Anticonvulsant and Antidepressant effects of *Daniellia oliveri* (Rolfe) Hutch and Dalz Aqueous extract in Pilocarpine Model of Temporal Lobe Epilepsy in mice

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ABSTRACT

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| The objective of this study is to evaluate the anticonvulsant and of *Daniellia oliveri* in pilocarpine model of temporal lobe epilepsy. *Muss musculus* Swiss mice were divided into 7 groups of 6 animals. They were treated with distilled water (10 mL/kg, p.o.) for the negative control group; *Daniellia oliveri* aqueous extract (21.21, 53.03, 106.06, and 221.12, mg/kg, *per os*) for the test groups; sodium valproate (300 mg/kg, intraperitoneally) for the positive control group; and distilled water (10 mL/kg; *per os*) for the sham group; respectively. One hour after the administration of different treatments to mice, status epilepticus was induced by injection of a single dose of pilocarpine (360 mg/kg). During the second day of experiment, mice were injected with picrotoxin 1 mg/kg to induced convulsions one hour after the treatment of mice. The antidepressant effect of the plant extract was assessed on the seventh day by using the forced swim test, followed by the open field test. GABA and GABA-transaminase activity were estimated in the hippocampus on mice. *Daniellia oliveri* (106.06, and 221.12, mg/kg) significantly increased the latency time to status epilepticus and the seizures, decreased the number and duration of seizures compared to negative control groups of mice. During forced swimming, *Daniellia oliveri* significantly increased the duration of climbing, the duration of swimming and decreased the duration of immobility. In addition, it restored behavioural parameters in the open field test. It also increased in GABA and a significant decreased in GABA-transaminase activity. These results suggest that *Daniellia oliveri* extracthas anticonvulsant and antidepressant effects. These mechanisms could be done by the improvement of GABAergique axis, justifying its use by the traditional healers as an alternative therapy for the management of epilepsy and depression. |

*Keywords: Daniellia oliveri, epileptogenesis, pilocarpine, status epilepticus, convulsions, depression.*

1. INTRODUCTION

Among the most chronic diseases affecting humanity are diseases of the central nervous system, notably epilepsy (Schröder et *al.,* 2014). Considered one of the most common and widespread neurological disorders in the human population (Erkeç and Arihan, 2015; Xia et *al*., 2018), it is defined as a brain disease characterised by abnormal electrical activity causing seizures or unusual behaviour, sensations and sometimes loss of consciousness (WHO, 2001). Mesial temporal lobe epilepsy (TLE) is considered to be the most severe, since the seizures that accompany it in 70% of cases are refractory to most anti-epileptic drugs (Lignelet, 2011). Seizures result from an imbalance between excitatory and inhibitory activities in the brain resulting from excessive glutamatergic excitation or low GABAergic inhibition (Hui Yin et *al*., 2013). TLE is similarly materialised through its comorbidities. Nearly 65% of patients with TLE have cognitive problems, mainly memory problems or depression (Faure, 2014; Oddo et *al.,* 2003). Suicide rates are reported to be much higher than in the general population (Kanner, 2014). Depression can increase the risk of developing unprovoked seizures six fold. In addition, it can increase the risk of treatment resistance, surgical failures and side effects (Kanner, 2009). The identification of suicide as a major cause of death in people with epilepsy demonstrates the severity of depression in these individuals. In subjects with brain lesions of infectious, traumatic, ischaemic, congenital, haemorrhagic and convulsive origin, there is no treatment to prevent or inhibit the development of epilepsy or epileptogenesis (Pitkänen and Kubova, 2004; Temkin, 2009). Furthermore, people are unable to find anti-epileptic drugs capable of treating both epilepsy and underlying illnesses such as depression. The only drug treatments available target symptoms rather than the less important causes of epilepsy (Boštjan et *al.,* 2012; Brookes et *al.,* 2004, Sridharamurthy et *al.,* 2013). Given the limitations in the use of available anti-epileptic drugs and the severity of the underlying diseases of epilepsy, there is a need to develop other drugs with fewer side effects, particularly those that treat the underlying disease of epileptogenesis (Ngo Bum et *al.,* 2009; Taiwe et *al.,* 2015; WHO, 2001; Kamalraj, 2011; Erkeç and Arihan, 2015). Phytotherapy is therefore an appropriate solution, since in Africa, it plays an important role in the management of illnesses, and almost 80% of the world's population uses medicinal plants due to their real effectiveness (Akerele, 1988; Dialloet *al.,* 2010).

*Daniellia oliveri* is a plant with numerous curative effects, including beneficial effects on gastrointestinal disorders (Ahmadu et *al.,* 2003; Malagas, 1992) and amnesia (Beppe et *al*., 2020). It is also used to heal tumours, vaginal fistulas, abscesses, diabetes (Jegede et *al.,* 2006), epilepsy, migraines, anxiety, schizophrenia and headaches (Ngo Bum et *al.,* 2011), and also has an anti-inflammatory and analgesic effect (Traoré et *al.,* 2021). The aim of this study was to evaluate the anticonvulsant and antidepressant effects of *Daniellia oliveri* aqueous extract in pilocarpine model of temporal lobe epilepsy and eventually study the GABAergic involvement.

2. material and methods

**2.1. Collection and identification of biological plant material**

Fresh barks of *Daniellia oliveri* were harvested in the Mayo-Tsanaga division (Far-North Region, National Herbarium of Cameroon (HNC) by comparing it to the Cameroon) and identified at the specimen deposited under the voucher number 24916HNC. Briefly, barks of *Daniellia oliveri* were peeled off, cut to pieces, and air-dried at room temperature. Dried root samples were then ground into a coarse powder.

**2.2. Preparation of the decoction of *Daniellia oliveri***

The extract *Daniellia oliveri* was prepared, mimicking strictly the traditional healer’s procedure. A total of 10 g of powdered dried leaves were macerated in 50 mL of distilled water, boiled for 20 min, and allowed to cool to room temperature. Following cooling, at room temperature, the mixture was filtered using Whatman No.1 filter paper, and the filtrate (extract) was considered as the stock solution. The amount of dry matter in the extract was determined by evaporating water in a drying oven (50°C). A solid residue of 0.37 g was collected. The yield of the extraction was therefore 7.34%. From the stock solution (4.9 mg/mL), less concentrated solutions were made by dissolving at ratios 1/2, 1/4, and 1/10. These solutions were thus administered in mice per os (p.o.) at doses of 21.21, 106.06, 221.12 and 221.12 mg/kg, respectively.

**2.3. Qualitative phytochemical analysis of *Daniellia oliveri***

The tests of phytochemical characterization of the decoction of *Daniellia oliveri* were carried out by qualitative colorimetric methods. The main groups or chemical families among others determined were alkaloids, flavonoids, tannins, sterols and triterpenes, saponins and phenols.

**2.4. Chemical substances used and their origin**

We used chemical substances supplied by the Sigma Chemical laboratory St. Louis, USA: pilocarpine, sodium valproate, methylscopalamine, and imipramine. All the reagents used for the quantification of the biochemical parameters of the hippocampus were also from Sigma Chemical, St. Louis, USA.

**2.5. Animal material**

Adult male Swiss mice (*Mus* *musculus* Swiss; 20 - 25 g) were used in this . These animals were provided by the Laboratoire National Vétérinaire (LANAVET) of Garoua- Cameroon and were acclimated at the animal house of the University of Ngaoundéré. The animal house was maintained constantly at 25 °C on a 12 h light-dark cycle. The protocols were performed in concordance with the International Guide for the Care and Use of Laboratory Animal (National Institute of Health; publication No. 85-23, revised 1996) and the Cameroon National Ethical Committee, Yaounde (No. FW-IRB00001954).

**2.6. Pharmacological tests**

**2.6.1 Induction of temporal lobe epilepsy and the study of anticonvulsant effects**

On the first day of the experiments, 42 white *Mus musculus* Swiss mice were weighed and divided into 7 groups of 6 animals, as follows: - Four test groups received the different doses of *Daniellia oliveri* (21.21, 106.06, 221.12 and 221.12 mg/kg, *per os*); - One negative control group received distilled water (DW :10 mg/kg *per os*); - A positive control group received sodium valproate (VS: 300 mg/kg, i.p.); - A normal control group received distilled water (DW:10 mg/kg *per os*). The injection protocol was similar to those previously described by Cavalheiro et *al.*, 1991. Forty minutes after these administrations, a single low dose of N-methyl-scopolamine (1 mg/kg, i.p.) was administered to groups of animals except the normal group in an attempt to reduce the cholinergic effects of pilocarpine in the periphery (Covolan and Mello, 2006). Twenty minutes after this injection, the mice received a single injection of pilocarpine (360 mg/kg, i.p.), a muscarinic cholinergic agonist, via the same route. The normal control received neither N-methyl-scopolamine nor sodium valproate. Then they were returned to their cages and observed individually for 6 hours the initial state of malaise called status epilepticus (SE) according to the Racine scale ranging from 0 to 5 stages: - Stage 0: no response; - Stage 1: hyperactivity and vibrissae clonus; - Stage 2: head nodding, head clonus and myoclonic jerks; - Stage 3: unilateral forelimb clonus; - Stage 4: bilateral forelimbs elevation and clonus; - Stage 5: tonic-clonic seizures with loss righting reflex, (Racine, 1972; Taiwe 2015). The parameter as the latency time of status epilepticus was recorded. Mice that reached stage 5 according to the Racine scale were retained for further experiments.

*Excitus* and convulsions were induced by picrotoxin in mice 24 hours after the acute pilocarpine-induced *status epilepticus* test. This spontaneous neuropathology was facilitated by intraperitoneal injection of a sub-convulsive dose of picrotoxin (1 mg/kg) to mice. Briefly, animals were treated for the second day, or twenty-three hours after the injection of pilocarpine, with distilled water for group 1 and 2, the respective doses of the extracts for group 3 – 6, and sodium valproate for group 7, respectively. One hour later, a sub-convulsive dose of picrotoxin (1 mg/kg) was injected intraperitoneally to mice (groups 2 to 7), except group 1 that was injected intraperitoneally with saline. Each animal was observed immediately for a period of 30 min, and the incidence of seizures (the latency time to first clonic seizure, latency time to first tonic seizure, the number clonic seizures, duration of clonic seizures, number tonic seizures, and the duration of tonic seizures) were noted. Tonic-clonic seizures involve both tonic (a sudden stiffness or tension in the muscles of the arms, legs or trunk) and clonic (twitching or hock-like jerks of a muscle or a group of muscles) phases of muscle activity. The latency of tonic-clonic seizures was used to determine the seizure score. This score was calculated according to the following formula : Score = 1- negative control group latency/test group or positive control group latency (Malhotra and Gupta, 1997).

Seven days after the previous study, the mice were used for the evaluation of the antidepressant effects of the plant extract. Another group of mice was added and served as a positive control for the depression test, and given orally imipramine (15 mg/kg, i.p.). The first test was the forced swimming test, followed by the open field test. At the end of these behavioural tests, mice were sacrificed by cervical dislocation. Their brain and then the hippocampus were collected for the evaluation of the biochemical parameters.

**2.6.2. Effects of *Daniellia oliveri* on locomotor activity and exploratory behaviour in mice with epilepsy**

After the evaluation of the anticonvulsant effects, the behavioural effects of *Daniellia oliveri* were evaluated in animals with status epilepticus, which showed convulsions characteristic of temporal lobe epilepsy. The animals were submitted to a forced swimming test, and then in an open field respectively for the evaluation of the antidepressant effects of the plant and its effects on locomotive activities and exploration (Belzung, 1999).

**2.6.2.1. The forced swimming test**

The mice were all subjected to the forced swimming as reported by (Porsolt et *al.,* 1977). The mice were individually introduced into a glass cylinder. The forced swimming test consists of two phases, an induction or pre-test phase and a test phase or actual test. During the induction phase, the animals were placed individually into the water for 15 min. After 24 h, during the test phase the mice were placed in the same glass cylinder for 6 min. During the six minutes of observation, the movements (swimming, climbing) and the duration of immobility of the mice were recorded. Immobility was defined when the animal did not make any movement for at least 2 second, or made only those movements that are necessary to keep the nose above the water. A batch of normal mice was added for the forced swimming test. The latter received an acute administration of imipramine (15 mg/kg i.p.) during the test period as a positive control for the depression test.

**2.6.2.2. Open arena test open field test**

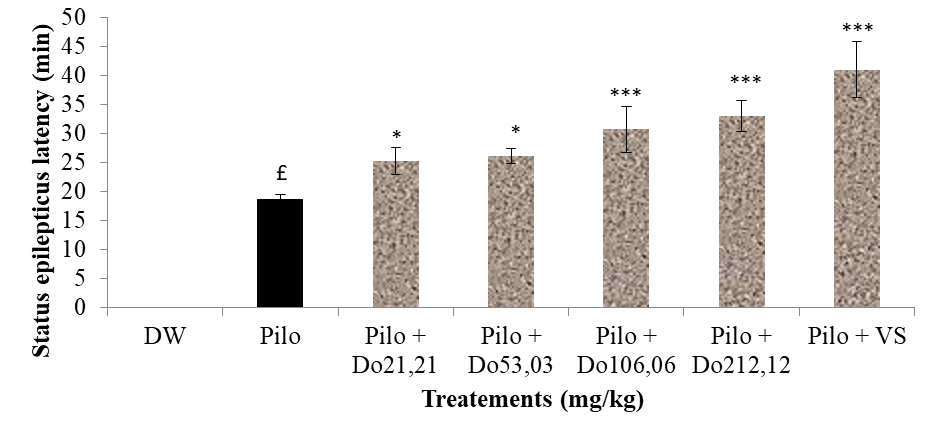
The method used in our experiments is the one described by (Belzung, 1999). The open field test is commonly used to evaluate the level of locomotor activity, the exploration and the emotional reactivity in rodents (Belzung, 1999). After the forced swim test, the animals were thoroughly cleaned with a towel and then returned to their starting cages for one hour to reduce neophobic responses associated to the experimental environment (Belzung, 1999). One hour after undergoing the forced swim test, each mice was observed for a duration of 5 minutes. The test consisted of placing the mice one after the other in the center of the device, in order to allow them free exploration. Several behavioural parameters were evaluated: the number of lines crossed, the number of cleanings, the number of straightenings, the time spent in the center of the experimental device. After 5 minutes of watching, the mice was simply put back in its original cage and the experimental device was cleaned with ethyl alcohol (70 °C).

3. results

**3.2 Behavioural and anticonvulsant effects of *Daniellia oliveri* decoction**

**3.2.1. Effects of *Daniellia oliveri* decoction on** *status epilepticus* ***(SE*)**

One-way ANOVA revealed a significant effect in the different groups following treatment with *Daniellia oliveri*  and pilocarpine on *status* *epilepticus* latency [F (6, 35) = 111.5, P < 0.001]. The latency of onset of *status* *epilepticus* greater than before in the negative control compared to the normal control, ranging from 0.00 ± 0.00 min in the latter to 18.67 ± 0.87 min in the negative control. *Daniellia oliveri*  induced a significant increase in this time compared to the negative controls to 25.20 ± 2.33; 26.09 ± 1.26; 30.71 ± 3.94 and 33.03 ± 2.68 min in mice treated with 21.21, 53.03, 106.06 and 212.12 mg/kg of *Daniellia oliveri*  respectively. The same is true for sodium valproate, which induced a significant increase in the latency time of onset of convulsions to 41.04 ± 4.77 min (Fig. 1).

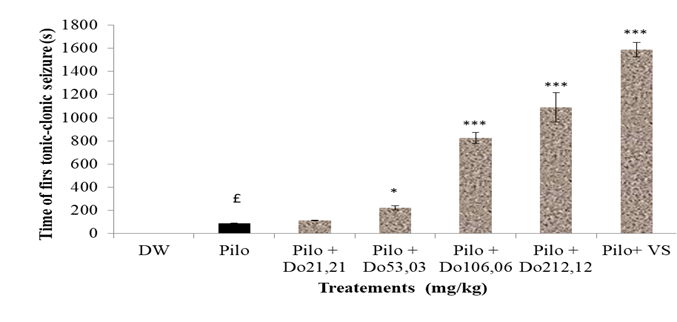


**Figure 1: Effects of *Daniellia oliveri* on the latency of onset of status epilepticus.**

Each bar represents the mean ± MSE of the group, n = 6. \*p<0.05; \*\*\*p<0.001; significant difference compared to negative control and £££p<0.001 compared to normal control. DW: normal control; Pilo: negative control; Pilo + VS: positive control treated with sodium valproate (300 mg/kg).

**2.2.2. Effects of Daniellia oliveri on the latency time of tonic and clonic seizures induced by pilocarpine**

One-way ANOVA revealed a significant effect of Daniellia oliveri and pilocarpine in the different groups on tonic and clonic seizure latency [F (6, 35) = 705.8, p<0.001]. The latency time of tonic and clonic seizures increased extensively between normal and negative controls.. Daniellia oliveri induced a significant increase in this time compared to the negative controls to 113.83 ± 2.92, 224.83 ± 16.53, 824.83 ± 48.26 and 1090.20 ± 125.73 sec in those treated with the respective doses of 21.21, 53.03, 106.06 and 212.12 mg/kg of the decoction. The same was true for sodium valproate whose latency time increased to 1587.80 ± 62.64 sec (Fig. 2).



**Figure 2: Effects of *Daniellia oliveri* on the latency of the first tonic and clonic seizure 24 hours after pilocarpine administration.**

Each bar represents the mean ± MSE of the group, n=6. \*p<0.05; \*\*\*p<0.001; significant difference compared with negative controls and £p<0.5 compared with normal controls. DW: normal control; Pilo: negative control; Pilo + VS: positive control treated with sodium valproate (300 mg/kg).

**2.2.3. Effects of** *Daniellia oliveri* **on the duration and number of clonic convulsions induced by pilocarpine 24 hours after the induction of status epilepticus**

One way ANOVA demonstrated a significant effect in the different groups following treatment with *Daniellia oliveri*  and pilocarpine in the different groups on the number of clonic convulsions [F (6, 35) = 189.9, p<0.001]. The number of clonic convulsions in mice 24 hours after induction of status epilepticus was significantly increased between normal and negative controls. The percentage of clonic convulsions being 100% in the animals of the negative control lot treated with distilled water, it decreases to 56.18, and 78.98% in those treated respectively with the doses 106.06 and 212.12 mg/kg. Sodium valproate also induced a significant decrease in the number of convulsions to 3.16 ± 0.98 (Table 1).

Similarly, one-way ANOVA showed a significant effect in the different groups following treatment with *Daniellia oliveri*  and pilocarpine on the duration of clonic convulsion [F (6, 35) = 242.9, p<0.001]. The duration of seizures increased significantly between normal and negative controls. This duration increased from 0.00 ± 0.00 sec in normal controls to 42.83 ± 5.413 sec in negative controls. Administration of *Daniellia oliveri*  to mice significantly and dose-dependently decreased this value to 2.33, 5.43, 50, 61.09 % in the mice treated respectively by the doses 21.21; 53.03; 106.06 and 212.12 mg/kg of the decoction of *Daniellia oliveri* . We also note a significant decrease in the duration of convulsions in the mice of the positive control batch treated by sodium valproate which passes to 6.66 ± 2.07 sec, that is to say a percentage of 84.45% (Table 1).

**Table 1:** **Effects of *Daniellia oliveri* on the duration and number of clonic convulsions induced by pilocarpine**.

|  |  |  |  |
| --- | --- | --- | --- |
| **Groups** | **Doses (mg/kg)** | **Number of clonic seizures** | **Duration of clonic seizures (s)** |
| DW | --- | 0.00 ± 0,00 | 0.00 ± 0.00 |
| Pilo | --- | 24.33 ± 2.06£££ | 42.83 ± 5.41£££ |
| *Do* + Pilo | 21.21 | 17.50 ± 1.97\*\*\* | 41.83 ± 2.78 |
| *Do* + Pilo | 53.03 | 15.33 ± 1.03\*\*\* | 40.50 ± 1.64 |
| *Do* + Pilo | 106.06 | 10.66 ± 1.21\*\*\* | 21.33 ± 2.73\*\*\* |
| *Do* + Pilo | 212.12 | 6.33 ± 2.16\*\*\* | 16.66 ± 1.63\*\*\* |
| VS | 300 | 3.16 ± 0.98\*\*\* | 6.66 ± 2.06\*\*\* |

Each value represents the mean ± MSE of the group, n = 6 \*\*\*p<0.001; significant difference compared with negative controls and £££p<0.001 compared with normal controls. DW: normal control; Pilo: negative control; Pilo + VS: positive control treated with sodium valproate (300 mg/kg).

**2.2.4. Effects of *Daniellia oliveri* on the number and duration of tonic convulsions induced by pilocarpine 24 hours after induction of *status epilepticus***

One-way ANOVA revealed a significant effect of *Daniellia oliveri*  and pilocarpine treatment in the different groups on the number of tonic convulsions [F (6, 35) = 24,24, p<0.001]. The percentage of the number of convulsions being 100% in the animals of the negative control lot treated with distilled water, it decreased to 13.05, 17.36, 45.69, and 50% for the doses 21.21; 53.03; 106.06 and 212.12 respectively. The reference substance sodium valproate administered at the dose of 300 mg/kg also induced a significant decrease in the number of seizures to 2.66±0.51 seizures, a percentage of 65.27% (Table 2).

One-way ANOVA revealed a significant effect in the different groups following treatment with *Daniellia oliveri*  and pilocarpine on the duration of tonic convulsion [F (6, 35) = 143.0, p<0.001].The duration of tonic seizures in mice was significantly increased between normal and negative controls. Administration of *Daniellia oliveri*  to mice significantly and dose-dependently decreased this value to 11.33 ± 1.21, 12.16 ± 1.47, 10.66 ± 0.81, and 8.33 ± 0.81 sec in mice treated with 21.21; 53.03; 106.06; and 212.12 mg/kg *Daniellia oliveri*  respectively. The percentage and varies at 22.71, 17.05, 27.28 and 47.17% for doses 21.21; 53.03; 106.06 and 212.12 respectively. There was also a significant decrease in the duration of convulsions in the positive control mice treated with sodium valproate (Table 2).

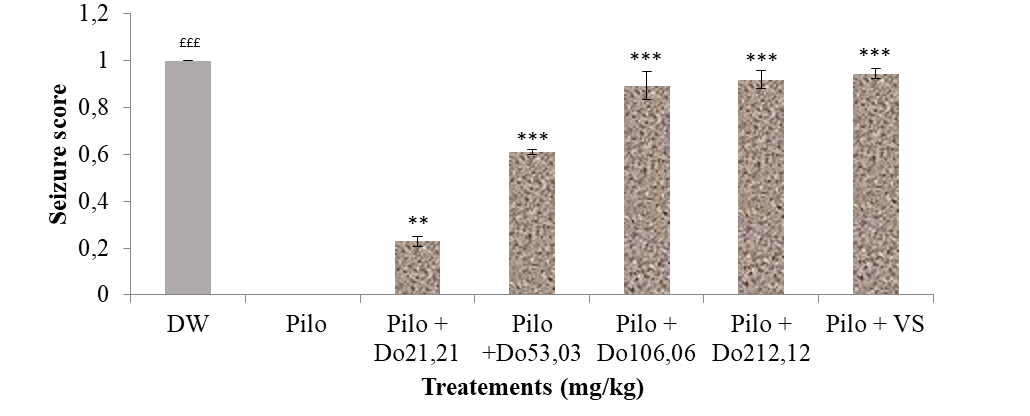
**Table 2: Effects of *Daniellia oliveri* on the number and duration of tonic convulsions induced by pilocarpine.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Groups** | **Doses (mg/kg)** | **Number of tonic seizures** | **Duration of tonic seizures (s)** |
| DW | --- | 0.00 ± 0.00 | 0.00 ± 0.00 |
| Pilo | --- | 7.66 ± 1.21£££ | 14.66 ± 0.81£££ |
| *Do* + Pilo | 21,21 | 6.66 ± 1.50 | 12.16 ± 1.47\*\* |
| *Do* + Pilo | 53,03 | 6.33 ± 1.36 | 11.33 ± 1.21\*\*\* |
| *Do* + Pilo | 106 ,06 | 4.16 ± 2.13\*\* | 10.66 ± 0.81\*\*\* |
| *Do* + Pilo | 212,12 | 3.83 ± 1.32\*\*\* | 8.33 ± 0.81\*\*\* |
| VS | 300 | 2.66 ± 0.51\*\*\* | 4.33 ± 1.36\*\*\* |

Each value represents the group mean ± MSE, n=6. \*\*p<0.01; \*\*\*p<0.001; significant difference compared with negative controls and £££p<0.001 compared with normal controls. DW: Normal controls; Pilo: Negative control; Pilo + VS: Positive control treated with sodium valproate (300 mg/kg).

**2.2.5. Effects of** *Daniellia oliveri* **on pilocarpine-induced tonic and clonic seizure score**

The pilocarpine-induced tonic and clonic seizure score reduced significantly between the normal and negative controls. This score increased considerably to 0.228 ± 0.02 in those treated with the 21.21 mg/kg dose, 0.609 ± 0.01 in those treated with the 53.03 mg/kg dose, and 0.893 ± 0.06 in those treated with the 106.06 mg/kg dose of *Daniellia oliveri* . The highest dose of the plant 221.2 mg/kg induced a significant intensification in seizure score at 0.919 ± 0.04. Sodium valproate administered at the dose of 360 mg/kg induced a significant proliferation in seizure score to 0.944 ± 0.02 (Fig. 3).



**Fig. 3: Effects of *Daniellia oliveri* on pilocarpine-induced tonic and clonic seizure scores.**

Each bar represents the mean ± MSE of the group, n = 6. \*\*p<0.01; \*\*\*p<0.001; significant difference compared with negative control. DW: normal control; Pilo: negative control; VS + Pilo: positive control treated with sodium valproate.

**2.3 Antidepressant effects of** *Daniellia oliveri* **in epileptic mice subjected to forced swimming in a pool**

**2.3.1. Effect of** *Daniellia oliveri* **on climbing duration, swimming duration and immobility duration**

The figure shows the effects of *Daniellia oliveri*  on climbing time, swimming time and immobility time in mice given pilocarpine and subjected to the forced swimming test.

Analysis of variance revealed a significant difference in climbing duration between the groups treated with *Daniellia oliveri* and pilocarpine, and subjected to forced swimming tests [F (7, 40) = 126.4, p<0.001]. A significant difference between the climbing duration of the normal and negative controls which were 67.66 ± 3.77 sec and 44.66 ± 3.66 sec respectively. The decoction promoted a significant increase in the duration of escalation which varied from 44.66 ± 3.66 sec in the negative control mice treated with distilled water to 54.67 ± 4.33, 71.50 ± 6.83, 93.83 ± 2.88, 111.5 ± 6.83 sec in those treated with the doses of 21.21, 53.03, 106.06 and 212.12 mg/kg of the plant respectively. Similarly, there is a significant increase in climbing duration to 125.70 ± 4.77 sec for imipramine used in this experiment as the reference antidepressant (Table 3). Analysis of variance revealed a significant difference in duration of swimming between the groups treated with *Daniellia oliveri*  and pilocarpine, and subjected to forced swimming tests [F (7, 40) = 96.04, p<0.001]. The duration of swimming in the normal controls compared to the negative controls increased but not significantly. It increased from 52.33 ± 5.11 sec to 61.83 ± 2.16 sec. *Daniellia oliveri*  significantly and dose-dependently increased the swimming time from 61.83 ± 2.16 sec in the negative control mice to 71.17 ± 3.12, 80.17 ± 4.5, 95.83 ± 1.22 and 116.5 ± 5.83 sec in those treated with 21.21, 53.03, 106.06 and 212.12 mg/kg of *Daniellia oliveri* decoction respectively. This duration was also significantly increased to 142.2 ± 14.83 sec in animals treated with imipramine (Table 3). One-way ANOVA revealed a significant effect of *Daniellia oliveri*  in the different groups on climbing duration [F (7, 40) = 247.2, p<0.001]. The duration of immobility in the normal controls compared to the negative controls increased significantly from 91.16 ± 4.50 sec to 116.83 ± 3.05 sec respectively. The duration of immobility decreased significantly in the animals treated with the different doses of the decoction compared to the negative control. This duration varied from 116.80 ± 3.05 sec in mice of the negative control lot to 84.33 ± 10.89, 35.17 ± 3.83, 22.17 ± 1.50 sec in those treated with the respective doses of 21.21, 53.03 and 212.12 mg/kg of *Daniellia oliveri* . The duration of immobility increased to 4.83 ± 0.55 sec in animals given imipramine at a dose of 15 mg/kg (Table 3).

**Table 3**: Effect of *Daniellia oliveri* on climbing, swimming, and immobility time.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Groups | Doses (mg/kg) | Climbing duration | Swimming duration | immobility duration |
| DW | --- | 67.66 ± 3.77 | 61.83 ± 2.16 | 91.16 ± 4.50 |
| Pilo | --- | 44.66 ± 3.66£££ | 52.33 ± 5.11£££ | 116.83 ± 3.05£££ |
| *Do* + Pilo | 21,21 | 54.67 ± 4.30 | 71.17 ± 3.12 | 84.33 ± 10.00 \*\*\* |
| *Do* + Pilo | 53,03 | 71.50 ± 6.83\*\*\* | 80.17 ± 4.50\*\*\* | 84.67 ± 3.33 \*\*\* |
| *Do* + Pilo | 106,06 | 93.83 ± 2.88 \*\*\* | 95.83 ± 1.22 \*\*\* | 35.17 ± 3.83 \*\*\* |
| *Do* + Pilo | 212,12 | 111.5 ± 6.83 \*\*\* | 116.5 ± 5.83 \*\*\* | 22.17 ± 1.5 \*\*\* |
| VS | 300 | 118.2 ± 5.83 \*\*\* | 146.3 ± 7.66 \*\*\* | 17.33 ± 2.77 \*\*\* |
| IMIP | 15 | 125.7 ± 4.77 \*\*\* | 142.2 ± 14.83 \*\*\* | 4.83 ± 0.55 \*\*\* |

Each value represents the mean ± MSE of the group, n=6. \*\*\*p<0.001; significant difference compared with negative control and £££p<0.001 compared with normal control. DW: Normal controls; Pilo: Negative control; Pilo+ VS: Positive control treated with sodium valproate (300 mg/kg); IMIP: Positive control treated with imipramine (15 mg/kg).

**2.3. Effects of** *Daniellia oliveri* **on scanning behaviour in epilepticized mice** **placed in the open field**

Table IV shows the effects of *Daniellia oliveri*  on the number of lines crossed, the number of righting, the number of cleaning, and the time spent in the center of the open field in pilocarpine-treated mice subjected to the open arena test.

One-way ANOVA revealed a significant effect of *Daniellia oliveri*  in the different groups on the number of Rearing [F (7, 40) = 23.94, p<0.001]. The number of turnarounds in the normal controls compared to the negative controls increased but not significantly from 5.66 ± 1.22 to 7.66 ± 0.66 respectively. Decoction significantly decreased the number of turnarounds from 7.66 ± 0.66 in the negative control mice to 3.16 ± 1.55, 3.00 ± 0.66, 1.33 ± 0.44 and 1.66 ± 0.66 turnarounds in those treated with 21.21, 53.03, 106.06 and 212.12 mg/kg of the plant respectively. Imipramine likewise significantly decreased the number of straightening, giving a value of 1.5 ± 0.25 (Table 4).

Analysis of variance revealed a significant difference in the number of crossings between the groups treated with *Daniellia oliveri*  and pilocarpine. [F (7, 40) = 191.7, p<0.001]. The number of lines crossed in the normal controls compared to the negative controls decreases but not significantly, it goes from 6.83 ± 1.16 to 3.33 ± 0.77 respectively. The number of lines crossed increased significantly in the mice treated with the different doses of *Daniellia oliveri*  compared to those of the negative control batch. The number of crossed lines ranged from 3.33 ± 0.77 in the negative control mice to 5.50 ± 20, 5.83 ± 1.16, 14.50 ± 0.83 and 16.50 ± 1.50 crossed lines in those treated with 21.21, 53.03, 106.06 and 212.12 mg/kg of the decoction respectively. The number of crossed lines was significantly increased in mice treated with imipramine to 28.50 ± 1.66 crossed lines (Table 4).

One-way ANOVA revealed a significant effect of *Daniellia oliveri*  and pilocarpine treatment in the different groups on the number of Grooming [F (7, 40) = 15.41, p<0.001]. The number of clean-ups in normal controls compared to negative controls decreased but not: significantly from 2.50 ± 0.83 to 1.16 ± 0.27 respectively. The number of cleanups in mice treated with different doses of *Daniellia oliveri*  increases significantly to 1.50 ± 0.50, 1.83 ± 0.55 3.33 ± 0.88 and 3.83 ± 0.55 cleanings for the respective doses of 21.21, 53.03, 106.06 and 212.12 mg/kg of the decoction. Imipramine also significantly increased the number of clean ups to 4.16 ± 0.88 (Table 4).

Analysis of variance revealed a significant difference in time spent in the center between the groups treated with *Daniellia oliveri* and pilocarpine. [ F (7, 40) = 95.97, p<0.001]. The time spent in the center in normal controls compared to negative controls decreased significantly from 6.33 ± 0.66 to 1.83 ± 0.831 sec, respectively. Mice treated with the different doses of *Daniellia oliveri*  showed a significant increase in the time spent in the center compared to those in the negative control lot. This ranged from 1.83 ± 0.83 sec in mice of the negative control lot to 12.50 ± 0.66 sec, 14.66 ± 1.88 sec, 22.83 ± 2.16 and 23.66 ± 3.55 sec in those treated with the respective doses 21.21, 53.03, 106.06 and 212.12 mg/kg of the decoction. The time spent in the center was significantly increased in mice treated with imipramine 15 mg/kg, giving a value of 26.33 ± 1.22 sec (Table 4).

**Table 4**: Effects of *Daniellia oliveri* on exploration behaviour in mice placed in the open field test.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Groups | Doses (mg/kg) | Rearing | Crossing | Grooming | Centre time (s) |
| DW | --- | 5.66 ± 1.22 | 6.83 ± 1.16 | 2.50 ± 0,83 | 6.33 ± 0.66 |
| Pilo | --- | 7.66 ± 0.66 | 3.33 ± 0.77 | 1.16 ± 0.27 | 1.83 ± 0.83£ |
| *Do* + Pilo | 21.21 | 3.16 ± 1.55\*\*\* | 5.50 ± 2.00 | 1.50 ± 0.50 | 12.50 ± 0.66 \*\*\* |
| *Do* + Pilo | 53.03 | 3.00 ± 0.66\*\*\* | 5.83 ± 1.16 | 1.83 ± 0.55 | 14.66 ± 1.88 \*\*\* |
| *Do* + Pilo | 106.06 | 1.33 ± 0.44\*\*\* | 14,50 ± 0.83\*\*\* | 1.33 ± 0.88\* | 22.83 ± 2.17 \*\*\* |
| *Do* + Pilo | 212.12 | 1.66 ± 0.66\*\*\* | 16,50 ± 1.50\*\*\* | 3.83 ± 0.55\*\*\* | 23.66 ± 3.55 \*\*\* |
| VS | 300 | 1.83 ± 0.83\*\*\* | 27,66 ± 1.33\*\*\* | 5.00 ± 0.66\*\*\* | 24.33 ± 1.33 \*\*\* |
| IMIP | 15 | 1.50 ± 0.50\*\*\* | 28,50 ± 1.66\*\*\* | 4.16 ± 0.88\*\*\* | 26.33 ± 1.32 \*\*\* |

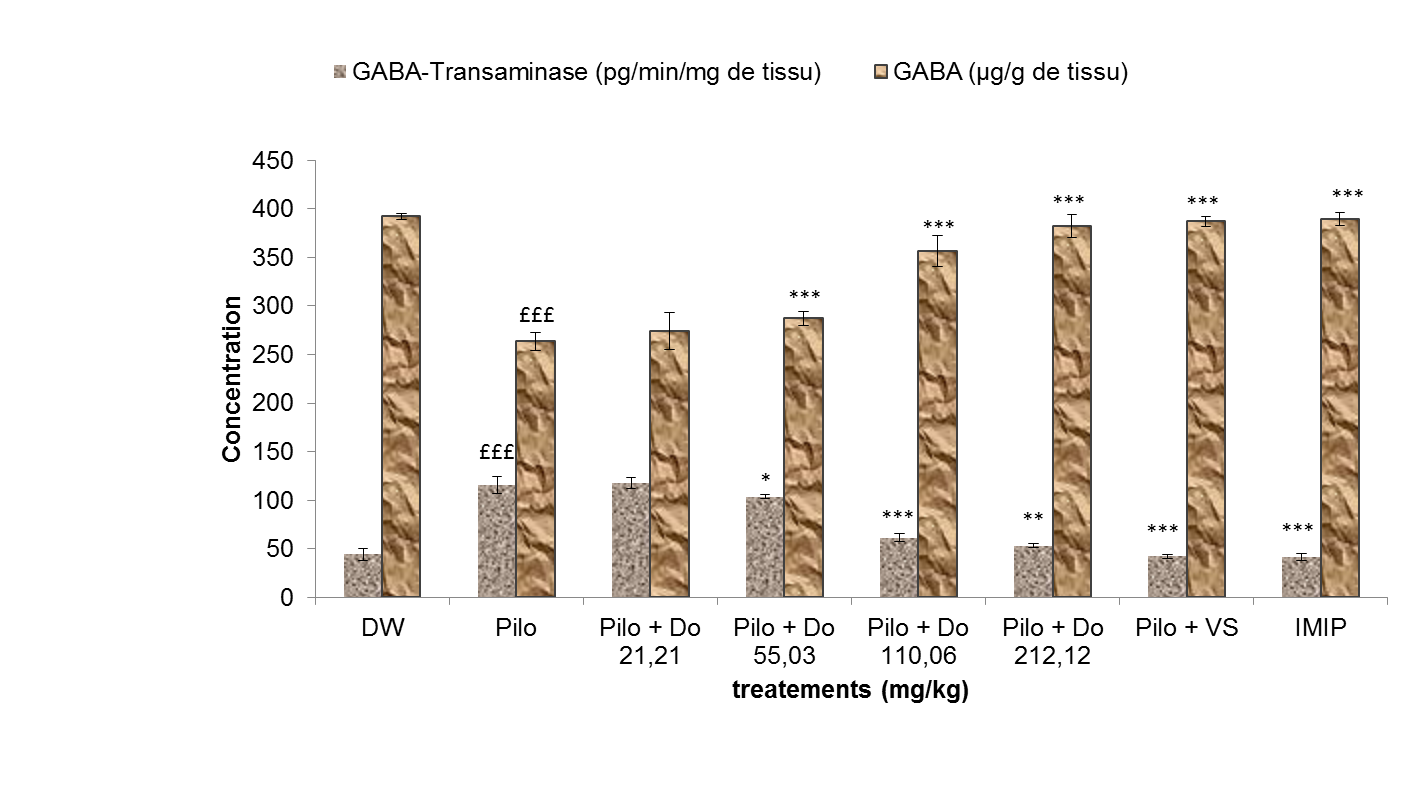
Each value represents the mean ± MSE of the group, n=6. \*p<0.05; \*\*\*p<0.001; significant difference compared with negative control and £p<0.05 compared with normal control. DW: normal control; Pilo: negative control VS: positive control treated with sodium valproate (300 mg/kg); IMIP: positive control treated with imipramine (15 mg/kg).

**2.4. Effects of *Daniellia oliveri* on some biochemical parameters in the hippocampus**

**3.4.1. Effects of *Daniellia oliveri* on GABA and GABA-transaminase**

The figure 5 summarizes the effects of the decoction of *Daniellia oliveri* on the concentration of ''Gamma amino butyric acid'' (GABA) and the activity of GABA-transaminase (GABA-T) in the hippocampus of mice. One-way ANOVA revealed a significant effect in the different groups of GABA concentration following treatment with *Daniellia oliveri*  and pilocarpine [F (7, 40) = 94.55, p<0.001]. It was found that there was a significant decrease in the concentration of GABA in the negative controls compared to the normal controls, which were 392.16 ± 2.83 and 263.50 ± 9.33 μg/g, respectively. The decoction of the plant promoted a significant increase in the concentration of GABA in the animals of the test groups, which varied from 263.50 ± 3.33 μg/g of tissue in the mice of the negative control lot to 274.83 ± 5.83; 287.16 ± 7.16; 356.66 ± 15.88 and 382.16 ± 12.16 µg/g of tissue in those treated with the respective doses of 21.21, 53.03, 106.06 and 212.12 mg/kg of the decoction. The same is true for sodium valproate (300 mg/kg), which induced a significant increase in GABA level up to 387.5 ± 3.33 μg/g tissue compared with the negative control.

The one-way ANOVA also showed a significant effect in the different groups on GABA-transaminase activity following treatment with *Daniellia oliveri*  and pilocarpine [F (7, 40) = 192.1, p<0.001]. There was a significant increase in GABA-transaminase activity in the negative controls compared to the normal controls, with values of 115.66 ± 8.33 and 44.16 ± 4.5 pg/min/mg respectively. *Daniellia oliveri*  promoted a significant decrease in GABA-transaminase activity from 115.66 ± 8.33 pg/min/mg tissue in the negative control mice treated with distilled water to 117.66 ± 5.33, 103.83 ± 1.86, 61.5 ± 3.83 and 53.16 ± 2.22 pg/min/mg tissue in those treated with 21.21; 53.03; 106.06 and 212.12 mg/kg of the plant respectively. The intake of sodium valproate also significantly decreased this movement, giving a value of 44.16 ± 2.16 pg/min/mg of tissue.



**Fig. 4: Effects of *Daniellia oliveri*  decoction on ''Gamma amino butyric acid'' (GABA) concentration and GABA-transaminase (GABA-T) activity in the hippocampus of mice.**

Each bar represents the mean ± MSE of the group, n=6. \*p<0.05; \*\*\*p<0.001; significant difference compared with negative controls and £££p<0.001 compared with normal control. DW: Normal controls; Pilo: Negative control; VS +Pilo: Positive control treated with sodium valproate (300 mg/kg); IMIP: Positive control treated with imipramine (15 mg/kg).

**4. DISCUSSION**

The aim of the present study was to evaluate the preventive and antidepressant effects of *Daniellia oliveri* during epileptogenesis, on the animal model of the mesial temporal lobe induced by pilocarpine in mice.

Injection of pilocarpine causes severe myoclonic jerks followed by multiple tonic-clonic and motor seizures in rodents (Cavalheiro et *al.,* 1991). This model perfectly mimics the main features of human temporal lobe epilepsy (Cavalheiro, 1995). Pretreatment with clonazepam, phenobarbital or sodium valproate prevents limbic seizures and protects against SE-related cell damage. These drugs indicate that early inhibition of SE can prevent frequent spontaneous seizures (Lemos et *al.,* 1995). Our first study showed the presence of alkaloids, flavonoids, tannins, sterols, triterpenes, saponins and phenols in the decoction. Pretreatment of mice with *Daniellia oliveri*  significantly protected the mice from the effects of SE. It also significantly decreased the percentage and duration of convulsions at 212.12 mg/kg (78.98% and 50% for the number of clonic and tonic convulsions respectively and 61.09% and 43.17% for the periods of clonic and tonic convulsions). The protection against pilocarpine-induced convulsions in mice suggests that *Daniellia oliveri*  possesses antiepileptic properties have a broad spectrum of activity (El-Azab and Moustafa, 2012).

The acute phase of TLE in the pilocarpine model is marked by a significant imbalance between neuronal inhibition and excitation (Cavalheiro et *al.,* 1994). One of the main mechanisms for controlling hyperactive nervous disorders such as epilepsy is to increase the overall concentration of GABA, which is the main inhibitory signalling in the central nervous system, and in particular in the brain (Taiwe et *al*., 2016 ; Moto et *al.,* 2018), by inhibiting the activity of GABA-T (Belebon et *al.,* 2004 ; Taiwe et *al*., 2016 ; Moto et *al*., 2018), or by simplifying GABAergic neurotransmission via R-GABA (Morimoto et *al*., 2004). In the present study, pilocarpine significantly decreased GABA and increased GABA-T activity. In contrast, decoction of *Daniellia oliveri* significantly reduced GABA-T activity in the hippocampus, which may be at least partly responsible for the observed increase in GABA concentration. These results suggest that this extract would be capable of restoring and maintaining the balance between neuronal excitation and inhibition in the mouse hippocampus during acute attacks of TLE in the pilocarpine model, and would thus have preventive effects. This could be similar to an inhibitor of GABA-T by triterpenoids (Awad et *al*., 2009).

With regard to depression caused by temporal lobe epilepsy, the forced swimming test, which is a widely used test for assessing the activity of pharmacological substances (Porsolt et *al.,* 1977) was used. Indeed, one of the main causes of the onset of depression is regular exposure to stress (Foyet et *al*., 2017). In the forced swimming test, *Daniellia oliveri* induced an increase in climbing time, swimming time and a decrease in immobility time in mice. These results reveal the antidepressant effects of the plant (Porsolt et *al.,* 1977; Cryan et *al*., 2002). The increase in the activity of the serotonin system reduces immobility and increases swimming time, while the noradrenergic system results in a reduction in immobility and an increase in climbing (Detke et *al.,* 1995). Extracts containing flavonoids also have an antidepressant effect on TNF (Ngoupaye, 2014). The antidepressant effect of the plant was confirmed outdoors by the significant increase in the number of cleanings, lines crossed, time spent in the centre of the apparatus and the decrease in the number of straightenings. The increase in the number of lines crossed, the number of cleanings and the time spent in the centre in the open arena indicates an increase in locomotor activity and the level of exploration (Kash et *al*., 1999; Ngo Bum et *al*., 2009). All these properties are attributable to the different chemical combinations present in the *Daniellia oliveri*  decoction.

5. Conclusion

To condense, the data presented here prove that the extracts of *Daniellia oliveri* . Exerts a preventive and antidepressant property in pilocarpine-induced epileptogenesis in mice, while protecting the brain against SE, increasing the brain concentration of GABA and attenuating the activity of GABA-transaminase. Furthermore, it suggests that *Daniellia oliveri*  would have antidepressant properties appreciations to the tests of forced swimming and OF. The results of the phytochemical screening permit us to appreciate in part the preventive and antidepressant property of the plant, thus justifying its use in the treatment of central nervous system diseases such as epilepsy and depression. In the current experiments, we plan to determine the antiepileptogenesis and antidepressant effect of *Daniellia oliveri* on a model of chronic induction of epilepsy by pilocarpine, as part of identifying the different antiepileptogenic and antidepressant mechanisms by which the plant acts; and even finalize the toxicological study of the plant.

**CONSENT**

It is not applicable.

**STATEMENT OF ETHICAL APPROVAL**

The protocols were performed in concordance with the International Guide for the Care and Use of Laboratory Animal (National Institute of Health; publication No. 85-23, revised 1996) and the Cameroon National Ethical Committee, Yaoundé (No. FW-IRB00001954).

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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