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Anticonvulsant and Sedative Effects of *Cassia alata* (Fabaceae) in Mice

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ABSTRACT

From bibliographic research, we have listed *Cassia alata* as a plant supposed to be anticonvulsant and sedative, which is used in traditional medicine in Congo. Our work allowed us to assess the sedative and anticonvulsant effects of *Cassia alata* leaves aqueous extract.

The acute toxicity study showed that the aqueous extract of this plant does not present any toxicity by the oral route up to the dose 3200 mg / kg. *Cassia alata* (up to 800 mg / kg) promote increased body weight. This toxicity study allowed us to select two doses (200 and 400 mg/kg) for pharmacological studies.

The sedative effect was assessed with two tests: motor activity and potentiation of barbiturate sleep in mice. The experimental animal model of generalized convulsions induced by strychnine made it possible to demonstrate the anticonvulsant activity.

It follows that at doses of 200 and 400 mg, the extract of *Cassia alata* significantly increases and reduces, respectively the time to onset and the duration of convulsions. At the same therapeutic doses, this extract significantly increases and reduces, respectively, the time to onset and barbiturate sleep. Motor activity is significantly reduced by the extract at doses of 200 and 400 mg / kg.

The chemical screening made it possible to highlight the presence of alkaloids, tannins, saponosides, flavonoids and free anthraquinones in this extract.

Keywords: anticonvulsant, sedative, phytochemistry, *Cassia alata*, mice.

I. INTRODUCTION

Anxiety is probably the most basic of emotions. Anxiety reactions are observed in all animal species. Clinical anxiety is one of the fundamental elements of mental pathology. Anxiety can act on diarrhea debacles, stomach disorders, spasms and in any kind of diffuse pain. It also acts on the cardiovascular system and sexual activity. In the population, all anxiety disorders have a prevalence of about 15 % per year. This is one of the most common mental disorders. Generalized anxiety disorders affect 2 to 6 % of adults, slightly more women than men (Rakotonina et *al.*, 2001).

Insomnia is a common symptom in clinical consultations. 20 to 30 % of the population suffers from mild insomnia, 5 to 15 % of the population suffers from severe insomnia, 15 to 20 % of adults occasionally use sleeping pills, 10 % use it regularly. In the 30-60 age group, 9% of men and 4% of women suffer of sleep apnea syndrome (Rakotonina et *al.*, 2001).

Sedatives are used for anxiety and nervous tension, they relieve pain and help sleep in case of insomnia. They also help to relax agitated subjects. The subject feels calm; his breathing and reflexes slow down.

There are many sedatives, the most common are tranquilizers, antidepressants, anxiolytics, sleep disorders and sleeping pills or hypnotics. They are used before anesthesia or any other stressful act. Patients in the intensive care unit used regulary sedatives (Datta & Maclean, 2007; Lucindo et *al.*, 2008).

Convulsions may be epileptic or non-epileptic, febrile convulsions occur in children between 6 months and 5 years. 9 to 35% of the first crises are complex. Febrile neurological convulsions are the most common neurological problem in pediatrics, affecting approximately 3% of the world's infant population. The prevalence of febrile convulsions is 13 to 48 ‰ and varies according to the points of the globe (Dumas et *al.*, 1963; Senga et *al.*, 1985; Mamadou Koné, 2006).

Convulsions are the symptom of a large number of diseases including stroke, cerebral trauma, brain tumor or cerebral hemorrhage, malaria, typhoid fever, infection such as meningitis, severe hypoglycaemia, lack of oxygen in the brain, alcoholic and drug poisoning (Dumas et *al*., 1963; Wariuru and Appleton, 2004; Moyen et *al*., 2010).

Although several anticonvulsant and sedative medications are available to treat convulsions and anxiety, it have a great necessity to look for a new drugs because of resistance, side effects, drug interactions and expensive costs(Richens et Perucca 1993; Knudsen et *al*., 1996).

In African countries many patients do not receive appropriate treatment for multiple reasons: social, cultural, economic, accessibility and availability of drugs (Nsonde Ntandou et *al.* 2018). As major alternative of treatments, they use medicinal plants, which are a socio-environmental and cultural integration in the countries of Africa, where the socio-cultural and geographical environment is the local pharmacy (Nsonde Ntandou et *al.*, 2017). Scientific validation of these treatments is necessary in order to guarantee safety and assurance on their effectiveness among users. *Cassia alata* is one of intertropically widespread medicinal plant used in Africa (Uganda, Ghana, DR Congo, Congo, Cameroon, Gabon and Nigeria…), in Indonesia, and in Latin America (Guatemala, Martinique, and Brazil…). Leaves, flowers, and fruits of *Cassia alata* are used against diabetes, anti-inflammation, pain, fever convulsion, cerebral malaria, anxiety, epilepsy, constipation, dermatitis, HIV, urogenital (gonorrhea, bilharzioses) and liver affections, and infectious diseases (as antibacterial and antifungal agents)(Palanichamy and Nagarajan, 1990; Crockett et *al.*, 1990; Ibrahim and Osman, 1995 ;Hazni et *al*., 2008; Kayembe et *al.*, 2010 ; Takashi Saito et *al*., 2012, Suagwu et *al*., 2014; Bassoueka et *al.*, 2015). Numerous pharmacological studies have been carried out on *Cassia alata*, but few have focused on the activity of this plant on the central nervous system. Previous pharmacological investigations demonstrated antibacterial, antifungal, analgesic, anti-inflammatory, antiplasmodial, hypoglycemic, antimutagenic and antipyretic activities (Palanichamy and Nagarajan, 1990; Somchit et *al.*, 2003; Kayembe et *al.*, 2010; Takashi Saito et *al*., 2012; Timothy et *al.*, 2012; Ibrahim and Osman, 2015). We did not find bibliographic references of the works carried out on the anticonvulsivante and sedative activities of these plants. Thus, in order to provide a scientific basis for the use of this plant against convulsions, insomnia and anxiety, this study aims to evaluate the sedative and anticonvulsant effects of *Cassia alata* (Fabaceae) leaves aqueous extract.

II. MATERIAL AND METHODS

1. Plant material

Leaves *of Cassia alata* were collected in the savanna of south of Brazzaville (Congo). It was identified by comparison with specimens of the national herbarium by Professor Jean-Marie MOUTSAMBOTE. Sample was dried at room temperature and protected from the light, then pulverized, in the Laboratory of Animal Physiology and

Physiopathology of the Faculty of Science and Techniques at the Marien Ngouabi University at Brazzaville, in the Republic of Congo.

2. Animal material

The animal material is constituted by males and females *Mus musculus* mice of Swiss albino strain of body weight between 20 and 25 g, at least 3 months old raised at the pet shop of the Institut de Recherche en Sciences de la Santé (IRSSA) of Brazzaville-Congo. They were housed under standard conditions (25 ± 5° C, 40-70 % RH, 12h light/dark cycle) and fed with a standard died and water ad libitum. They were handled according the ethical rules of animal experiments published by the International Association for the Study of Pain (Canadian Council 1980; Zimmermann, 1983).

III. METHODS

3.1. Preparation of extract

After drying, 50 g of powdered of *Cassia alata* leaves were boiled (at 100 ° C) in 500 ml of distilled water for 30 minutes. After cooling, the mixture was filtrated with cotton, then evaporated in the balloon heater at reduced pressure with 50-60 ° C for 48 hours. The dry residue of mass 5.9 g is collected with a yield of 11.8 g. The dry decoction is dissolved in distilled water before administration.

3.2. Acute toxicity study

The acute toxicity of *Cassia alata* aqueous extract was evaluated in mice. After sigle dose of treatment animal was observed for 14 days. The study was conducted in accordance with OECD Guideline 423 (Organization for Economic Cooperation and Development) for the testing of chemical solutions described by (Ondele and *al.*, 2015; Boumba and *al.*, 2018*)*. It allows to determine the lethal dose (LD50) and the therapeutic dose of the extracts to be used.

Protocol:

Six (6) lots of the five (5) mice per cage are distributed as follows:

– Lot 1 (control): mice received 0.5 ml / 100 g of distilled water orally, per mouse;
– Lots 2, 3, 4, 5 and 6: mice were treated with the aqueous extract of the leaves of *Cassia alata* at the respective doses of 200, 400, 800, 1600 and 3200 mg / kg orally, per mouse.

After administration of the products, mice were placed in individual cages for observation for 2 hours. These observations concerned the following toxicity parameters: mobility, alertness and response to external stimuli. The body weight of each animal was measured for 14 days.

3.3. Evaluation of the anticonvulsant effect

3.3.1. Strychnine-inducted convulsions test

The test consists of inducing tonic convulsions within 10 minutes and then death in the mice by administration of strychnine (3 mg / kg, i.p) one hour after oral administration of the products (Ngo Mbum and *al.*, 2004; Bassoueka and *al.*, 2016).

Six (4) lots of five (5) mice each are constituted and treated as follows:

– 1er lot (control) received distilled water 0.5mL / 100g per mouse;
– 2nd lot (reference) received Clonazepam at a dose of 3 mg / kg intraperitoneally per mouse;
– 3rd and 4th lots were treated with aqueous extracts of *Cassia alata* at doses of 200 and 400 mg / kg per mouse respectively;

Animals that do not have convulsions during this period or that have convulsions without dying are declared protected. The onset threshold of seizures, the duration as well as the mortality in each lot were determined.

3.3.2. Effect of extract on motor activity

We evaluated the effect of *Cassia alata* on the locomotor activity in mice

placed in a grid cage. The test were carried out according to the method described by Boissier and Simon (1967). We use the grid cage which has 16 holes at equal distance, measuring 40 × 40 cm and 1.8 cm thick. Four (4) lots of five (5) mice each are constituted and treated orally as follows (kanyonga and *al.*, 2009):

- 1st lot (control) received distilled water 0.5mL / 100g per mouse;
- 2nd lot (reference) received the diazepam at a dose of 10 mg / kg per mouse;
- 3rd and 4th lots were treated with *Cassia alata* aqueous extract at doses of 200 and 400 mg / kg.

One hour after administration of the products, animals were placed in a grid cage. The numbers of squares traveled by the animal after five minutes were thus determined for the evaluation of the motor activity.

3.3.3. Effects on barbiturate sleep

The study was conducted according the test of Rakotonina and *al.* (2001), described by Moniruzzaman and *al.* (2015) that we have modified. The barbiturate sleep potentiation test consists in inducing sleep in the mouse by intraperitoneal injection of phenobarbital (Gardénal ® Injection 200 mg / kg), one hour after administration of products. Five (5) lots of five (5) mice each were constituted and treated orally as follows:

- 1st lot (control) received distilled water at 0.5 mL / 100 g per mouse;
- 2nd lot (refence) were treated with Gardenal® (70 mg / kg);
- 3rd and 4th received respectively 200 and 400 mg / kg of *Cassia alata* aqueous extracts.

After 3 to 20 minutes, the sleeping mice were lying on their side. The time of onset and duration of sleep of each animal was determined (Rakhshandah et *al*.,2010). The duration of sleep corresponds to the time that elapses between the moment when the mouse loses the righting reflex and the moment when this reflex reappears. The loss or appearance of the reflex was measured by tickling the inner pavilion of the ear with horsehair. Unwoken mice were reactivated by moving the paw on the stimulated side.

3.4. Determination of the chemical profile of *Cassia alata* leaves aqueous extract

To identify the different chemical groups or secondary metabolites (alkaloids, flavonoids, tannins, free anthraquinones, and saponosides) in ordor to establish relation between pharmacological effects and chemical composition of extract, a chemical screening was carried out. For this purpose, we used classical phytochemical tests based on coloring and precipitation reactions (Sofowora, 1996).

3.4.1. Search of alkaloids

To 0.5 g of the plant material was added 15 ml of ethanol. After stirring for 30 minutes, the extract was filtered. To 5 mL of the filtrate obtained, 3 mL of 1N hydrochloric acid and a few drops of the MEYER reagent were added. The test is positive when there is a yellowish-white precipitate.

3.4.2. Search of flavonoids

In a test tube was poured 3.5 mL of solution of each extract and 1.5 mL of isoamyl alcohol, then 3 mL of concentrated hydrochloric acid followed by a few grains of magnesium chips. The appearance of a characteristic coloration indicates the type of flavonoids present:
orange-pink: presence of flavones;
purplish pink: presence of flavanones;
red: presence of flavonols.

3.4.3. Search of tannins

In a test tube, 2.5 mL of each aqueous extract was mixed with 1.5 mL of 1% iron trichloride ($FeCl_3$). The appearance of a black or greenish blue color indicates that the test is positive.

3.4.4. Search of saponosides

2 g of powder of each plant are put in 100 ml of distilled water for a decoction for 30 minutes, after cooling and filtration; the

volume is readjusted to 100 ml. In a series of ten test tubes 1, 2, 3, 4, 5, 6, 7, 9 and 10 mL of plant extract were distributed. The volume of each tube was adjusted to 10 mL with distilled water and then shaken each tube horizontally for ten (10) to fifteen (15) seconds. Each tube was placed in vertical position for 15 minutes and then the height of the persistent foam was measured. If the height is greater than or equal to 1 cm, it indicat that the plant extract contains saponosides.

3.4.5. Search of free anthraquinones

From 2.5 mL of the aqueous extract of each plant, 1 mL of 10% sodium hydroxide (NaOH) was added. The test is positive when there is a red color.

3.5. Statistical analyzes

The results expressed in means averaged of the standard error were subjected to one-way analysis of variance followed by the Student-Fischer t-test. The difference observed was significant when the value of t calculated is, in absolute value, greater than the value of t read in Student's t table.

IV. RESULTS

I.1. Acute toxicity study

1.1. Effects of *Cassia alata* aqueous extract on behavior, general condition and mortality

The study of acute toxicity in mice shows that the aqueous extract of *Cassia alata* was well tolerated, no mortality was observed until the dose of 3200 mg / kg. According to the globally harmonized classification system of the OECD (2001), this extract can be classified in category 5 with the LD50 higher than 3200 mg / kg.

The aqueous extract of *Cassia alata* administered orally at the doses of 200, 400, 800, 1600 and 3200 mg / kg, causes a decrease in spontaneous mobility, sensitivity to pain induced by pinching of the tail, the reaction to external stimulus and lead to sleep compared to control mice (distilled water 0.5 mL / 100g, per os).

Table 1: General state of animals after administration of aqueous extracts of *Cassia alata*

Parameter	**Treatments**					
	Distilled Water	***Vitex madiensis* Oliv leaves aqueous extract**				
	10 mL/kg	**200 mg/kg**	**400 mg/kg**	**800 mg/kg**	**1600 mg/kg**	**3200 mg/kg**
Mobility	N	D	D	D	-	--
Aggressiveness	N	A	A	A	A	A
Salt state	N	N	N	N	N	N
Pain sensitivity	N	D	D	D	-	A
Vomiting	A	A	A	A	A	A
Vocalization	A	A	A	A	A	A
Erection pilot	A	A	A	A	A	A
Tail state	N	N	N	N	N	N
Ptosis	A	A	A	A	-	+
Falling asleep	A	A	A	A	+	+
Vigilance	+	+	+	-	-	-
Deaths number	A	A	A	A	A	A
A : Absent ; N : Normal ; + : yes ; -very weak; -- : no reaction ; D :decrease ; n=5 mice						

1.2. Effect of *Cassia alata* aqueous extract on the weight evolution of mice

Figure 1 shows the evolution of the weight of the mice after administration of *Cassia alata* leaves aqueous extract (200, 400, 800, 1600 and 3200 mg / kg). The animals showed a significant ($p < 0.05$) increase in body weight compared to the first day and a control group, except at doses of 1600 and 3200 mg / kg.

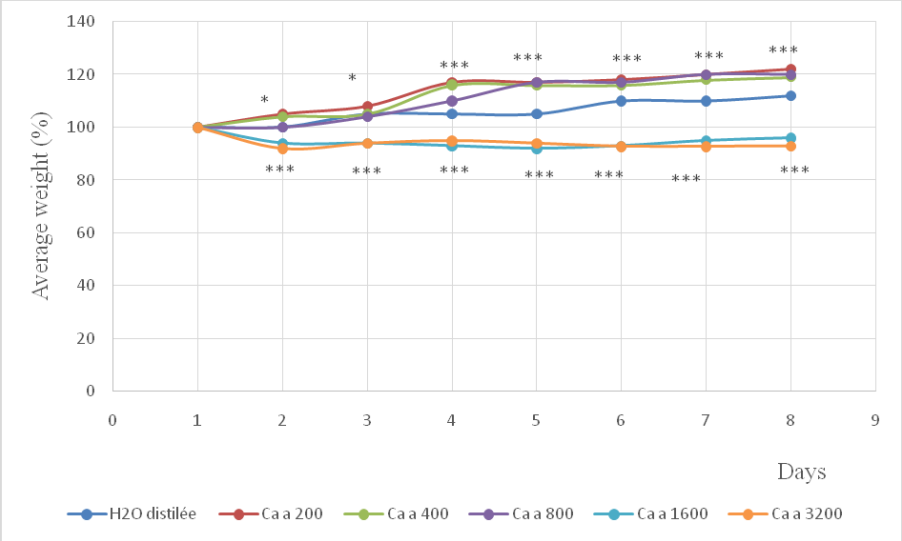

Figure 1: Effect of Cassia alata aqueous extract on the weight evolution of the mice, the values are expressed on average ± ESM, n = 5, ** p <0.05; *** p <0.001, Ca a = Cassia alata

1.2. Anticonvulsant effects of *Cassia alata* leaves aqueous extracts

Table 2 shows that the aqueous extract of *Cassia alata* leaves at doses of 200 and 400 mg / kg increase the threshold of appearance and reduce the duration of convulsions significantly

Table 2: Effects of the aqueous extracts on the convulsions induced by strychnine			
Products	**Doses**	**convulsions onset threshold (min)**	**Duration of convulsions (min)**
Distillid water	0,5mL/ 100 g	2,80 ± 0,37	9,40 ± 0.40
Clonazepam	3 mg/kg	7,80 ± 0,66 ***	3,00 ± 0,44 **
Cassia alata Extract	200 mg/kg	5,40 ± 0,24 *	3,00 ± 0,31 **
	400 mg/kg	6,40 ± 0,24 **	2,40 ± 0,24 **
Values are means ± ESM, with n = 5; *** p <0.001; * p <0.05; ** p <0.01 significant difference compared to the control (distilled water). (***p < 0.001).			

I.3. Sedative effects of the aqueous extract of *Cassia alata*

3.1. Effect of aqueous extracts of *Cassia alata* on motor activity

The results obtained in Table 3 show that the aqueous extract of *Cassia alata* significantly reduces the motor activity at doses of 200 and 400 mg / kg.

Table 3: Effects of *Cassia alata* aqueous extracts on motor activity in mice.		
Products	**Doses**	Number of squares crossed after five (5) minutes
Distillid water	0,5 mL/100 g	267,00 ± 2,66
Diazepam	10 mg/kg	163,40 ± 4,27 ***
Cassia alata aqueous extract	200 mg/kg	185,00 ± 3,87 ***
	400 mg/kg	160,40 ± 5,74 ***
Values are means ± ESM, with n = 5; *** p <0.001 significant difference compared to the control and NS: non-significant difference compared to the control (distilled water).		

3.2. Effect of *Cassia alata* aqueous extract on the barbiturate sleep

Table 4 shows that at doses of 200 and 400 mg / kg, the extract: decrease the time of onset of barbiturate sleep and increase the duration of barbiturate sleep significantly (*** p <0.001) in mice.

Table 4 : Effects of *Cassia alata* aqueous extract on barbiturate sleep			
Produits	**Doses**	**convulsions onset threshold (min)**	**Sleep duration (hour)**
Distilled water	0,5 mL/100 g	16,60 ± 0,24	12,76 ± 0,19
Diazepam	10 mg/kg	6,80 ± 0,37 ***	19,76 ± 0,19 ***
Cassia alata aqueous extract	200 mg/kg	9,20 ± 0,37 ***	16,96 ± 0,31 ***
	400 mg/kg	4,00 ± 0,44 ***	17,00 ± 0,31 ***
Values are means ± ESM, with n = 5; *** p <0.001 significant difference compared to rats given distilled water.			

I.4. Chemical profile *Cassia alata* leaves aqueous extract

The chemical groups highlighted in *Cassia alata* leaves aqueous extract by tube reactions are shown in Table 5. The presence of flavonoids, alkaloids and tannins has been demonstrated in this extract.

Table 5: Results of the chemical screening of *Cassia alata* leaves aqueous extract

Cassia alata	Chemical families						
	Alkaloids	Saponosides	Tannins	Free anthraquinones	Flavonoids		
					Flavones	flavanones	flavonols
Extract	++	-	+	+	+	-	+

+: scarce; ++: abundant; +++: very abundant; -: negative test.

V. DISCUSSION

Bibliographic research has retained *Cassia alata* that is supposed to be anticonvulsant and sedative (Bassoueka et *al*., 2015). This study was conducted with the aim of evaluating the anticonvulsant and sedative effects that explains the uses of this plant in traditional medicine.

It is very important to evaluate the acute toxicity of extracts from traditional plants. The study of the acute toxicity of an extract or a drug is essential for the determination of the LD50 which makes it possible to adapt the treatment to the limits of tolerance, thus to fix the therapeutic dose (Philippe et al., 2004; Nsonde Ntandou et *al*., 2017). This study showed that the aqueous extract of *Cassia alata* used caused sedation in mice, which was manifested by falling asleep, as well as decreased spontaneous mobility, pain sensitivity, and stimulus response. However, no mortality is observed after oral administration at doses of 200, 400, 800, 1600 and 3200 mg / kg of the aqueous extract of *Cassia alata*. Thus, the doses of 200 and 400 mg / kg were chosen for the rest of the work. However, this extract is considered to be of low toxicity with an LD50 greater than 3200 mg / kg according to the Globally Harmonized System (OECD 423, 2001). This result is similar with those find by Roy et al. (2016) in the acute toxicity study of *Cassia alata* aqueous extract, sample of India.

The weight change analysis showed a significant increase in the weight of the mice treated with the aqueous extracts of *Cassia alata* up to the dose of 800 mg / kg. A diet that exceeds the coverage of energy needs leads to an increase in body weight, the deficiency leads to weight loss (Mohamed et *al*., 2014). This observation suggests that this extract contains chemicals that, at a dose below 1600 mg / kg, would promote hungry.

To evaluate the sedative effect of *Cassia alata,* two pharmacological tests were carried out, this is the evaluation of the effect of the two extracts on the motor activity of mice and the potentiation of barbiturate sleep (Narwal et al., 2012.; Rakhshandah et al., 2010).

Under our experimental conditions, at doses 200 and 400 mg / kg, the aqueous extract of *C. alata* significantly reduces the motor activity compared to distilled water. Indeed, it was noted a significant decrease in motor activity by diazepam at 10 mg / kg used as a reference molecule. It was found that the mice that received diazepam had an average of 163.40 squares traveled compared to the average of 267.00 squares traveled by the mice that received distilled water, a decrease of 38.80%.

At a dose of 400 mg / kg, the extract seems to have the same effects as diazepam on the decrease in motor activity with an average of 160.40 squares traveled by the mice, a decrease of 39.92%. This tranquilizing effect is related to the presence of alkaloids in the leaves of *Cassia alata*. The extract of *C. alata* decreases the time of onset and increases, the duration of barbiturate sleep at doses of 200 and 400 mg / kg, significantly. Diazepam 10 mg / kg was used as the reference product (Kyung et *al*., 1996). There has thus a decrease in the time to onset of barbiturate sleep by diazepam, which goes from 16.60 minutes to 6.80 in the control lot; a decrease of

59.03%. Diazepam increases the duration of barbiturate sleep from 12.76 minutes for controls to 19.76 minutes; an increase of 35.42%.

However, the extract appears to be more effective than diazepam in reducing the time to onset of the barbiturate sleep at 400 mg / kg with a reduction of 75.90% for *Cassia alata*.

The potentiation of barbiturate sleep is thought to be due to the presence of alkaloids and flavonoids in this extract (Silva et *al*., 2011).

These observations suggest that the extract has some sedative properties of tranquilizers and hypnotics, which may be involved in the anticonvulsant activity described below (Geoffrey et *al.*, 1995).

A literature review on the phytochemical and pharmacological properties of different *Cassia species* by Shoba Sundaramoorthy et *al*.(2014) reported that *Cassia siamea* an another species of Cassia genus has sedative effects, in particular anxiolytic related to the presence of alkaloids and flavonoids (Bilala et *al.*, 2005; Silva et *al*., 2001). Thus, this work allows us to support our results obtained on the sedative effects of *C. alata* which would be due to the presence of alkaloids and flavonoids highlighted in our study. Indeed, there are almost the same chemical groups in all species of *Cassia*.

Among the most commonly employed animal models in the search for new anticonvulsant drugs is the strychnine test, it is thought to be predictive of anticonvulsant drug efficacy against generalized tonic-clonic seizures (Makarovsky et *al.*, 2008; Probst et *al.*, 1986).

The anticonvulsant activity of the extract was studied using strychnine as convulsant; this substance produces marrow convulsions. The injection of strychnine into the animal first induces hyperexcitability, an increase in reflexes and convulsions (Bassoueka et *al.*, 2016).

Under our experimental conditions, the aqueous extract of *Cassia alata* significantly increases and decreases, respectively the threshold of appearance and the duration of convulsions at doses of 200 and 400 mg / kg. The reference product used is clonazepam (Rivotril *) at a dose of 3 mg / kg. Clonazepam significantly increases the time to onset of convulsions, from 2.8 minutes (for control) to 7.80 minutes; an increase in the onset of convulsions of 64.10%. The duration of convulsions is significantly reduced by clonazepam from 9.40 minutes (negative controls) to 3 minutes, a reduction of 68.08%. This anticonvulsant activity is maybe due to the presence of flavonoids in the leaves of *Cassia alata*.

A literature review on the phytochemical and pharmacological activities of different Cassia species by Sundaramoorthy et *al*. (2014) reports that *Cassia fistula* and *Cassia sophera* have anticonvulsant effects due to the presence of flavonoids in these plants (Sundaramoorthy et al., 2016). As part of the same genus in the phylogenetic classification, and having almost the same chemical composition, the anticonvulsant activity of *Cassia fistula* and *Cassia sophera* confirms the results obtained in our work on the anticonvulsant effect of *Cassia alata*.

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