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GABA-A Receptor Complex in the Anxiolytic Properties of *Parkia biglobosa* in Mice

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Abstract *Parkia biglobosa* (Mimosaceae) is a plant about 10 to 15 meters high and is present in the Sudano-sahel region. It is used in Cameroon traditional medicine to treat hypertension, joint pain, zona and in osteopathy. The present study was aimed at studying the anxiolytic properties of the aqueous extract of *Parkia biglobosa* in mice. The pharmacological tests such as tests of Hyperthermia Induced-Stress (HIS), Open field(OF) and elevated plus maze (EPM) were used. Four doses of the plant extract 10; 25; 50 and I00 m/kg were equally used. The value of SIH was 2.27 ℃ in the negative control group and 1.30 ℃ with mice treated by Phenobarbital 20 mg/kg. Treatments of the animals with gradual doses of *P. biglobosa* led to HIS significant decrease to 1.43 ℃ corresponding to the dose of 100 mg/kg and representing more than 80% of the value obtained by the reduction of body temperature. In the EPM test there was a significant increase in percentage of entries into the open arms from 28.76% for the negative control group to 69.08 and 70.95% for 50 and 100 mg/kg respectively. The diazepam (DZP) 0.3 mg/kg increased this value to 73%. Then, in the test of the benzodiazepine antagonist, it was observed that the percentage of time spent in open arms decreased from 30% in the negative control group to a significant value of 11% in the distilled water and FG7142, treated groups, whereas this percentage increased significantly to 63.3, 66.6 and 50% at doses of Distilled water and 50 mg/kg, Distilled water and +100 mg/kg, and also flumazenil and 100 mg/kg of aqueous extract of plant respectively. Subsequently, Gaboxadol(GAB) agonist and Bicuculine(BIC) competitive antagonist of Gaba receptor sites were used as reference substances of Gaba site of GABA-A receptors complex and this test showed a significant increased in the percentage of time spent in the open arms from 14.54% for the negative control group to 39.11, 43.45 and 33.97% for Distilled water and Gaboxadol, Distilled water and 50 mg and ED+100 mg/kg groups of the aqueous extract of plant respectively, while there was a significant decrease in this percentage to 7.82, 9.49, 9.55 and 6.94% for BIC+ED, BIC+GAB, BIC+50 and BIC+100 mg/kg groups respectively. These results reveal that *P. biglobosa* showed anxiolytic properties in the mice model tests.

Keywords Anxiety, *P. biglobosa*, Complex Gaba-A receptor

1. Introduction

Neurological and psychological diseases are the most debilitating among diseases affecting the mankind. They are responsible for terrible suffering for the people which are victims and many others difficulties for their families and the national and international community [1]. Anxiety disorders affect about 10% of the world population and making them a public health problem [2, 3]. The physiological anxiety allows the body to adapt to the difficult conditions of its environment is defined as an emotional state of short duration, with a sudden stop period once the aversive event completed. It is a kind of confusion accompanied by a paralyzing sensation of imminent peril and undetermined after an external or internal factor [4]. Pathological anxiety occurs when the response of the individual to an anxiety event becomes excessive and even affects the ability of the latter to lead a normal life after an emotional hyperactivity condition. Symptoms persist even without trigger [5]. It does not exist today medication that can completely cure an anxiety disorder. The treatments prescribed by modern medicine (anxiolytics; antidepressants) are not always better to patients. Their long-term action at specific receptors leads

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to tolerance, dependence and insensitivity. This leads to a long term inefficacy. For their nature, these products cause many side effects including sedation and muscle relaxation, which are not desired for a good anxiolytic or antidepressant. Finally, these drugs are very expensive for people in poor countries [1]. So, maybe the solution could come by the use of medicinal plants, including Parkia biglobosa (Bent). popularly known as "néré" in bambara tongue in Mali [6, 7] and "Zira" in Gbaya tongue in Cameroon [8]. This plant is used the treatment of osteopathy, zona and hypertension [9] so Phytochemical characterization showed previously that it contains flavonoids, alkaloids, tannins, saponins, terpenes, terpenoides, and steroids.

2. Material and Methods

2.1. Plant Material

Stem barks of *P. biglobosa* were collected at the Far-North Region of Cameroon during November 2012. The botanical identification of the plant was done by the National Herbarium of Cameroon where the voucher specimen was conserved under the reference number 58972 /HNC.

2.2. Preparation of Aqueous Extract

Decoction of *P. biglobosa* was prepared according to the instructions from the traditional healer and administered in a volume of 10 ml/kg of body weight. Stem bark was cleaned and using a mechanical grinder. The aqueous extract of plant was prepared immediately before the administration. For this study, 5 g of the powder of the bark was macerated in 50 ml of distilled water for 1 h. The mixture was boiled during 20 min at 150 ℃. After, cooling, it was collected and filtered using watt man paper number 1 to obtain the stock solution. This solution (red color) corresponded to a concentration of 100 mg/ml and diluted in distilled water for less concentrated solutions. Furthermore, to determine the amount of dry matter absorbed, the filtrate of *P. biglobosa* was evaporated in an oven at 60 ℃, until obtaining 0.5 g of brown powder (ie a yield of 10%) of the paper.

2.3. Animals

Naïve white mice Mus *musculus Swiss* of both sex were used in this study. Animals of 20 ± 2 g and two months old were obtained from the LANAVET (laboratoire national veterinaire) of Garoua. Animals were housed in standard Plexiglas cages at 25 ±2 ℃, on a 12/12 hour-light-dark cycle. They were supplied with food and water *ad libitum*. For each test, mice were divided into 6 groups apart of agonist and antagonist tests where animal were divided into 8 groups. One negative control group received distilled water as vehicle, Specific substances were used as positive control according to the methods and test groups received different doses of plant extracts. The studies were conducted according to the National Ethics Committee of Cameroon (Reg.No. FWA-IRB00001954).

2.4. Chemical

All the chemicals used in this study were as analytic grade. The diazepam Sigma (dzp, 0.3, 0.5 and 2 mg/kg, i.p.) and THIP (4, 5, 6, 7-Tetrahydroisoxazolo [5, 4-*c*] pyridin-3-ol hydrochloride) or Gaboxadol (2 mg/kg i.p.) were used as the standard anxiolytic drugs. The Phenobarbital (20 mg/kg, i.p.) was used as an anxiolytic and antipyretic drugs so that the RO151788 or flumazenil (6 mg/kg) and FG7142 or β-carboline (3 mg/kg) was used as antagonists. All drugs were obtained from Sigma® (U.S.A.).

2.5. Procedure

2.5.1. Hyperthermia Induced-Stress in Group-Housed Mice

The hyperthermia induced-Stress was performed according to the method described by Borsini in 1989 [10] with the modification to this paradigm by Olivier in1997 [11, 12] resulted in the reduction of the number of animals needed per study, favourable for ethical, statistical and economical reason. This test was based on the influence of the plant via barbiturates receptors for increasing the temperature of mice subjected to the stressors [13]. These animals were evenly divided into 6 groups of 10 animals each. Then, they were treated with distilled water (10 mg/kg, po) for the negative control group, the different doses of P. biglobosa extract and the phenobarbital (20 mg/kg,ip) as positive control group The first use of SIH test in anxiety research accurred after it was noted that removing mice one by one from a group –house cage increased body temperature of the last mouse compared to the first. Here the first rectal temperature measurement (T1) is the basal unstress core temperature but also functions as a stressor, whereas the second rectal temperature measurement (T2) is the stress induced body temperature which is increased due to the stress experienced from the first temperature measurement [3]. The difference in temperature (T= T2 –T1) is defined as the HIS response.

2.5.2. Elevated Plus Maze Test

The hyperthermia induced-Stress The test of elevated plus maze was described in accordance with the method of Rodgers and Dalvi (1997) [14]. This test is based on the study of the spontaneous behavior of the animal on the anxiety paradigm of EPM [15]. Having sensitivity to benzodiazepine such as diazepam; this test allows us to access the possible involvement of the benzodiazepine site of the Gaba-A complex for anxiolytic effects of the plant. Animals were divided into 6 homogeneous groups of 5 animals each. They are treated with distilled water (10 ml /kg, po) for the negative control group, diazepam (0.3 mg /kg, ip) for the positive control group and the different doses of the P. biglobosa for testing groups. After administration of different substances, they are returned to their original cages to reduce phobic responses due to the experimental environment [13]. One hour after administration of the various treatments, mice were placed one after the other in the center of the platform of the elevated plus maze. The

behaviour of each mouse was observed for a period of 5 minutes and Behavioral parameters were evaluated and performed according to the method described by Borsini in 1989 [10] with the modification to this paradigm by Olivier in1997 [11, 12] resulted to the reduction of the number of animals needed per study, favourable for ethical, statistical and economic data.

2.5.3. Open Field Test

Open field test is used to evaluate the exploratory activity and emotional response in animals. The apparatus consisted of wood walls and clear floor (50 x 50x10 cm) divided into 17 squares. The 1 inner squares in the center and 16 squares in the periphery along the walls and placed in bright light room. After 30 min of administration of test extract, standard drug and vehicle, treated mice were placed individually on one corner of the apparatus and observed for the next 5 min. Animals were placed individually in one of the corner squares the observed parameters and time spent in center, number of squares crossed and rearing were taking for 5 min.

2.5.4. Study of Benzodiazepine Site of GABA-A Receptor Complex on the Anxiolytic Properties of *P. biglobosa* by Using the β-carboline and Flumazenil

On this mechanism of action test, the involvement of benzodiazepines site of the GABA-A receptor complex for anxiolytic properties by *P. biglobosa* was evaluated. The β-carboline (FG7142), inverse agonist of the receptor site of the GABA-A receptor complex of benzodiazepines and Flumazenil (RO151788), competitive antagonist of the receptor site of benzodiazepine of GABA-A receptor complex and distilled water were used [14, 15]. The β-carboline (6 mg/kg, ip.) and the flumazenil (3 mg/kg, ip) were administered in mice 30 minutes after treatment of mice by the plant extract at 50 and 100 mg/kg doses [16]. One hour after administration of the extract, mice were placed one after the other in the centre of the elevated plus maze and conventional and ethological variables were observed and recorded for a period of 5 minutes.

2.5.5. Study of the Involvement of Gaba Sites of GAbA-A Receptors Complex on the Anxiolytic properties of *P. biglobosa* by Using Gaboxadol and Bicuculline

The involvement of Gaba site of GABA-A receptor complex for anxiolytic properties by *P. biglobosa* was evaluated. The THIP (gaboxadol) an agonist Gaba site of GABA-A receptor complex and bicuculline a competitive antagonist of Gaba site of GABA-A receptor complex were used. The THIP (2 mg/kg, ip.) and Bicuculline (3 mg/kg; i.p.) were administered and 30 minutes after the treatment of mice by the plant extract at 50 and 100 mg/kg doses. One hour after administration of plant, the mice were placed one after the other in the center of the elevated plus maze and conventional and ethological variables were observed and recorded for a period of 5 minutes.

2.6. Statistics

The values of the negative control group were compared to the values of the tested groups and positive control group in each test. The analyses of variance (ANOVAs) followed by Tukey's (HSD) test were used and p value below 0.05 was considered significant.

3. Results

3.1. Effect of the Decoction of *P. biglobosa* on the Body Temperature

3.1.1. Mean Rectal Temperature

Figure 1 shows a highly significant ($p<0.01$) and dose-dependent of mean rectal temperature of the mice treated with different doses of the P. biglobosa extract compared to the negative control group. The mean rectal temperature decreased from 34.03 ± 0.67 ℃ in the mice of the negative control to 31.81 ± 0.46 ℃ compared to those receiving the plant extract at 100 mg/kg so that 31.55 ± 0.42 ℃ was the value corresponding to the group having received Phenobarbital (20 mg/kg).

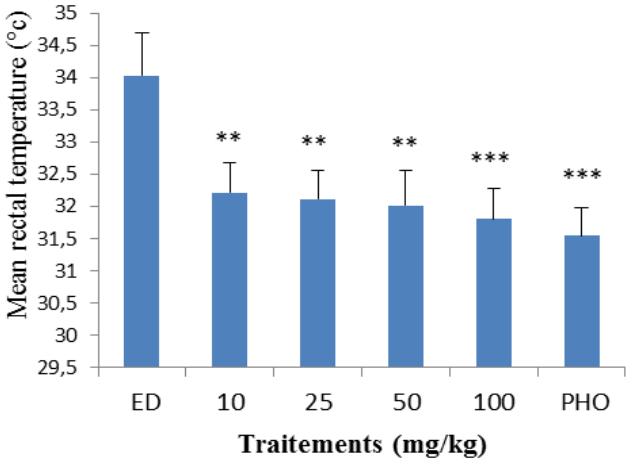

Figure 1. Effects of *P. biglobosa* on Mean Rectal Temperature (℃)

Each bar represents the Mean of rectal temperature. P values for groups' comparison were obtained by one way ANOVA followed by Tukey's post-hoc test **p<0.01; ***p<0.001 vs distilled water treated group. Error bars represent the ± S.E.M. ED negative control treated by distilled water, 10, 25, 50, and 100 (*P. biglobosa* 10, 25, 50 and 100 mg/kg), PHO positive control treated by Phenobarbital (20 mg/kg).

3.1.2. Effects of Decoction of *P. biglobosa* on Stress-induced Hyperthermia

The value of SIH decreases significantly ($p<0.001$) from 2.27 ℃ in the negative control group at 1.43 ℃ for the group of 100 mg/kg dose and representing more than 80% of the value obtained of the reduction of temperature body. The mice treated with Phenobarbital 20 mg/kg reduce

significantly ($p<0.001$) this value at 1.30 ℃.

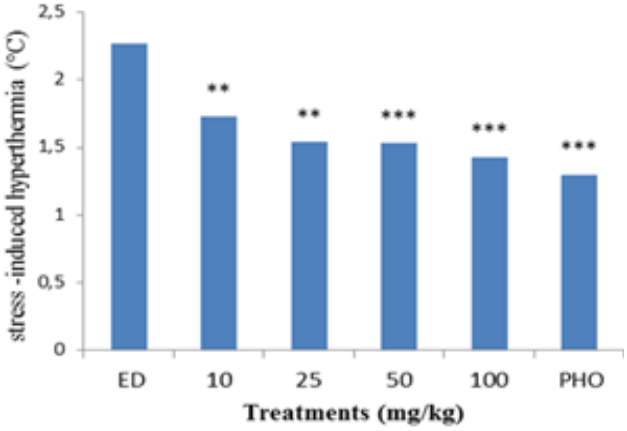

Figure 2. Effects of *P. biglobosa* on stress-induced hyperthermia. Each bar represents the SIH. P values for groups' comparison were obtained by one way ANOVA followed by Tukey's post-hoc test. **p<0.05; ***p<0.01 vs distilled water treated group. ED negative control treated by distilled water, 10, 25, 50, and 100 (*P. biglobosa* 10, 25, 50 and 100 mg/kg), PHO positive control treated by Phenobarbital (20 mg/kg)

3.2. Effects of Single Administration of Decoction of *P. biglobosa* on Elevated Plus Maze Parameters

Figure 3A shows the number of entries in the open arms of the EPM to 5 of the negative control group while *P. biglobosa* extract caused a significant increase (**p<0.01) of this number to 14 entries for the mice treated with the dose of 100 mg/kg. The positive control has increased that number also to 14 entries. Figure 3B shows a significant increase ($p<0.001$) in the percentage of entries into the open arms of 28.76% for negative control group to 69.08 and 70.95% for the 50 and 100 mg/kg doses of the plant extract. The DZP increased this value to 73%. Figure 3C shows a significant increase ($p<0.01$) in the time spent in open arms from 17.54 seconds (s) to the negative control group to 97.72 s of 50 mg/kg dose of plant extract. The DZP has increased this value at 98.72 s. The Figure 3D shows a significant increase ($p<0.001$) of percentage of time spent in the open arms of 7.25% for the negative control group at 40.07% for 50 mg/kg dose of plant extract. The DZP has increased equally this value to 39.86%.

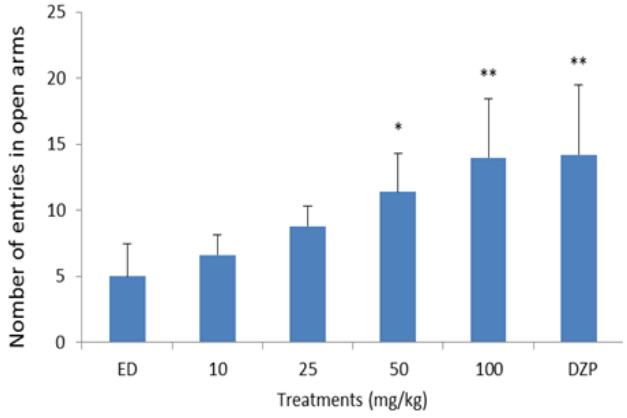

Fig.3A

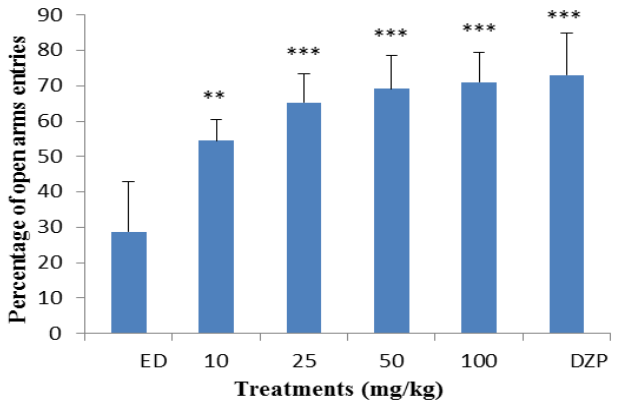

Fig.3B

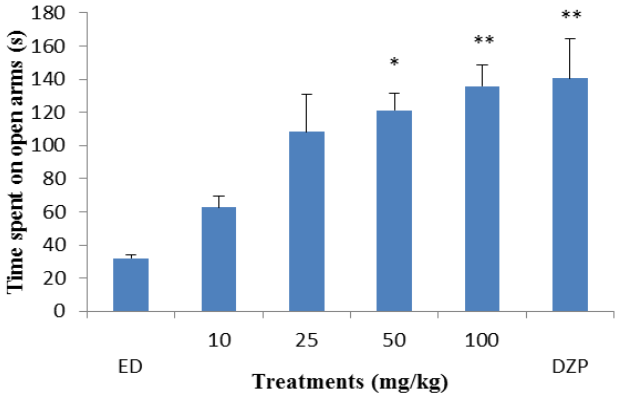

Fig.3C

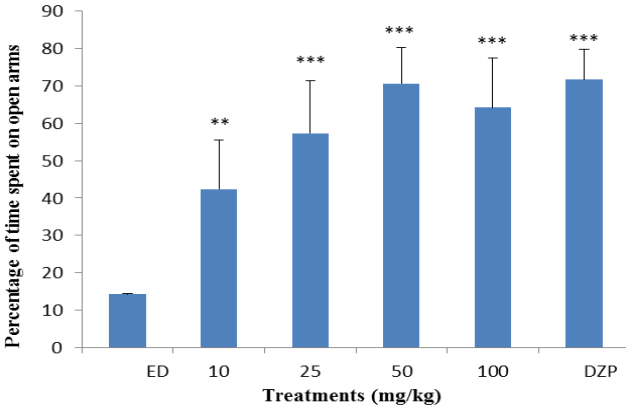

Fig.3D

Figure 3. Effect of single administration of *P. biglobosa* on the parameters of EPM. A (open arms entries); B (percentages of open arms entries); C (Time spent in the open arms); D (percentages of time spent on open arms) Data represented as mean ± S.E.M. P value for groups comparison were obtained by one way ANOVA followed by Tukey's post-hoc test.(*p<0.05); (**p<0.01) and (***p<0.001 vs distilled water treated group. ED negative control treated by distilled water, 10, 25, 50 and 100 (*P. biglobosa* 10, 25, 50 and 100 mg/kg), DZP (diazepam at the dose of 3 mg/kg)

3.3. Effects of Single Administration of Decoction of *P. biglobosa* on Open Field Parameters

Figure 4A shows the time spent in center of open field (OF) from 5 s of negative control group while *P. biglobosa* extract caused a significant increase ($p<0.001$) of this time to 10 s for the mice treated with doses 50 and 100 mg/kg.

The positive control has increased that time also to 10 s. Figure 4B shows a significant decrease ($p<0.05$) of the number of crossing into OF from 14 for negative control group to 11 for the 50 and 100 mg/kg dose of plant extract. The DZP has decreased also this value at 10.

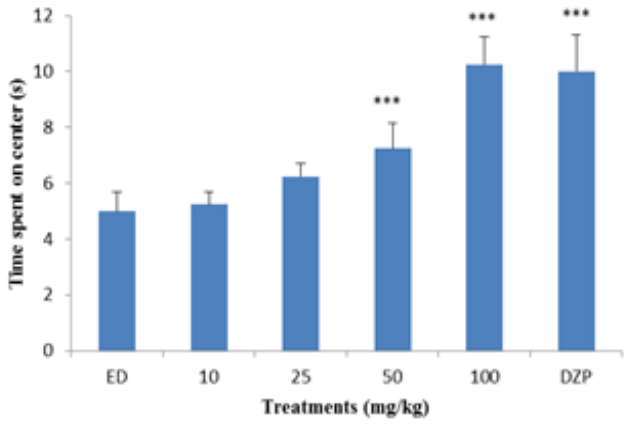

Fig.4A

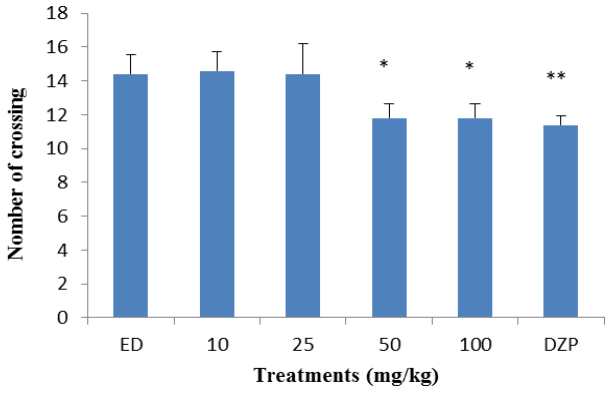

Fig.4B

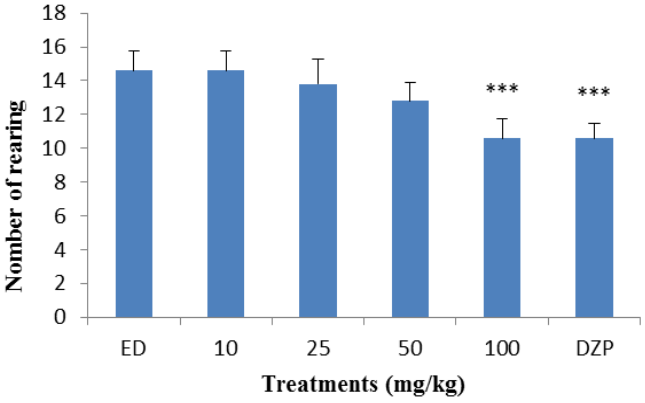

Fig.4C

Figure 4. Involvement of benzodiazepine site of GABA-A receptor complex on the anxiolytic properties of P. biglobosa by using the FG 7142 and RO 151788 on the parameters of EPM. A (time spent on center); B (Number of crossing); C(Number of rearing). Data represented as mean ± s.e.m. P values for groups' comparison were obtained by one way ANOVA followed by Tukey's post-hoc test. *p<0.05; **p<0.01, ***p<0.001 vs ED negative control treated by distilled water, 10; 25; 50 and 100 (*P. biglobosa*, 10; 25; 50 and 100 mg/kg), DZP (diazepam at 0.3 mg/kg dose)

3.4. Study of the Involvement of Benzodiazepine Site of GABA-A Receptor Complex on the Anxiolytic Properties of *P. biglobosa* by Using the FG 7142 and RO 151788

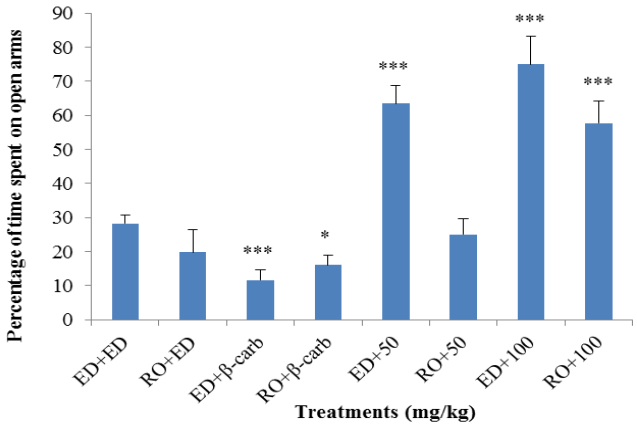

Fig.5A

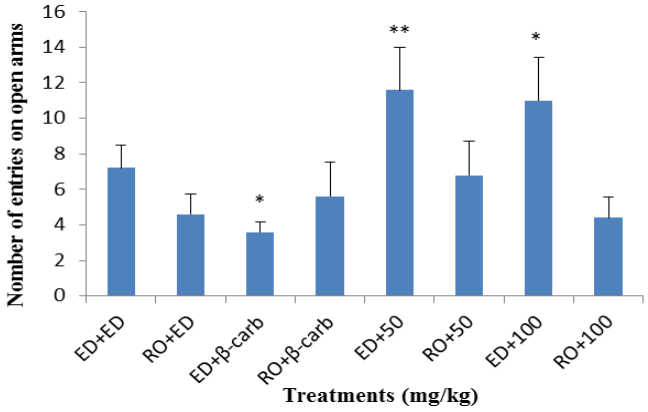

Fig.5B

Figure 5. Involvement of benzodiazepine site of GABA-A receptor complex on the anxiolytic properties of *P. biglobosa* by using the FG 7142 and RO 151788 on the parameters of EPM. A(Percentage of time spent on open arms); B(Number of entries on open arms) Data represented as mean ± s.e.m. P value for groups' comparison were obtained by one way ANOVA followed by Tukey's post-hoc test. *p<0.05; **p<0.01, ***p<0.01 vs ED negative control treated by distilled water, 10; 25; 50 and 100 (*P. biglobosa*, 10; 25; 50 and 100 mg/kg), DZP (diazepam at 2 mg/kg dose), RO (flumazenil 6 mg/kg), β-carb (β-carboline 3mg/kg)

Figure 5A shows the percentage of time spent on the open arms that decreases significantly($p<0.001$) from 30% for the negative control group to the significant value of 11% for the group that received water and FG7142, while this percentage has increased significantly($p<0.001$) at 63.3, 66.6 and 50% for ED+50, ED+100 and RO+100. In Contrast, the percentage of time spent in the closed arms has increased significantly ($p<0.001$) from 71.73% for the negative control group to 83.93% for water and FG7142 group. So that low percentages as 25, 06 and 36.46% are obtained for ED+50 and ED+100 doses. Figure 3B shows that the number of entries into the open arms significantly decreased ($p<0.01$) from 7.2 for negative control group at 3.6 for the group having received water and FG7142. So that this number

increased significantly ($p<0.01$) to 11.6 and 11 to ED+50 and ED+100 doses respectively. However, the number of entries into the closed arms significantly increases ($p<0.01$) from 9.4 for the negative control group at 13 to RO+b-carbo and this number has decreased to 5.6 and then at 4.6 for RO+50 and RO+100 respectively.

3.5. Study of the Involvement of Gaba site of GABA-A Receptor Complex on the Anxiolytic Properties of *P. biglobosa* by Using the Gaboxadol and Bicuculine

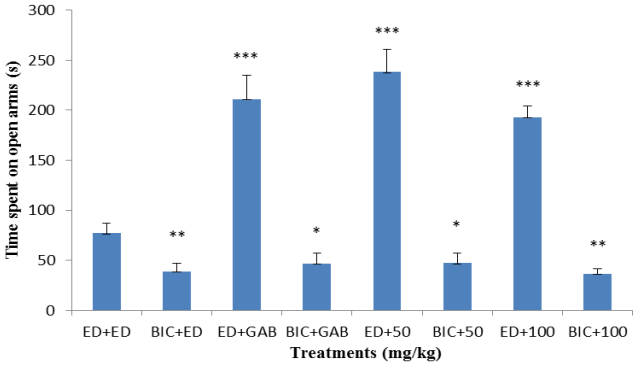

Fig.6A

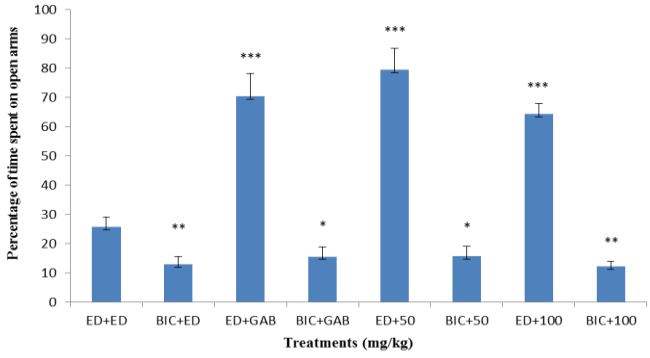

Fig.6B

Figure 6. Involvement of Gaba site of GAbA-A receptor complex on the anxiolytic properties of *P. biglobosa* by using the Gaboxadol and Bicuculine on the parameters of EPM. A (Time spent on open arms); B (Percentages of time spent on open arms). Data represented as mean ± S.E.M. P value for groups' comparison were obtained by one way ANOVA followed by Tukey's post-hoc test. *$p<0.05$; **$p<0.01$, ***$p<0.001$, vs distilled water treated group. ED negative control treated by distilled water, 10; 25; 50 and 100 (*P.biglobosa*, 10; 25; 50 and 100 mg/kg), DZP (diazepam at the dose of 2 mg/kg), GAB (thip or gaboxadol 2 mg/kg), BIC (bicuculine 3 mg/kg)

Figure 6A shows a significant increase($p<0.001$) of the time spent in the open arms from 43.64 s for negative control group to 117.34, 130.35 and 101.93 s for ED+GAB, ED+50 and ED+100 mg/kg groups of the plant extract respectively. So that this time has decreased significantly to 23.48, 28.47,28.67 and 20.83 s for the BIC+ED,BIC+GAB, BIC+50 and BIC+100 respectively. However, there is a significant decrease ($p<0.001$) of this time in the closed arms to 116.44 sec for negative control group at 56.14, 41.95 and 58.73 s for groups ED+GAB, ED+50 and ED+100 mg/kg of the extract of plant respectively while there is significant increase ($p<0.01$) of this time at 134.48, 131.67, 130.12 and 134.24 s for BIC+ED, BIC+ GAB, BIC+50 and BIC+100. The figure 5B shows a significant increase ($p<0.001$) in the percentage of time spent in the open arms of 14.54% for the negative control group; 39.11, 43.45 and 33.97% for ED+GAB, ED+50 and ED+100 mg /kg groups of the plant extract respectively While there is the significant decrease ($p<0.01$) in this percentage to 7.82, 9.49, 9.55 and 6, 94% for BIC+ED, BIC+GAB, BIC+50 and BIC+100 respectively.

4. Discussion

In the study, figure 1 shows a highly significant reduction of mean rectal temperature of 34.03 ℃ for distilled water at 31.81 ℃ and 31.55 ℃ for 100 mg/kg dose and the DZP respectively. This test is based on the fact that a correlation exists between the emotional state and body temperature in animals because it is established by Lecci in 1990 that anxiolytics drugs reduce the body temperature of mice model [17-19]. Figure 2 shows a significant reduction of hyperthermia Induced stress (HIS) ranging from 2.27 ℃ for distilled water at 1.43 ℃ for the dose 100 mg/kg. Phenobarbital (PHO), reference anxiolytic of barbituric reduced the temperature to 1.30 ℃ at a dose of 20 mg/kg [20]. These results suggest that the plant extract like the PHO would have anxiolytics and antipyretic properties [21, 22]. This extract would act on the receptor complex GAbA-A, precisely at the level of barbiturates receptor sites by extending the opening of voltage-dependent chloride channel to produce the anxiolytic effect [21, 22]. The test of EPM is based on the study of the spontaneous behaviour of animals on the paradigm anxiety [23, 24]. Having sensibility to benzodiazepine anxiolytic reference types such as diazepam. This test allows us to access the possible involvement of the benzodiazepine site of the receptor complex GABA-A to the anxiolytic effects of plant extract. Figure3 by A, B, C and D show a number of behavioural parameters with a significant increase of number of entries, the time spent and their percentages in the open arms. While *P. biglobosa* potentiated the number of entries, the time and their percentages in the open arms because enhance of number of entries, the time spent and his percentages and decrease of these parameters demonstrated the effect of plant extract. These results indicate anxiolytic properties of this extract [25]. The properties of *P. bglobosa* may be related to the presence of certain compounds in the extracts as flavonoids, alcaloids, phenolic compounds and tannins that activate barbiturates, benzodiazepines and/or GABA receptors in the GABA-A receptor complex [26, 27] and therefore reflect a decrease anxiety [28, 29]. These results show once more a decrease of anxiety in animals. As the DZP, the extract of the plant would act on the GABA-A receptor complex, precisely at the benzodiazepine receptor sites for reducing the opening time of the voltage-dependent chloride channel [30]. Figure 4A gives the time spent in center of OF that significantly reduces the negative control group to the group that received 50 and 100 mg/kg of plant

extract. Also 4B and C give the number of crossing and number of rearing on OF that significantly reduces the negative control group to the group that received 50 and 100 mg/kg of plant extract, proof that the locomotion and exploratory activity are not important and show anxiolytic effect, so emotional response in animals by the extract of the plant through the GABA-A receptor complex. The β-carboline (FG7142), inverse agonist and flumazenil (RO151788) competitive benzodiazepine antagonist sites act as anxiety factors. According to the results obtained with Figure 5 A and B give percentages of time spent and the number of entries into the open arms that significantly reduces the negative control group and the group that received water and FG7142, while this percentage increases significantly doses ED+50, ED+100 and RO+100 then we have the opposite results for the closed arms, because arising from the antagonism of two standard benzodiazepines sites to reduce or increase anxiety, proof that it would be a mediation by the extract of the plant through the benzodiazepine site of the GABA-A receptor complex. The THIP agonist and competitive antagonist as bicuculline for Gaba receptor sites are used as controls. Figure 6 A and B shown a significant increase of time spent and their percentage in the open arms. The Gaba is the major inhibitory neurotransmitter of the brain substance and it is deeply involved in anxiety. The Inhibition of GABAergic neurotransmission way is known as causing anxiety effect while its stimulation leads to the anxiolytic effect [31, 32]. Drugs that enhance GABA neurotransmission as the gaboxadol reduce the anxiety [15, 14].

5. Conclusions

In summary, the objective of this study was to further examine by SIH and EPM, an involvement of *P. biglobosa* in anxiolytic effect through GABA-A receptor complex. It has observed the significant increase of opened arms entries, time, percentages and the decrease of same parameters in closed arms. Our results had demonstrated that the decoction of plant extract possesses anxiolytic properties as indicated in our mice model; Reason is why this plant has an importance in traditional medicine.

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