IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2022 Vol.:25, Issue:2

Behavioral and Biochemical Studies on Chronic Stress Models in Rats Treated with *Macaranga barteri* Mull. and Arg (Euphorbiaceae) Aqueous Leaf Extract

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Submitted: 27 July 2022
Accepted: 20 August 2022
Published: 30 September 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Depression, FST, OFT, biochemical markers, *Macaranga barteri*, fluoxetine

ABSTRACT

This study was undertaken to evaluate the curative potential of an aqueous leaf extract of *Macaranga barteri* (EAMb) on induced chronic depression in rats. Thus, 5 groups of 6 rats each, including 4 stressed rats' groups with seven (7) different "stressors" applied daily in a random fashion for 28 days and a control group (unstressed rats) were used. Thereafter, depressed rats were treated for 28 days with either distilled water, fluoxetine or EAMb (125 and 500 mg/kg bw). The amounts of food and water consumed, the weight of the rats, the antidepressant activity through the forced swimming time, and the locomotor activity of the rats were evaluated every week. Serum parameters such as blood glucose, triglycerides, AST and ALT on days 0, 14 and 28 were assessed. The results showed a decrease in the amounts of food and water consumed by the depressed rats coupled with body weight loss. The treatment with125 and 500 mg/kg bw of EAMb to depressed rats resulted in a revival of their eating behavior as well as their weight. EAMb was equally observed to significantly reduc the immobility time of depressed rats during forced swimming. On locomotor activity in rats, EAMb did not affect impaired movements. Depressed rats exhibited hyperglycemia, elevations in AST and ALT and hypotriglyceridemia which significantly decreased EAMb intervention. EAMb had a curative effect on depressed rats, similar to that of fluoxetine.

1. INTRODUCTION

Depression is a mental disorder that causes great psychological distress. It affects a large number of biological processes, disrupting various functions such as sleep, appetite and metabolism.[1] It is a common pathology that affects more than 350 million people worldwide. It accounts for 4.3% of the global burden of disease.[2] In Côte d'Ivoire, according to the WHO, depression accounts for approximately 20% of consultations in adult psychiatry services and 10% of cases followed in child psychiatry.[3] Literature-wise, these numbers are underestimated since some patients do not get tested. Several treatments in modern and traditional medicine are available for the management of depression. In modern medicine, drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs), tricyclic antidepressants, Monoamine Oxidase Inhibitors (MAOIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) as well that other antidepressants, including agomelatine and mianserin, are used.[4]However, complaints such as narrow spectrum, undesirable side effects, limited response, high drug prices, lack of mental health care facilities and frequent relapses are often reported during treatment.[5,6] In folk medicine, different parts of certain plants with antidepressant properties are involved in the preparation of various recipes. These plants play a very important role in the prevention and/or care of people with depression.[7] These include, among others, the leaves of *Eclipta alba* (Asteraceae) and the seed of *Ziziphispinosae* (Rhamnaceae).[8,9] intending to contribute to the search for new substances in the field of mental health, this study focused on *Macaranga barteri*, a plant used in traditional medicine to treat various ailments such as gonorrhea, ulcers, stomatitis, amnesia and anxiety.[10] A study of the preventive effects of the aqueous extract of *Macaranga barteri* leaves conducted by Oussou *et al*.[11]showed that this extract prevents depression by acting like clomipramine, a tricyclic antidepressant that uses monoaminergic pathways. Thus, the objective of this work is to study the curative effect of the aqueous extract of the leaves of *M. barteri* on depressed-induced rats.

2. MATERIAL AND METHODS

2.1 Material

2.1.1 Animal

The experiments were carried out on albino rats' strain (*Rattus norvegicus*) whose age and weight varied from 08 to 12 weeks and between 120 and 200 g respectively. These animals

were fed with pellets manufactured by "Ivograin" in Abidjan and tap water *ad libitum*. They were kept in the animal facility of the Laboratory of Physiology, Pharmacology and Pharmacopoeia (LPPP) of the NanguiAbrogoua University (Abidjan, Côte d'Ivoire). The house's daily temperature was around 22°C and a 12-hour dark/light cycle. The various experimental protocols were followed following the protocols for the protection of experimental animals of the European Council of Legislation 87/609/EEC.[12]

2.1.2 Plant

The fresh leaves of *M. barteri* were collected in the forest of NanguiAbrogoua University (Abidjan, Côte d'Ivoire) and identified by botanists from the same university. They were authenticated at the National Floristic Center of the Félix Houphouet-Boigny University (Abidjan, Côte d'Ivoire) where a sample had been deposited, identified and preserved in the national herbarium under the number 14735 on April 6, 1979.

2.1.3 Drug

Fluoxetine (Merinal®; Algeria) was used in this work.

2.2 Methods

2.2.1 Preparation of the aqueous extract of the leaves of *Macaranga barteri*

The extraction method adopted was done by Zirihi *et al*.[13]Briefly, *M. barteri* leaves were cut into small pieces and dried in the Laboratory for two weeks. These small pieces were ground using an electric grinder. Thereafter, 100 g of these leaves powder were decocted in one-liter distilled water for 15 min. The decoction obtained was filtered on hydrophilic cotton and thereafter on Whatman n˚1 filter paper. The filtrate was dried using an oven at 45°C for 48 hours. 14.6 grams of powder obtained represented the aqueous extract of *M. barteri* leaves (AEMb).

2.2.2 Method of the induction of depression in rats

The methods used to induce depression in rats were those described by Wu *et al*.[14] 42 rats were divided into six batches of seven rats each. five batches underwent seven "stressors" for four weeks. Each "stressor" is randomly selected only once a week for four weeks. These "stressors" consisted of (1) depriving the rats of water for 24 hours; (2) starving the animals for 24 hours; (3) pinch the tails of the rats for 90s; (4) leave the rats with their wet litter for 24

hours, including 100 g of litter for 200 mL of water; (5) swimming the rats in water heated to 42°C for five minutes; (6) swimming the rats in ice water at 4°C for five minutes; (7) tilt the rat cages at an angle of 45° from the horizontal for 24 h. At the end of the four weeks of stress suffered by the animals, the forced swim (FST) and open field (OFT) tests were carried out to assess their states of depression. Stressed rats that have a statistically longer immobility time than unstressed rats were considered depressed and retained for the evaluation of the curative effect of the aqueous extract of *M. barteri*.

2.2.3 Experimental protocol for the Forced Swimming Test (FST)

The method used was described by Porsolt *et al*.[15] The forced swimming test or FST was undertaken in rats in two phases, the pre-test, and the test, separated by an interval of 24 hours. To this end, the experimental rats (healthy and depressed) underwent a pre-test 24 hours before the test itself. This pre-test consisted of forcing the rats to swim individually for 15 minutes in an opened cylindrical container (size: 30 x 25), containing water up to 20 cm from the bottom of the container whose temperature was 25 ± 1°C. The rats were removed from the water and then dried with a clean, dry towel before being returned in their cages. The water used for swimming is renewed after the passage of each rat to maintain its cleanliness.

The forced swimming test was performed on the same animals and under the same conditions as the pre-test but this time the swimming time was six minutes. When the animals cease all movement except that necessary for their survival i.e. when the animals are passively floating in the water in a slightly hunched but upright position with the nose just above the surface, they are considered motionless. The immobility time was determined from the 2nd minute over 6 minutes. Each exercise was recorded with a camera (kodak, Japan).

2.2.4 Experimental protocol of the locomotor activity test or Open Field Test (OFT)

The measurement of rats' locomotor activities was implemented in a space called an "open field". This field was a wooden box (72×72×36 cm) with the floor divided into 16 equal squares using a marker.[16,17]Each healthy or depressed animal was placed in the left corner of the cage and its movements were recorded for 6 minutes using a camera (kodak, Japan).[18] Between sessions, the cage was cleaned with 10% alcohol to eliminate odors, and waste and to avoid the possible transmission of stress from one animal to another. The camera was then connected to a computer for the exploitation of the video. The number of lines crossed by the

rat with its four legs and the number of vertical positions i.e. when the rat is standing on the hind legs were determined to assess its depressive state and also to dissociate the antidepressant activity of stimulant activity.

2.2.5 Effects of different treatments on depressed rats

The different doses of the extract and fluoxetine were prepared extemporaneously by dissolving the powder in distilled water and administered daily by oral route for 28 days to the rats divided into different groups.

Group I: Non-depressed rats were orally administered with distilled water (1 mL/100 g of rat).

Group II: Depressed rats were orally administered with distilled water (1 mL/100 g of rat).

Group III: Depressed rats were orally administered with 125 mg/kg bw of EAMb.

Group IV: Depressed rats were orally administered with 500 mg/kg bw of EAMb.

Groups V: Depressed rats were orally administered with 10 mg/kg bw of fluoxetine (standard drug).

The amounts of food and water consumed by the rats were daily measured. The forced swimming time, the locomotor activity and the body weight of the rats were assessed every week. Blood samples were taken at the beginning of the experiment, on days 14 and 28 from the retro-orbital sinus under anesthesia according to the experimental protocol used by Weiss *et al*.[19] and modified by Descat.[20] The blood samples collected in the tubes containing potassium oxalate and sodium fluoride were centrifuged at 3000 rpm for 5 min and the plasma obtained was used for blood glucose determination and those in the dry tubes were centrifuged at 3000 rpm for 5 min for the determination of some biochemical parameters such as transaminases and triglycerides by enzymatic methods using a semi-automated ROBONIK spectrophotometer (India).

2.3 Data analysis

Statistical analysis of the data was performed using GraphPad Prism 5.01 (San Diego, CA). The results were expressed as a mean followed by the standard error on the mean (M ± SEM). The student t-test and the Tukey-Kramer post-test were used for averaging. The threshold of significance was set at $p < 0.05$.

3. RESULTS

3.1 Effects of different treatments on anthropometric parameters of depressed rats

3.1.1 Effect of different treatments on the food consumption

Figure 1 presented the results of the food consumption by the different groups of rats. It indicated that the non-depressed animals (Group I) had an average food consumption of 199 ± 1.43 g/day. This food consumption remained constant throughout the experiment (28 days). On the other hand, the daily food consumption in depressed rats was significantly ($p<0.001$) lowered in the first week of the experiment compared to that of group I. These values were respectively 93 ± 6.25; 89.3 ± 5.30; 67.5 ± 8.61 and 101 ± 4.44 g/day respectively for batches II, III, IV and V.

On days 7, 14 and 21, no significant difference ($p>0.05$) was observed between the daily food consumption in depressed rats treated with the total aqueous extract of *M. barteri* leaves at doses of 125 and 500 mg/kg bw (batch IV and V), as well as those treated with 10 mg/kg bw of fluoxetine (batch III) compared to the batch of depressed rats treated with distilled water (batch II). However, after 28 days, the depressed rats treated with the total aqueous extract of the leaves of *M. barteri* at doses of 125 and 500 mg/kg bw and those treated with fluoxetine 10 mg/kg bw increased by significantly ($p<0.01$) their food consumption compared to depressed rats treated with distilled water (154 ± 5.47 g/day) to reach 195 ± 2.58; 196 ± 2.71 and 197 ± 2.47 g/day, respectively. The results showed that the rats that received the various treatments found a level of consumption similar to that of the non-depressed rats.

3.1.2 Effect of different treatments on water consumption

The results of the quantity of water consumed by different groups of rats were presented in Figure **2**. They showed that the non-depressed rats (Group I) consumed approximately 400 mL/day while that of depressed rats was 207 ± 11.1 mL/day. The depressed rats treated with the total aqueous extract of *M. barteri*, at doses of 125 and 500 mg/kg bw (Groups III and IV) and those treated with fluoxetine (Group V) resumed drinking water unlike those of group II (untreated depressed rats).

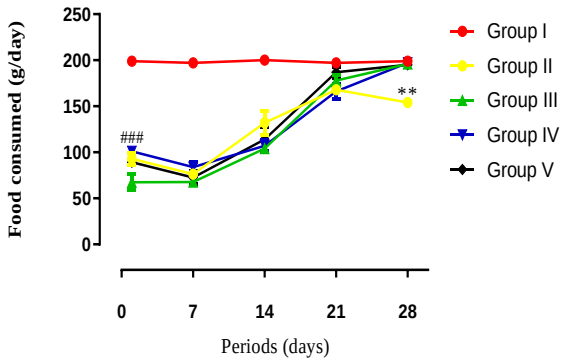

Fig. 1: Effect of the total aqueous extract of *M. barteri* on the amount of the food consumed by the rats

p<0.001 significant difference between batch I and batches II, III, IV and V at the same period.

** *p*<0,01 p<0.01 significant difference was observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract and Fluoxetine (Batches III, IV and V) at the same period.

The batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III and IV**: batches of depressed rats treated with respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

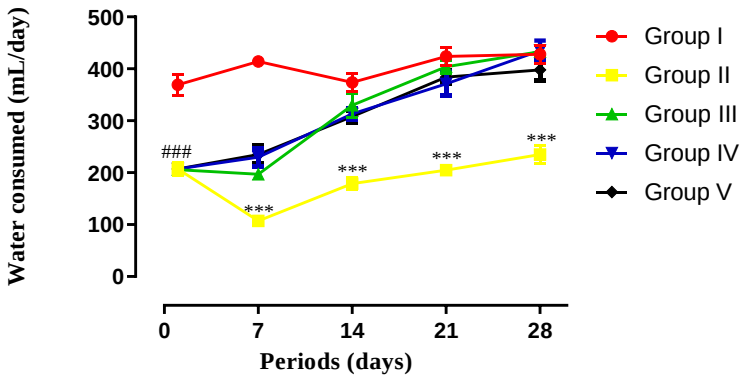

Fig. 2: Effect of the total aqueous extract of *M. barteri* on the quantity of water consumed by the rats

p<0.001 significant difference between batch I and batch II, III, IV and V at the same period.

**p<0.01; *** p<0.001 significant differences were observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract and Fluoxetine (Batches III, IV and V) at the same period.

Batch I: a batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III** and **IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: a batch of depressed rats treated with fluoxetine.

3.1.3 Effect of different treatments on the rats' body weight

The body weight of the animals in batch I (non-depressed rats) increased gradually throughout the experiment. Indeed, the weight which was 182.0 ± 7.24 g at the beginning (day 0) increased to reach 198.0 ± 5.56 g at the end of the experiment.

As for the animals of batches II, III, IV and V, i.e. those which were depressed, their weights were respectively 130 ± 8.47 g, 114 ± 8.99 g, 118 ± 9.3 g, and 104 ± 4.79 g, on day 0. In these groups of rats, untreated ones (Group II) showed a significant decrease (p<0.001) in their weight compared to the non-depressed rats (Batch I). Indeed, this batch of rats weighted 98.8 ± 22.70 g, on the 28th day against 198.0 ± 5.56 g for Batch I, for the same period.

The treatment of rats with *M. barteri* extract and fluoxetine promoted a gradual increase in the weight of depressed rats (lots III, IV and V) compared to those of the untreated depressed rats (Group II). This increase was significant (p<0.05, p<0.01 p<0.001) from the 21st day. At the end of the experiment, the treated rats regained weights similar to those of undepressed rats (**Figure 3**).

3.2 Effect of AEMb on rats immobility time during the FST

Table 1 showed the results of the effect of AEMb on the immobility time of depressed rats during the forced swimming test. These results showed that the initial immobility times (D_0) of the rats of groups II, III IV and V were significantly higher (p<0.001) compared to those of the non-depressed rats (Group I). These values were 233±2.33 s (Group II); 234±1.78s (Group III); 238 ± 1.2 s (Group IV) and 236 ± 1.96 s (Group V) against 158 ± 7.5 s for Group I. These results implied that the rats of groups II, III IV and V were depressed at the very

beginning of the experiment. The immobility time of the untreated depressed rats (Group II) remained significantly increased ($p<0.05$) compared to that of the non-depressed rats (Group I) throughout the experiment. 125 and 500 mg/kg bw of AEMb and fluoxetine (10 mg/kg bw) significantly decreased ($p<0.05$ and $p<0.001$) the immobility time of depressed rats compared to untreated depressed rats from the 7th day till the 28th-day treatment versus untreated depressed rats (Group II). The immobility time of the rats treated with the AEMb reached 160 ± 23.4 and 150 ± 11.3 seconds against 171 ± 7.45 (untreated depressed group of rats) on the 28th day.

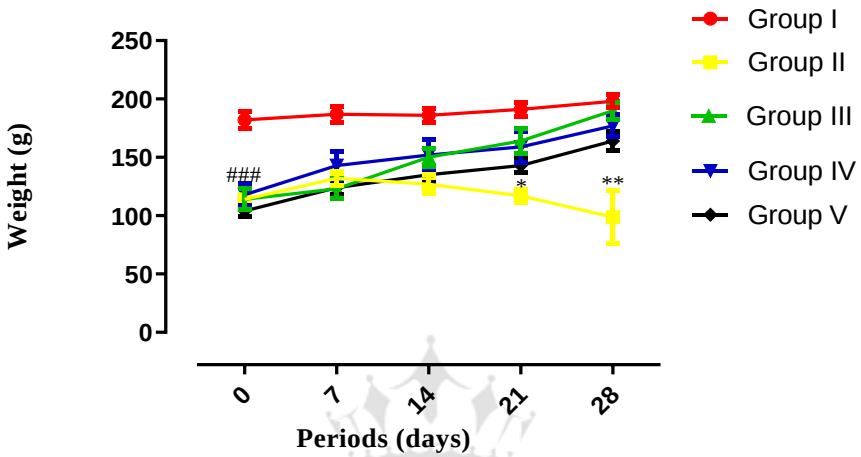

Fig. 3: Effect of the total aqueous extract of *M. barteri* on the growth of the rats

$p<0.001$ significant difference between batch I and batch II, III, IV and V at the same period.

*$p<0.01$; ** $p<0.001$ significant differences were observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract and Fluoxetine (Batches III, IV and V) at the same period.

Batch I: batch of non-depressed and untreated rats; **Batch II**: a batch of depressed rats without treatment; **Batches III** and **IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

Table 1 : Effect of the total aqueous extract of *M. barteri* on the immobility time of rats during forced swimming

			Periods (days)		
Groups	**D_0**	**D_7**	**D_{14}**	**D_{21}**	**D_{28}**
Immobility time(s)					
I	158 ± 7.5	168 ± 9.05	178 ± 6.61	170 ± 16.7	171 ± 7.45
II	233 ± 2.33$^{###}$	232 ± 10.6$^{###}$	228 ± 10.0$^{#}$	232 ± 2.23$^{##}$	228 ± 10$^{##}$
III	234 ± 1.78$^{###}$	196 ± 21.3	192 ± 15.1	171 ± 26.9*	160 ± 23.4**
IV	238 ± 1.2$^{###}$	212 ± 8.63	209 ± 6.27	185 ± 4.86	150 ± 11.3***
V	236 ± 1.96$^{###}$	180 ± 5.91*	157 ± 6.49***	132 ± 4.55***	118 ± 7.37***

$^{#}p<0.05$;$^{##}$ $p<0.01$ $^{###}p<0.001$ significant difference observed between the batch of non-depressed rats and the batches of untreated depressed rats at the same period.

* $p<0.05$; ** $p<0.01$; *** $p<0.001$ significant difference was observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract and Fluoxetine (Batches III, IV and V) at the same period.

Batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III** and **IV**: batches of depressed rats treated with respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

3.3 Effects of AEMb on rats locomotor activity in the OFT

The results of the effects of the AEMb on the number of lines crossed and the number of standing positions by the rats during the open field test were recorded in **table 2 and 3** respectively. The rats of the control group (non-depressed rats) crossed 38.9 ± 6.33 lines and stood 11.4±1.94 times during the 6 minutes OFT. The values of these parameters did not change significantly with time. The number of lines crossed and the frequency of standing position by the rats were significantly lowered in depressed rats (Groups II, III, IV and V)

compared to those of the control group. There were respectively 13.1 ± 3.31; 10.0 ± 2.53; 12.8 ± 0.86 and 12.4±0.57 lines crossed. As for the frequency of standing position, values ranged from 3.43 ± 1.84; 3.00 ± 2.76; 3.2 ± 0.37 and 3.14 ± 0.40 times. Neither AEMb, norfluoxetine had a significant effect on the movement of the rats. Indeed, statistical analysis revealed no significant difference ($p>0.05$) between the movements of untreated depressed rats and those treated with *M. barteri* extract and fluoxetine. This implied that *M. barteri* extract and fluoxetine did not possess stimulating effects.

3.4 Effect of AEMb on the rats biochemical parameters

3.4.1 Effect of AEMb on the rats blood sugar levels

The results of the effect of AEMb on the rats' glucose levels were presented in **figure 4**. They showed that the glycemia of the non-depressed rats (group I) was 0.55 ± 0.02 g/L on day 0. This value didn't change significantly throughout the experimentation. The stress increased significantly ($p<0.001$) the glucose levels of rats to 1.01 ± 0.06; 0.90 ± 0.07; 0.90 ± 0.03 and 0.83 ± 0.04 g/L respectively for batches II, III, IV and V. The glucose levels remained constantly high in untreated depressed rats (Group II) till the end of the experimentation.

The treatment of the depressed rats with 125 and 500 mg/kg bw of AEMb as well as those treated with fluoxetine (10 mg/kg bw) significantly reduced ($p<0.01$) their sugar levels on days 14 and 28 compared to the depressed rats that received no treatment.

Table 2: Effect of total aqueous extract of *M. barteri* on the number of lines crossed by the rats in the open field

			Periods (days)		
Groups	**D_0**	**D_7**	**D_{14}**	**D_{21}**	**D_{28}**
I	38.9 ± 6.33	32.0 ± 5.90	37.6 ± 4.81	34.3 ± 7.89	36.6 ± 6.24
II	13.1 ± 3.31$^{###}$	11.4 ± 3.55	11.1 ± 3.06	13.5 ± 1.80	11.8 ± 1.89
III	10.0 ± 2.53$^{###}$	10.75 ± 2.84	11.25 ± 2.66	10.8 ± 3.85	11.5 ± 3.84
IV	12.8 ± 0.86$^{###}$	12.40 ± 0.24	11.40 ± 0.92	12.80 ± 2.44	11.2 ± 4.97
V	12.4 ± 0.57$^{###}$	12.00 ± 0.36	11.67 ± 0.49	12.00 ± 0.33	11.67 ± 4.25

$^{###}p<0.001$ significant difference was observed between the batch of non-depressed rats and the batches of untreated depressed rats during the same period. **Batch I**: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batch III** and **IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

Table 3: Effect of total aqueous extract of *M. barteri* on the number of vertical positions of the rats in the open field

			Periods (days)		
Groups	**D_0**	**D_7**	**D_{14}**	**D_{21}**	**D_{28}**
I	11.4 ± 1.94	10.3 ± 0.68	9 ± 0.9	11.1 ± 0.63	10.1 ± 0.85
II	3.43 ± 1.84$^{###}$	1.14 ±0.26$^{###}$	1.29 ± 0.52$^{###}$	1.28 ± 0.58$^{###}$	2.6 ± 1.09$^{###}$
III	3.00 ± 2.76$^{###}$	2.2 ± 1.46	1.75 ± 0.75	1.76 ± 1.76	3.75 ± 2.25
IV	3.2 ± 0.37$^{###}$	2.2 ±1.46	1.2 ± 0.49	1.4 ± 0.51	3.2 ± 1.46
V	3.14 ± 0.40$^{###}$	1.5 ± 0.34	1.67 ± 0.7	1.83 ± 0.47	2.5 ± 0.5

$^{###}p<0.001$ significant difference was observed between the batch of non-depressed rats and the batches of untreated depressed rats at the same period. **Batch I**: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III** and **IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

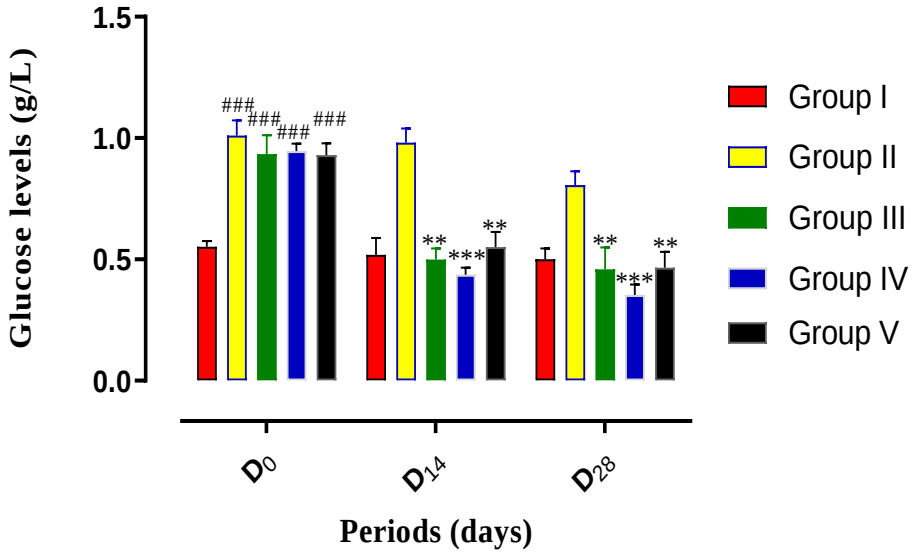

Fig. 4: Effect of the total aqueous extract of *M. barteri* on the rats' glycemia

$^{###}p<0.001$significant difference observed between the batch of non-depressed rats and those of untreated depressed rats at the same period.

** $p<0.01$; *** $p<0.001$ significant difference observed between the batch of untreated depressed rats (Group II) and the batches of depressed rats treated with the extract or fluoxetine. (Groups III, IV and V) at the same period.

Batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III and IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

3.4.2 Effect of AEMb on rats triglycerides levels

Figure 5 showed the results of the effects of AEMb on the triglycerides levels of the rats. They showed a level of 121.0 ± 13.10 mg/dL for this parameter in the non-depressed rats (Group I) varying very slightly during the 28 days of experimentation. The initial triglyceride levels (D_0) of the depressed rats (Groups II, III IV and V) were significantly low ($p<0.001$) compared to that of the non-depressed ones (Group I). They were respectively 73.0 ± 6.52; 69.6±15.00; 71.8 ± 7.19 and 74.3 ± 11.00 mg/dL for groups II, III, IV and V against 121.0 ± 13.10 mg/dL for group I. The triglycerides levels of untreated depressed rats (Group II) that is 73.0 ± 6.52 mg/dL remained significantly reduced ($p<0.001$) compared to non-depressed rats (Group I) throughout the experiment. During the 28 days treatment, no significant variation ($p>0.05$) was observed in depressed rats treated with fluoxetine (10 mg/kg bw) compared to untreated depressed rats. Fluoxetine did not restore the rats' triglyceride levels lowered due to depression. However, a significant increase ($p<0.01$) of this parameter was observed after 28 days of treatment of the depressed rats with the doses of EAMb (Groups III and IV) compared to the group II. Indeed, the triglycerides levels which were 69.6 ± 15.00 and 71.8 ± 7.19 mg/dL, on day 0 increased and reached 115 ± 13.5 and 117 ± 12 respectively, on day 28.

3.4.3 Effect of AEMb on the rats alanine-aminotransferase (ALT) activities

The results indicated that the ALT activity of the control rats (non-depressed rats) was 51.1 ± 5.48 U/L. The stressors induced a significant increase ($p<0.001$) of the activity of ALT in stressed rats compared to that of the non-depressed rats to 103 ± 5.34 U/L which remained significantly increased ($p<0.001$) throughout the experiment. The administration of either AEMb or fluoxetine to depressed rats had no significant effect ($p>0.05$) on their ALT

activity. The total aqueous extract of *M. barteri* leaves (125 and 500 mg/kg bw) and fluoxetine (10 mg/kg bw), therefore, did not reduce the ALT activity of depressed rats during the 28 days of treatment (**Figure 6**).

3.4.4 Effect of AEMb on rats aspartate-aminotransferase (AST) activities

The results showed that the AST activity of the control rats (non-depressed rats) was 174 ± 5.12 U/L. The stressors induced a significant increase ($p<0.001$) of the activity of AST in stressed rats compared to that of the non-depressed rats to 255 ± 12.7 U/L which remained significantly increased ($p<0.001$) throughout the experiment. The treatments of the stressed rats with AEMb or fluoxetine induced a significant decrease ($p <0.05$) of the AST activities compared to the batch of untreated depressed rats (Group II) (**Figure 7**).

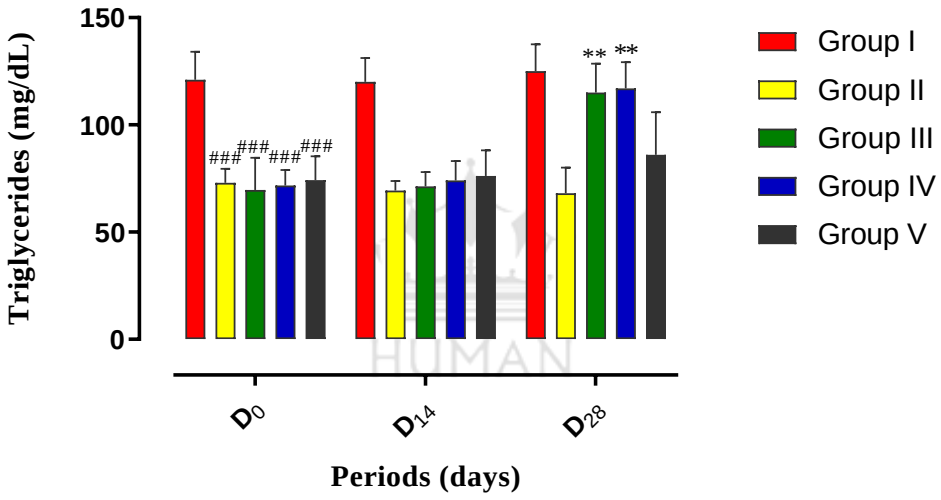

Fig. 5: Effect of the total aqueous extract of *M. barteri* on the level of triglycerides in the rats

$^{###}p<0.001$ significant difference was observed between the batch of non-depressed rats and the batches of untreated depressed rats at the same period.

** $p<0,01$ significant difference observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract (Batches III and IV) at the same period.

Batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III and IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

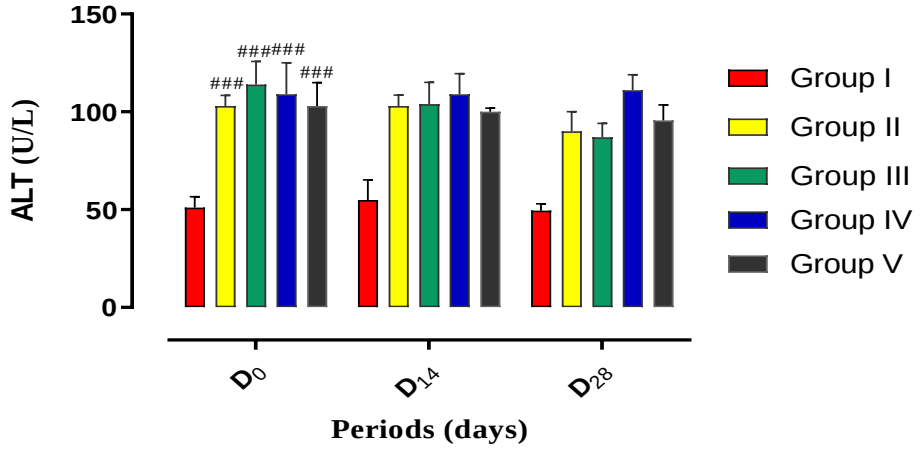

Fig. 6: Effect of the total aqueous extract of *M. barteri* on alanine-aminotransferase (ALT) activities in the rats

###$p<0.001$ significant difference was observed between the batch of non-depressed rats (Group I) and the batch of untreated depressed rats (Group 2), at the same period.

$p>0.05$ no significant difference was observed between the batch of untreated depressed rats (Group II) and the batches of depressed rats treated with the extract or Fluoxetine (Batches III, IV and V).

Batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III and IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V:** batch of depressed rats treated with fluoxetine.

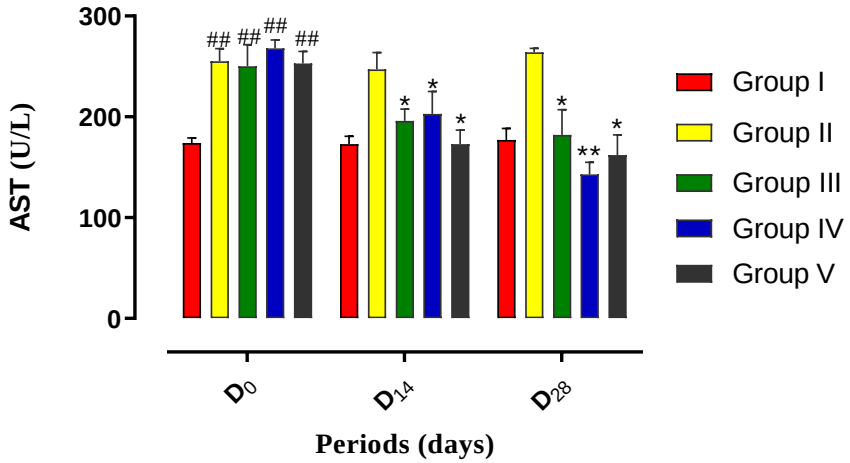

Fig. 7: Effect of the total aqueous extract of *M. barteri* on aspartate aminotransferase (AST) activities in rats

$^{\#\#}p<0.01$ significant difference observed between the batch of non-depressed rats (Group I) and the batches of untreated depressed rats (Group II), at the same period.

* $p<0.05$; ** $p<0.01$ significant difference observed between the batch of untreated depressed rats (Batch II) and the batches of depressed rats treated with the extract (Batches III; IV and V), at the same period.

Batch I: batch of non-depressed and untreated rats; **Batch II**: batch of depressed rats without treatment; **Batches III and IV**: groups of depressed rats treated with the respective doses of 125 and 500 mg/kg bw of EAMb; **Batch V**: batch of depressed rats treated with fluoxetine.

4. DISCUSSION

The present study was undertaken to evaluate the curative effect of the total aqueous extract of *Macaranga barteri* leaves (EAMb) on stressors-induced depression in rats.

The immobility time of the rats subjected to stress for 28 days increased significantly compared to non-depressed controls. The repeated administration of the total aqueous extract of *M. barteri* leaves significantly reduced the immobility time of depressed rats during the forced swimming test. This decrease could be due to a restoration of the proper functioning of neurotransmitters, especially serotonin. Indeed, EAMb had antidepressant effects, similar to those of fluoxetine as shown in the results. Fluoxetine is a known antidepressant that acts on the serotonin transporter site to inhibit the reuptake of this neur mediators, thus increasing its concentration in the synaptic cleft.[21,22] The effects of *M. barteri* are similar to those of *Foeniculum vulgare* according to studies conducted by Glory *et al*.[23] Indeed, these researchers showed that the dose of 200 mg/kg bw of the ethanolic extract of *F. vulgare* and the 10 mg/kg bw dose of fluoxetine induced a significant reduction in the immobility time in non-depressed rats. Locomotor activity is also important for the diagnosis of depression in rats according to Pan *etal*.[24] The number of lines crossed by the rats and the frequency of upright position is valued indices in the locomotor activity test in this study. After 28 days of treatment of the rat stress, the results obtained during the open field test showed that these two parameters of all the animals decreased significantly compared to the unstressed control rats. The significant reduction of this activity shows a depressed state of the animals according to the latter. However, some substances decrease the immobility time of rats during the forced swim test, but are not antidepressants. These are, for example, drugs that stimulate the central nervous system, such as cocaine or amphetamines, which in addition to reducing

the time of immobility of rats increase their mobility.[15] This is why it is imperative to evaluate the locomotor activity in order to dissociate the antidepressant activity from the stimulating activity. After the treatment of depressed rats with the total aqueous extract of *M. barteri* leaves at doses of 125 and 500 mg/kg bw and fluoxetine (10 mg/kg bw) for 28 days, the number of lines crossed did not varied significantly from that of untreated depressed rats. Similarly, no significant variation is observed on the frequency of the upright position. This, therefore, reveals that this extract does not have a stimulating effect but has a real curative power for depression in rats rather. This result is similar to those obtained by Wang *et al*.[9] Indeed, these authors showed that the antidepressant activities of the extracts of *Ziziphispinosae* and *Hypericum Perforatum* do not have stimulating effects due to their inactivity on the locomotion of rats. According to Kannur *et al*.[25], depression causes an imbalance of some biochemical parameters. Serum blood glucose, triglyceride, AST and ALT analyzes were undertaken to assess the impact of stress and the treatments given to the rats on the parameters mentioned above.

The results showed a significant increase in the blood sugar levels of the rats subjected to the stressors. This could be due to degradation of liver and muscle glycogen during stress. This result is supported by the results of the works of Knol*et al*.[26] and Golden *et al*. [27]who showed that depression increases the risk of developing type 2 diabetes and that there is also a bidirectional link between depression and type 2 diabetes. The treatment of depressed rats with the total aqueous extract of *M. barteri* leaves and fluoxetine induced a significant reduction of the blood sugar levels. The reduction of blood glucose by the extract could be done with a storage of glycogen in the liver and the muscles. These results are consistent with those obtained by Kothiyal and Ratan.[28] These two researchers showed that the aqueous extract of *Fagopyrum esculentum*, as well as diazepam, significantly reduce the high level of glycemia in stressed rats. As for triglycerides, their levels decrease during the depression process. This decrease could reveal an inhibition of food intake caused by chronic exposure to stressors.[29,30] The administration of the AEMb and fluoxetine significantly increased serum triglyceride levels. This could be due to the regulation of the functioning of the structures of the central nervous system whose actions at the peripheral level allow the reuse of glucose as an energy source, hence a reduction in the metabolism of triglycerides. Jian *et al*.[31] showed the opposite effect of the aqueous extract of Banxia-houpu on triglycerides. Indeed, these showed that chronic stress increased the level of triglycerides but the administration of the aqueous extract of Banxia-houpu significantly reduced the rate of this parameter.The results

showed disturbances in the activity of transaminases characterized by an increase in ALT and AST levels after one month of the rats' stress AST and ALT are sensitive markers in liver damage. They are found in the cytoplasm of hepatocellular cells, so their high levels in the blood indicate liver damage.[32] The depression induced by the various "stressors" applied chronically leads to liver damage by influencing the metabolism of hepatic phospholipid, glycerophospholipid and also the biosynthesis of bile acid (Hong-mei*et al*., 2016).[33] This promotes the accumulation of lesions in the liver which cause a weakening followed by the destruction of liver cells and tissues. The AST and ALT of depressed rats are subsequently dumped into the bloodstream; which would explain their increase.[34] The administration of doses of AEMb and fluoxetine causes a significant decrease in AST activities.

These results suggest that EAMb acts on the cascade of reactions involved by chronic stress in the induction of liver damage. These results are similar to those of Desai *et al*.[35] Indeed, they showed that the extract of *Hibiscus rosa-sinensis*, as well as cyanidin, significantly reduce the elevated AST levels of depressed rats.

5. CONCLUSION

The effects of the aqueous extract of *Macaranga barteri* (AEMb) were studied on depressed rat behavior and biochemical parameters. The results showed that AEMb restores these functions with an action similar to that of fluoxetine. Like fluoxetine, AEMb could be used in the treatment of depression.

ACKNOWLEDGEMENT

The authors are thankful to the Physiology, Pharmacology and Pharmacopoeia Laboratory staff for their technical help.

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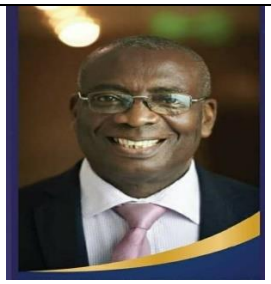	EHILE Ehouan Etienne Pharmacology and Pharmacopoeia, Department of Natural Sciences, Nangui Abrogoua University, Abidjan, Côte d'Ivoire