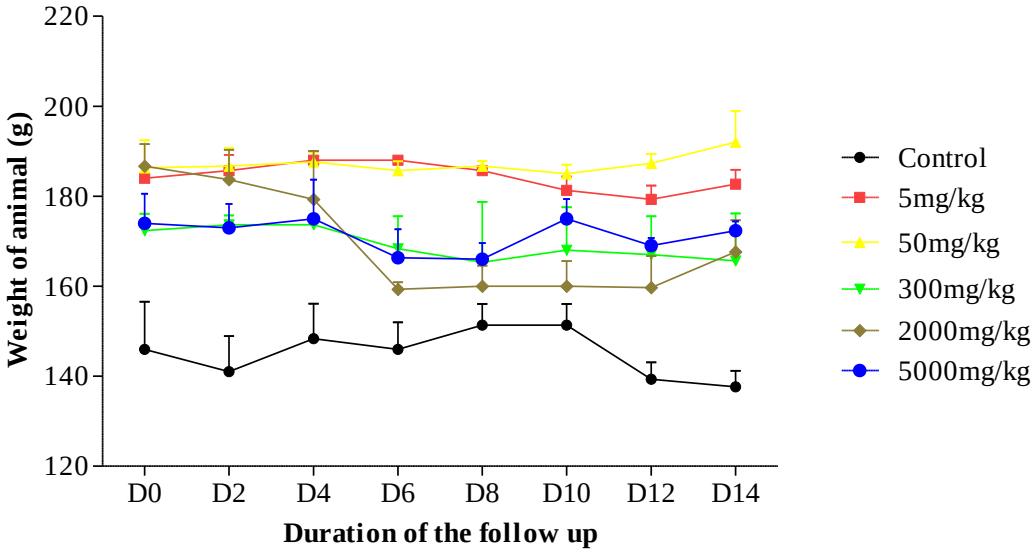

Fig-1: Effect of the aqueous extract of *P. ginseng* on the change in body weight of female rats after 14 days of administration. Each point represents the average weight ± ESM

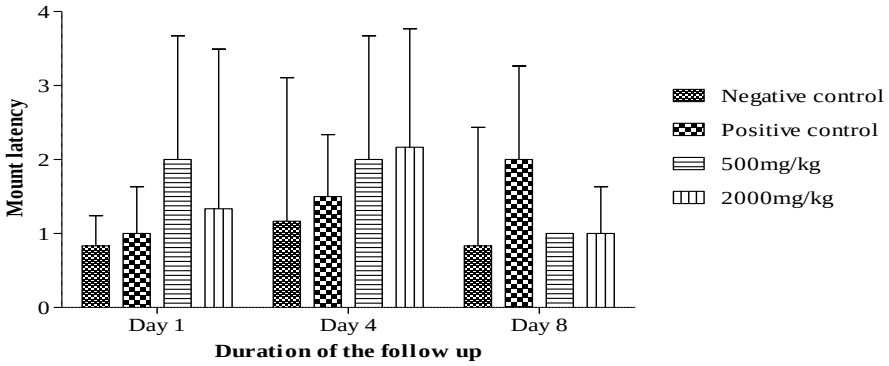

Fig-2: Effects of the aqueous extract of *P. ginseng* on the latency of sexual uprisings in normal and adult male rats. The data are presented in the form of a standard mean ± deviation. Comparisons were made against the negative (*) and positive (#) controls.

* Difference at p-value <0.05; ** Difference at p-value <0.01; *** Difference at p-value <0.0001

\# Difference at p-value <0.05; ## Difference at p-value <0.01; ### Difference at p-value <0.0001

Effect of the aqueous extract on the number of sexual uprisings

On the first day, a very significant decrease ($p < 0.01$) in the number of sexual uprisings was observed at 2000 mg/Kg dose compared with positive and negative control groups.

On the fourth day, a significant increase ($p < 0.05$) in the number of sexual uprisings was observed at

dose 500 mg/Kg compared with the negative control group. The number of sexual uprisings were 18.33 ± 11.55 for the 500 mg/Kg dose and was 3.00 ± 4.56 for the negative control group.

On the eighth day, significant increase ($p < 0.05$) and ($p < 0.01$) of the number of sexual uprisings was observed at 500 mg/Kg dose and 2000 mg/Kg dose compared with the negative control group. The number of sexual uprisings was 22.00 ± 9.88 for the 500 mg/Kg dose, 9.67 ± 19.79 for 2000 mg/Kg dose and 1.83 ± 3.25 for the negative control group (Fig. 3)

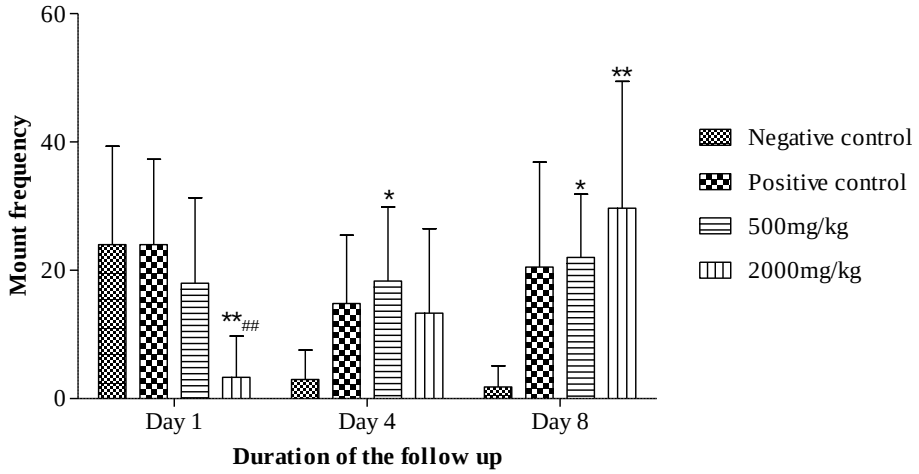

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Fig-3: Effects of the aqueous extract of *P. ginseng* on the rate of climb in normal and adult male rats. The data are presented in the form of a standard mean ± deviation. Comparisons were made against the negative (*) and positive (#) controls.

* Difference at p-value <0.05; ** Difference at p-value <0.01; *** Difference at p-value <0.0001
# Difference at p-value <0.05; ## Difference at p-value <0.01; ### Difference at p-value <0.0001

Effects of the aqueous extract on the number of intromissions

On the first day, a significant decrease ($p < 0.01$) and ($p < 0.05$) of the number of intromissions was observed at 2000 mg/Kg dose compared to positive and negative control group respectively.

On the fourth day, a significant increase ($p < 0.05$) in the number of intromissions was observed at 500 mg/Kg dose compared with the negative control group. The number of intromissions at 500 mg/Kg dose was of 15.83 ± 9.75 and for the negative control group of 2.17 ± 3.49.

On the eighth day, a very significant increase ($p < 0.01$) in the number of intromissions was observed at 2000 mg/Kg dose compared to the negative control group. The number of intromissions was at 2000 mg/Kg dose of 22.67 ± 13.25 and for the negative control group of 1.33±2.42. (Fig.4).

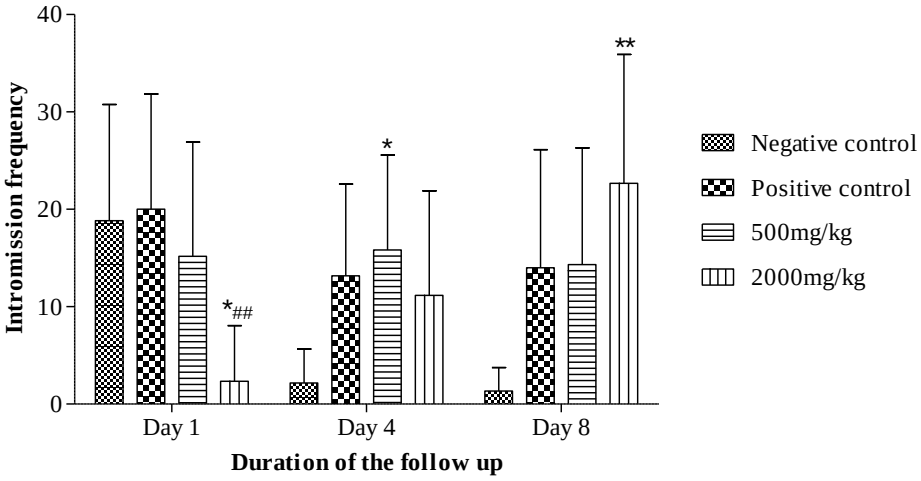

Fig-4: Effects of the aqueous extract of *P. ginseng* on the frequency of intromissions in normal and adult male rats. The data are presented as mean ± standard deviation. Comparisons were made with negative (*) and positive (#) controls

* Difference at P-value <0.05; ** Difference at P-value <0.01; *** Difference at P-value <0.0001
\# Difference at P-value <0.05; ## Difference at P-value <0.01; ### Difference at P-value <0.0001

Effects of aqueous extract on the number of erections

On the first day, a significant decrease ($p < 0.05$) in the number of erections was observed at dose 2000 mg/Kg compared to positive and negative control groups, respectively.

On the fourth day, a very significant increase ($p < 0.01$) in the number of erections was observed at dose 500 mg/Kg compared to the negative control group. The number of erections at 500 mg/Kg dose were of 22.33 ± 13.41 and of 1.83 ± 4.49 for the negative control group.

On the eighth day, significant increases ($p < 0.05$) and ($p < 0.01$) in the number of erections was observed at 500 mg/Kg and 2000 mg/Kg dose compared with the negative control group. The number of erections were at 500 mg/Kg dose of 19.67 ± 11.71, 26.67 ± 15.62 at 2000 mg/Kg dose and of 1.50±1.76 for the negative control group (Fig. 5).

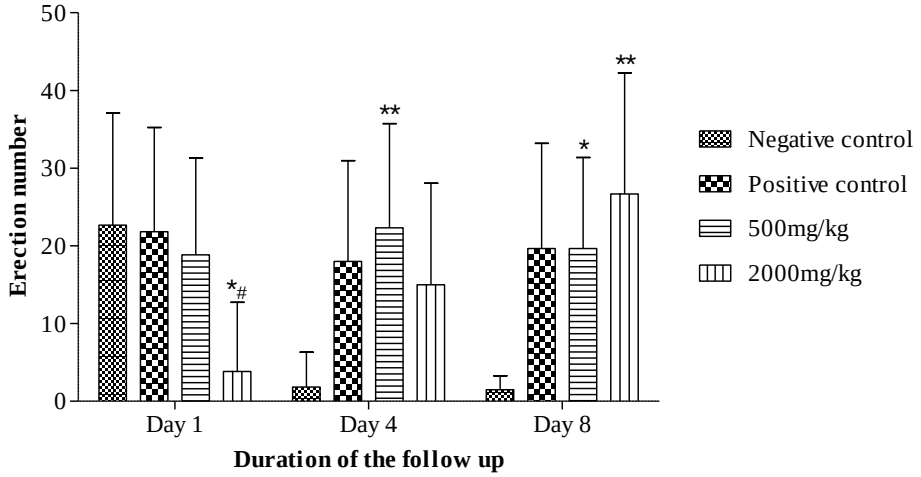

Fig-5: Effects of the aqueous extract of *P. ginseng* on the number of erections in normal and adult male rats. The data are presented as mean ± standard deviation. Comparisons were made with negative (*) and positive (#) controls.

* Difference at P-value <0.05; ** Difference at P-value <0.01; *** Difference at P-value <0.0001
\# Difference at P-value <0.05; ## Difference at P-value <0.01; ### Difference at P-value <0.0001

Effects of aqueous extract on the number of ejaculations

On the first day, no significant difference ($p < 0.05$) in the number of ejaculations was observed compared to positive and negative control groups, respectively.

On the fourth day, a significant increase ($p < 0.05$) in the number of ejaculations was observed at 500 mg/Kg dose compared with the negative control group. The number of ejaculations at 500 mg/Kg dose were of 22.33 ± 13.41 and of 1.83 ± 4.49 for the negative control group.

On the eighth day, significant increases ($p < 0.05$) and ($p < 0.01$) in the number of ejaculations were observed at 500 mg/Kg and 2000 mg/Kg doses compared with the negative control group. The number of ejaculations at 500 mg/Kg dose were of 26.67 ± 15.62, 26.67 ± 15.62 at the dose 2000 mg/Kg and of 1.50 ± 1.76 for the negative control group(Fig.6).

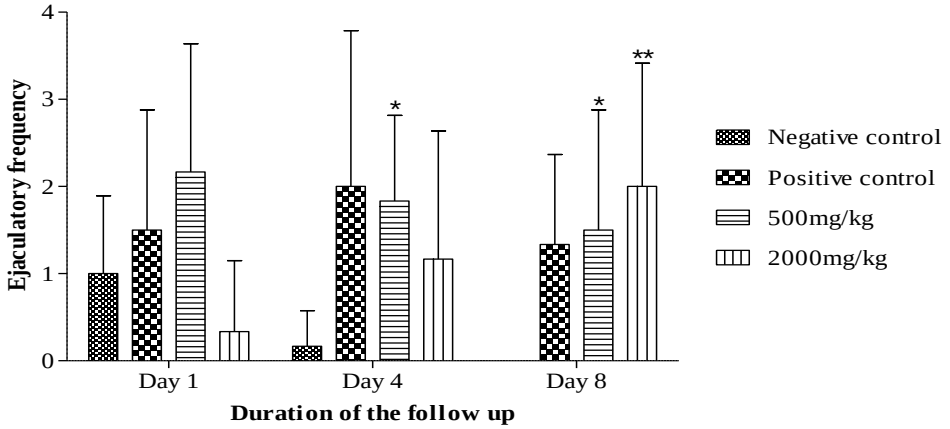

Fig-6: Effects of the aqueous extract of *P. ginseng* on the frequency of ejaculations in normal and adult male rats. The data are presented in the form of a standard mean ± deviation. Comparisons were made against the negative (*) and positive (#) controls.

.* Difference at p-value <0.05; ** Difference at p-value <0.01; *** Difference at p-value <0.0001

Difference at p-value <0.05; ## Difference at p-value <0.01; ### Difference at p-value <0.0001

DISCUSSION

The potential of a medicinal plant is attributed to the action of its phytochemical constituents. Phytochemical properties on the rhizomes of *Panax ginseng* revealed the presence of alkaloids, saponins and catholic tannins in large quantities; less sterols and a complete absence of flavonoids. The set of chemical groups thus identified, contains various pharmacological properties justifying the many virtues of *Panax ginseng* in traditional therapy [23]. The abundance of saponosides or ginsenosides, tannins and alkaloids would explain strong ability of *P. ginseng* to solve problems of erectile dysfunction through the large number of sexual uprisings and erections observed during the tests. ginsenosides would facilitate erection by inducing vasodilatation and relaxation of cavernous bodies *via* the production of nitric oxide by endothelial cells and nerve endings [24, 25]. Alkaloids tonify and stimulate muscles by excitement of the central nervous system allowing the improvement of the endurance and the resistance to the sexual act. These alkaloids thus diminish the feeling of exhaustion and facilitate the fulfillment of the sexual act [26]. On the other hand, according to [27], the tannins due to their affinity are used as antidotes for the alkaloids, which could explain their strong presence in relation to the alkaloids and therefore the strong power of *Panax ginseng* to solve the erectile dysfunction. However, the low sterol content and the virtual absence of flavonoids show that these molecules do not belong to the group of major constituents of red ginseng.

Acute toxicity showed that oral extracts of *P. ginseng* rhizome were administered orally to lots of young female rats at doses of 5 mg/Kg, 50 mg/Kg, 300 mg/Kg, 2000 mg/Kg and 5000 mg/Kg does not cause any change in behavior or death in the different batches. The LD_{50} is then greater than 5000 mg/Kg. *Panax ginseng* is therefore considered a non-toxic plant according to the toxicity scale [28]. These results confirm the safety of the traditional (decocted) use of ginseng.

The significant absence of latency of sexual uprisings suggests a stimulation of virility, characteristic of aphrodisiacs. It reflects the nervous tonus, indeed, in normal situations. This time is long and is an indicator of nervous week [29]. Moreover, the very significant decrease in the number of sexual uprisings, intromissions, erections and ejaculations at

the 2000 mg/Kg dose on days 1 and 4, and the very significant increase in these same copulatory parameters at day 8 of this same month dose compared to the negative control group showed that this dose had a late aphrodisiac effect. On the other hand, these copulatory parameters at a dose of 500 mg/Kg were very significant on days 1, 4 and 8. The effects of this aqueous extract at a dose of 500 mg/Kg would be similar to the reference product Viagra. Indeed, viagra is a powerful vasodilator that works by reversing vasoconstriction due to adrenaline vasodilation required to obtain an erection [30]. Similarly, significant increases in the number of sexual uprisings, intromissions, erections and ejaculations observed in this study showed that *P. ginseng* extract increased the libido of test rats [31]. This increase in libido was due to the existence of secondary metabolites contained in the rhizomes of *P. ginseng* which by its high content of ginsenosides would be considered a powerful aphrodisiac, especially as its main active agent had this conformation nature [32]. Similarly, its high content of tannins and alkaloids testified to its great capacity to solve erectile problems [33]. Thus, the extract of *P. ginseng* would act favorably on a blood flow to penile erectile and ejaculatory structures.

CONCLUSION

The general objective of this study was to evaluate the aphrodisiac activity of the aqueous extract of *Panax ginseng* rhizomes in male and normal and albino rats of Wistar strain. Phytochemical screening revealed the presence of various secondary metabolites. The acute toxicity study showed that the aqueous extract of *Panax ginseng* is non toxic with an LD_{50} greater than 5000 mg/Kg. The study of the aphrodisiac properties showed that rhizome extract of *P. ginseng* at a dose of 500 mg/Kg contains all the aphrodisiac properties that can improve erectile dysfunction in normal and adult male rats directly or similary to Viagra. *P. ginseng* rhizome extract at a dose of 2000 mg/Kg contains all the aphrodisiac properties that can improve erectile dysfunction in normal and adult male rats indirectly or after 3 doses of this dose after every 3 days.

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