



## Study of the Acute Toxicity and Antipyretic Activity of the Aqueous Extract of the Bark *Distemonanthus benthamianus* Baill (Caesalpinaceae: Leguminosae -Caesalpinioideae)

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### Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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### ABSTRACT

**Aims:** *Distemonanthus benthamianus* is a widespread plant in West Africa. The bark of its stem is used popularly to treat a variety of illnesses, including fever, bronchitis, rheumatism and malaria. The objective of this work is to evaluate the antipyretic activity of the aqueous extract of the bark of *Distemonanthus benthamianus*.

**Materials and Methods:** The aqueous extract of the bark of *D. benthamianus* was tested for their acute oral toxicity in rats. Antipyretic activity was studied in rats of the Wistar strain made feverish after subcutaneous injection of an aqueous suspension of brewer's yeast (*Saccharomyces cerevisiae*) 20% compared to aspirin.

**Results:** This study showed that administration of the extract at doses of 300, 2000 and 5000 mg / kg / kg dry extract in rats showed no acute toxicity or adverse effects. The results showed that the best antipyretic activity of the extract was recorded at a dose of 800 mg / kg, at the third hour, with a decrease in fever from  $39.29 \pm 0.14^{\circ}\text{C}$  to  $37.75 \pm 0.25^{\circ}\text{C}$ , i.e. a percentage inhibition of 57%

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against 62% for the standard molecule ( $p > 0.05$ ). At this dose, CRP was  $3.85 \pm 0.1$  mg / L compared to that of the healthy control which was  $2.78 \pm 0.35$  mg / L. The results of the albumin assay did not show a significant difference between the treated and untreated fever groups and the healthy control group. In addition, the results showed that the leukocyte level in the feverish control rats is very high ( $18.84 \times 10^3$  / mm<sup>3</sup> of leukocytes) compared to the healthy and treated control rats. **Conclusion:** The aqueous extract of the bark of *Distemonanthus benthamianus* is not oral toxic and has interesting antipyretic activities similar to aspirin. The results obtained confirm the validity of the traditional indication of this plant in the management of fever by African populations.

**Keywords:** *Distemonanthus benthamianus*; antipyretic; hyperthermia; fever.

## 1. INTRODUCTION

Fever is an above normal rise in body temperature as a result of a signal from the brain (hypothalamus) that increases the temperature in response, most often, to an infection. Symptoms caused by the increase in body temperature are chills, feeling cold, mottled skin and cold extremities. It can cause to a deterioration in general condition with fatigue, loss of appetite and irritability. Fever also causes increased heart and respiratory rates. This situation can be uncomfortable and therefore warrants treatment. The aim of the treatment is to eliminate this discomfort with antipyretics. However, according to the World Health Organization, 80% of the world's population has resort to herbal treatment for self-care, especially in developing countries [1]. In Ivory Coast, a major part of the population has resorted to traditional medicine to deal with health problems, given the problem of cost and accessibility of specialties.

*Distemonanthus benthamianus* Baill. is one of the many medicinal plants used by the population and especially in West Africa. *D. benthamianus* is used for its therapeutic virtues and especially in the treatment of malaria and fever [2,3]. The bark extract is also used as a laxative and pain reliever as well as parasitic infections [4,5].

The aqueous extract contains numerous molecules such as polyphenols, flavonoids, tannins, saponosides, terpenoids and alkaloids endowed with biological activities [6]. The aim of our study is to determine the acute toxicity and antipyretic properties of the aqueous extract of the bark of *D. benthamianus* Baill.

## 2. MATERIALS AND METHODS

### 2.1 Plant Material

The plant material consisted of the bark of *D. benthamianus* Baill. collected in Yakasse-Mé,

Ivory Coast. The sample was authenticated at the Botanical Garden of Felix Houphouët Boigny University by Yapo Assi Fulgence. This specimen listed in the herbarium index under the number 12473 of the said structure.

### 2.2 Animal Material

36 male and female Wistar rats weighing 120 to 140 g of body weight from the pet shop of the National School of Abidjan were used. They were fed standard with a free access to tap water and subjected to a rhythm of daytime night lighting (12 hours of lighting, 12 hours of darkness). The animals were fasted 24 hours before any experiment.

### 2.3 Methodology

#### 2.3.1 Preparation of plant extracts

The bark was cut up and then dried in the shade at room temperature for two weeks. The bark, which had become dry, was pulverized into a fine powder using an IKAMAG-RCT grinder. A total of 100 g of powder from the bark of the plant was dissolved in 1000 ml of distilled water and homogenized with a blender for 15 minutes at room temperature at a speed of 3000 rpm. The obtained homogenate was filtered through poplin cloth and then through cotton wool. The filtrate was dried in a med center venticell type oven at 40°C to obtain the dry extract [7]. The extract obtained, which is brown in color, is then stored until use.

#### 2.3.2 Acute oral toxicity study

It is used as a preliminary study for the subacute toxicity test and was demonstrated using the limit test method of protocol 423 of the OECD [8].

##### 2.3.2.1 Determination of the LD50 by the OECD method 423

The test was performed on female rats, young adults and 8 to 12 weeks old and their body

weights varied between ( $\pm 15\%$ ) of the mean initial weight of the animals.

Animals are selected at random, individually marked for identification, and kept in their cages seven days before administration of the substance, to acclimatize to laboratory conditions.

The LD50 will be determined from the limit tests at 300, 2000 and 5000 mg / kg / bw. For each batch, a single dose of the extract was administered and the effects on the behavior and life of the treated animal will be observed.

- Limit tests at 300 and 2000 mg/kg/ bw.

The animals will be divided into groups of three animals each. Two groups will receive one the dose of 300 mg/kg/bw and the other the dose of 2000 mg/kg/bw. Then the last group will receive the same dose of 2000 mg/kg/bw to confirm the first result. Otherwise, if the 2000 mg/kg/bw value is not found to be toxic, the higher dose (5000 mg/kg/bw) is used to determine the toxicity of the plant.

The animals will be deprived of food, but will have access to water for 3 hours and then weighed before the extract is administered. Using a cannula, the extract will be administered in a single dose at a rate of 1 ml/100 g/bw.

The animals will be deprived of another sixty minutes before they have access to food after administration of the product.

The last group of rats will be treated at 48 hours intervals. The animals will be observed individually after the treatment, at least once during the first thirty minutes on a regular basis then daily for 14 days in order to identify any changes in behavior [9].

- Limit tests at 5000 mg / kg / bw

The 5000 mg / kg / bw limit test will be performed when the LD50 is greater than 2000 mg / kg / bw. The administration of the extract will be carried out in the same manner and under the same conditions as those of the limit test at 2000 mg / kg / bw. Three rats will also be used for this test.

### 2.3.2.2 Observation

After administration of the extract, the animals will be observed individually and regularly during the first 24 hours that follow.

After these 24 hours the animals will be followed daily over a period of 14 days. Observations will focus on mobility, sensitivity to noise and pinching, feeding, the appearance of the buttocks and breathing.

## 2.3.3 Evaluation of the antipyretic activity

### 2.3.3.1 Principle

The subcutaneous injection of an aqueous suspension of brewer's yeast (*Saccharomycete cerevisiae*) 20% causes an increase in the rectal temperature of the rats. The evaluation of the antipyretic activity consisted of determining the rectal temperature of the rats following administration of the products [10].

### 2.3.3.2 Protocol

Animals were selected for the experiment after confirmation of their constant rectal temperature for approximately 4 days. The antipyretic activity of the extracts was evaluated using the method which induces fever by brewer's yeast. Thus 12 g of brewer's yeast was diluted in 60 ml of 0.09% NaCl to obtain 20% of brewer's yeast suspension. Hyperthermia is induced in rats by the subcutaneous injection of an aqueous suspension of brewer's yeast (*Saccharomycete cerevisiae*) 20% at a dose of 20 ml/kg [11,12].

The rectal temperature is taken before administration of brewer's yeast (basal T °). 16 hours after the brewer's yeast injection, the rectal temperatures of each animal were taken with a thermometer. All the animals which showed an increase in temperature of about 1.5°C were selected, so the different batches were made by homogenizing the initial temperatures T<sub>0</sub>. This experiment involved 6 homogeneous batches of 6 rats each:

- Healthy control group: rats not receiving yeast solution and receiving 0.9% saline solution (healthy MT).
- Control group with fever: Received 0.09% saline solution by gavage (TMF).
- Reference group: Receives acetylsalicylic acid at 100 m/kg/bw by gavage. EADB2 and EADB3 groups: these batches receive the aqueous extract at a dose of 400 mg/kg/bw and 800 m/kg/bw respectively.

Rectal temperature was measured every 1 hour and for 4 hours after administration of the test substances. Rectal temperature was measured

by inserting about 2 cm of a lubricated digital thermometer probe into the rectum of the rats.

The thermometer displays temperatures with an accuracy of 0.01°C. The values shown have been manually recorded.

The antipyretic activity of the products tested was estimated by determining the percentages of hyperthermia, calculated according to the equation

$$PIF = \frac{MF - MT}{MF}$$

PIF : Percent inhibition of fever,

MF : Average temperature of the feversh control batch,

MT : Average temperature of the treated areas

### 2.3.3.3 Evaluation of blood parameters

After testing for antipyretic activity in rats, blood was collected by incision from a small portion of the tail of the anesthetized rat (less than 5mm). To facilitate collection, the tail was pre-heated in water to induce vasodilation. Blood was collected in dry and EDTA tubes respectively for CRP and albumin assay as well as blood count (CBC) [13].

## 2.4 Statistical Analysis of Results

The results were expressed as an average with standard errors on the mean (Mean ± ESM). The Graphical representation of the data was made using Graph Pad Prism 7.0 software (Microsoft USA). Statistical analysis of the results was carried out using analysis of variance (ANOVA ONE WAY). The differences between the means were determined according to the Dunnet comparison test, p values lower than 0.05 is considered significant.

## 3. RESULTS

### 3.1 Acute Toxicity

Single administration at doses of 300, 2000 and 5000 mg/kg/bw revealed no clinical signs of toxicity during the 24 hours of observation and even during the two weeks of observation. Single administration at different doses did not caused any deaths during the two weeks of observation. Table 1 summarizes the different parameters on which the observations were made. No change in behavior was observed at the different doses

administered over the 14 days. At a dose of 5,000 mg/kg/bw, rats showed signs of sedation within the first 30 minutes. Table 2 shows the weight gains of the rats at the different doses. There is no significant variation (p> 0.05) in the weights of the treated rats compared to healthy controls was observed, which did not receive any products. According to the OECD 407 LD50 method, the LD50 of aqueous extract of *D. benthamianus* in rats is greater than 5000 mg/kg/bw.

### 3.2 Evaluation of Antipyretic Activity

Intra peritoneal injection of 20% brewer's yeast caused an increase in temperature in rats. Rats had an average basal temperature of 37.27°C; their temperatures rose to 39.23°C (on average after the yeast injection).

A significant difference was observed between the batches which received the yeast and the controls which did not receive brewer's yeast (healthy control) (P < 0.0001). One hour after the various treatments, a significant decrease in temperatures was observed between the treated batches and that of the fever control, which are the untreated rats, after the administration of brewer's yeast.

Acetylsalicylic acid showed a decrease in temperature from the first hour, from 39.07 ± 0.15°C to 38.17 ± 0.22°C, which corresponds to a percentage inhibition of 56.81%.

The batches treated with the aqueous extract of *D. benthamianus* all also experienced a decrease in temperature from the first hour. For batches EADB2 and EADB3, it was therefore observed respectively a decrease of 39.1 ± 0.14°C at 38.33 ± 0.26°C and of 39.13 ± 0.18°C at 38.11 ± 0.32°C, which corresponds respectively to percentages of 42.26% and 48.41% inhibition. The temperature drop was very marked at the third hour with a percentage inhibition of hyperthermia of 60.39%, 57.22% and 45.46% respectively for the Aspirin, EADB2 and EADB3 lots.

The results of Fig. 2 indicate that the CRP of the feversh control rats is significantly higher (p < 0.0001) than that of the healthy controls. It was also observed that there is a significant difference in the levels of the EAD2 and aspirin batches (p < 0.05) compared to the healthy controls. On the other hand,

there is no significant difference between EADB3 and healthy controls ( $p > 0.05$ ).

The result of the albumin level of the healthy control rats which is  $34.67 \pm 1.45$  g / L is higher than that of the rats of the other batches (Fig. 3). However, no significant difference ( $P > 0.05$ ) was observed between the different batches. Control rats with fever with a concentration of  $28 \pm 1.15$  g / L, recorded the lowest concentration. As for the leukocyte level of the feverish control rats, it is significantly higher ( $p < 0.001$ ) of the healthy controls. However, no significant difference ( $P > 0.05$ ) was observed between the white blood cell count of treated and healthy controls.

#### 4. DISCUSSION

Acute toxicity tests carried out in accordance with OECD protocol 423 [14] have confirmed that the aqueous extract is non-toxic. The results obtained did not reveal any particular signs of toxicity in rats during 14 days of observation. Oral administration of doses of 300, 2000 and 5000 mg / kg body weight of the extract has not resulted in mortality. In addition, monitoring of the evolution during the 14 days of observation showed a stability of the body weight of the rats tested compared to the controls. This proves that the plant did not cause obesity and weight loss. As a result, the aqueous extract of the bark

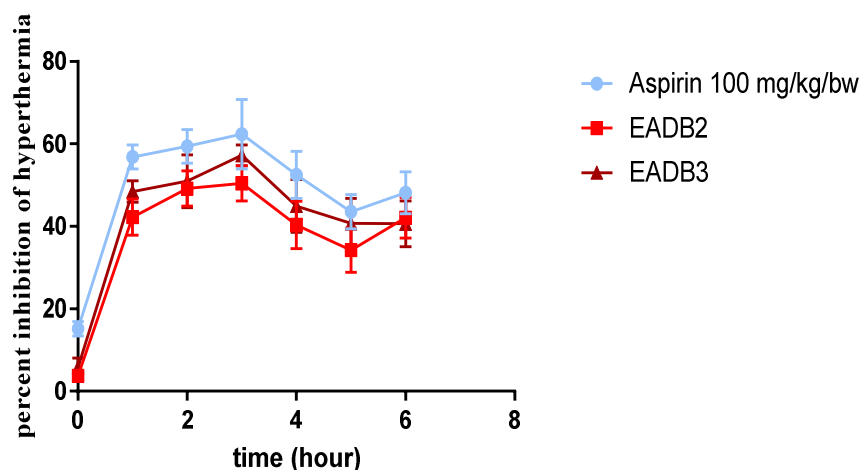
**Table 1. Summary table of signs of toxicity<**

Warning sign	Witness	EADB300	EADB2000	EADB5000
Calm	-	-	-	+ (WHILE 30 min)
Abdominal twists	-	-	-	-
Leg paralysis	-	-	-	-
Breathing	-	-	-	-
Loss of appetite	-	-	-	-
Drowsiness	-	-	-	-
Diarrhea	-	-	-	-
Debituria	-	-	-	-

Negative - ; positive +

**Table 2. Weight gain during acute toxicity**

Weight gain	Witness	EADB 300 mg/kg/bw	EADB 2000 mg/kg/bw	EADB 5000 mg/kg/bw
(P2-P0)/P0	0,71428571	0,52631579	0,53394355	0,63529412
(P7-P0)/P0	2,35714286	3,7593985	2,21205187	2,4117647
(P14-P0)/P0	4,28571429	4,58646617	4,50038139	4,4705882



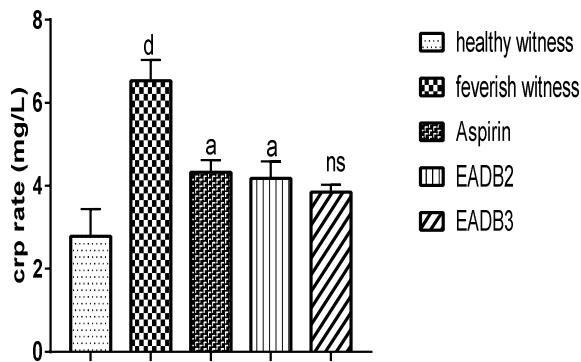
**Fig. 1. Percent inhibition of hyperthermia by EADB and Aspirin induced by brewer's yeast test**

**Table 3. Antipyretic effect of aqueous extract of *Ditemonanthus benthamianus* and acetylsalicylic acid on hyperthermia induced in rats by injection of brewer's yeast**

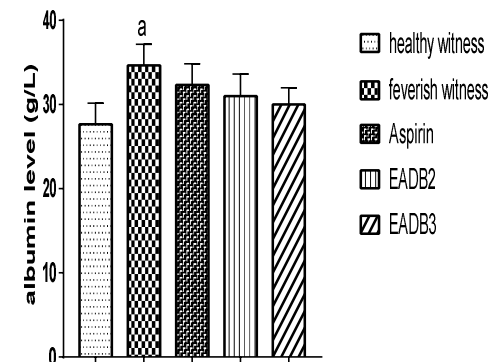
	Tbasal	T0	T1	T2	T3	T4	T5	T6
TMS	37.11±0.13	-	-	-	-	-	-	-
TMF	37.12±0.2	39.4±0.1	39.21±0.1	39.21±0.1	39.17±0.1	39.37±0.1	39.3±0.1	39.22±0.1
Aspirin	37.41±0.1ns	39.17±0.1ns	38.17±0.2a	38.01±0.2b	37.92±0.2b	38.37±0.1c	38.55±0.1b	38.42±0.1a
EADB2	37.45±0.2 ns	39.22±0.1ns	39.22±0.1ns	37.96±0.2b	37.86±0.2b	38.36±0.1c	38.51±0.1b	38.34±0.2b
EADB3	37.25±0.1 ns	39.29±0.1ns	37.97±0.3b	37.75±0.2c	37.81±0.2b	38.3±0.19d	38.49±0.1b	38.27±0.1a

ns: not significant; a : \*; b: \*\*; c : \*\*\*; d: \*\*\*\*

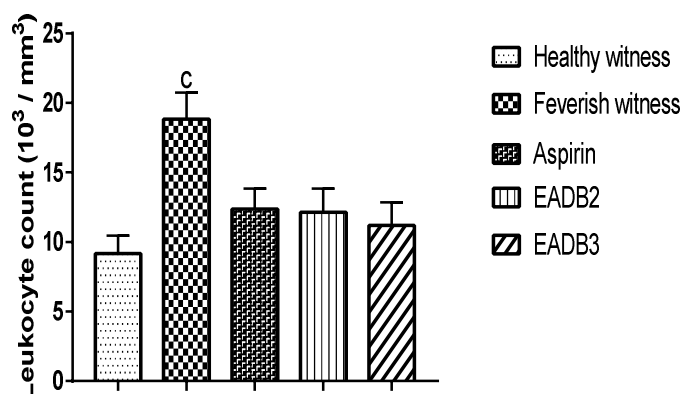
The values expressed are the average temperatures expressed in ° C ± SEM, \* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001 and \*\*\*\* P < 0.0001: is considered significant with respect to negative control



**Fig. 2. Serum CRP concentration level (mg / L) rats "Antipyretic test"**  
 ns: not significant; a : \*; d: \*\*\*\*; Values are the means of CRP levels (mg / L) ± S.M. (standard error on the mean) with n = 6, \* p < 0.01 and \*\*\*\* p < 0.0001: statistically different from the positive control



**Fig. 3. Effect of EADB and Aspirin on Albumin Levels (g / L)**  
 ns: not significant; a : \*  
 The values are the means of the levels of Albumin ± S.M. (standard error on the mean) with n = 6, \* p < 0.05: statistically different from the positive control



**Fig. 4. Effect of EADB and aspirin on the white blood cell count (10<sup>3</sup>/ mm<sup>3</sup>)**

ns: not significant; vs:\*\*\*

The values are the means of the blood cell counts  $\pm$  S.M. (standard error on the mean) with  $n = 6$ ,

\*\*\*  $p < 0.001$ : statistically different compared to the healthy control

of *D. benthamianus* belongs to category 5 and considered as a non-toxic substance by the oral route, according to the Globally Harmonized System of classification and labeling of chemicals [8,15]. The extract does not show any signs of toxicity to the feeding behavior of animals. These results confirm the safety of the traditional form of use of the bark of *D. benthamianus*. Some authors have also shown that plants of the same family do not exhibit high dose toxicity. *Caesalpinaceae* such as *Casia siaméa*, *Mezoneuron benthamianum* and *caesalpinia pulcherrina* have an LD50 greater than 2000 mg / kg / bw [16,17,18]. The LD50 of *Cassia fistula* was greater than 5000 mg / kg / bw [19] and the toxicity study of *Delonix regia* showed that the oral administration of 7500 mg / kg / bw showed no signs of toxicity [20].

Fever is caused by exogenous substances such as bacteria, endotoxins, microbial infections responsible for the production of pro-inflammatory mediators. These mediators stimulate the synthesis of prostaglandins (PGs) by exerting their action at the level of the hypothalamic center, thus causing a rise in the thermostat [12,21,22]. Inhibition of fever may be the mechanism of action of antipyretics by blocking the enzymatic activity of cyclooxygenase [23]. The study of hyperthermia induced by brewer's yeast, after administration of Aspirin, a reference antipyretic molecule and the extract of the plant at doses of 400 and 800 mg / kg / bw, revealed the antipyretic properties of this plant. In fact, unlike the feverish control rats,

Aspirin and extracts caused the temperature to drop below the temperature of the feverish control group rats.

Aspirin was used as the benchmark analgesic substance in this study, characterized by a plasma half-life of 2 hours and an absorption interval of 2 to 3 hours after oral administration [24].

The maximal activity of aspirin was observed in the first three hours namely 58.91%, 59.41% and 62.39% respectively at 1 hours, 2 hours and 3 hours after its administration.

The decrease in antipyretic activity over the following hours is related to the plasma half-life of the reference product. This work is consistent with the work done by some authors [25,26] with Aspirin at a dose of 100 mg / kg / bw. These results are similar to the antipyretic activities of certain *caesalpinaceae*, namely the bark *Cassia siamea*, the seeds of *Caesalpinia bonducella* which, from a dose of 200 mg / Kg, strongly reduced the fever induced by brewer's yeast [16,27].

The best antipyretic activity of EADB was recorded at a dose of 800 mg / kg, at the third hour, with a decrease in fever from  $39.29 \pm 0.14$  C to  $37.75 \pm 0.25$ °C, i.e. a percentage inhibition of 57% against 62.39% for the standard molecule ( $p > 0.05$ ). This presages an activity of the crude extract which would be equivalent to that of aspirin which is a pure molecule. The aqueous extract of *D. benthamianus* and aspirin reduced

the hyperthermia caused by the injection of brewer's yeast. Unlike hypothermic substances, aspirin and the aqueous extract of the bark of the plant did not cause the rectal temperature to drop below the rat's normal temperature which is between 37 and 37.5 °C. In addition, the products administered do not induce irreversible hypothermia because these effects wear off 4 hours after the different treatments, as has been observed with extracts of *Kaya senegalensis* [28].

The antipyretic effect of EADB could be linked to complex mechanisms involving immunoinflammatory reactions, with release of endogenous pyrogens and prostaglandins [29,30,31]. In fact, the subcutaneous injection of brewer's yeast induces fever by the synthesis of PGs. The plant would block the enzymatic activity of cyclooxygenase, thus inhibiting the synthesis of PGs through their action at the level of the hypothalamus, thus exerting their antipyretic effect [30]. It is possible that the antipyretic properties of aspirin and the aqueous extract of the bark of *D. benthamianus* are due to inhibition of cytokine release and prostaglandin biosynthesis [32,33]. The extract's antipyretic properties may be due to saponins, which are potent inhibitors of prostaglandins, as are flavonoids and phenolic compounds [34].

C-reactive protein, naturally occurring in plasma in trace amounts, increases in response to infection or tissue inflammation, within 4 to 6 hours of the onset of an inflammatory process [35,36]. It would also have a role in immunity by participating in the activation of the complement system, the mobilization and activation of leukocytes, the stimulation of phagocytosis and the secretion of cytokines by monocytes [37]. Hyperthermia reflects an inflammatory process, and therefore CRP is rarely normal [36,38]. Products administered to rats reduced the CRP of rats given brewer's yeast.

There is no significant difference in CRP between the batch treated with the extract at 800 mg / kg / bw and the healthy control. Indeed, previous studies have showed that a diet rich in antioxidants was inversely correlated with markers of inflammation (CRP, IL-6) in human plasma [39]. As for albumin level, the results indicate a non-significant decrease in the albumin levels of the rats which were administered by the yeast compared to the

control rats. In fact, the total protein concentration decreases appreciably in the first days of the inflammatory reaction, mainly due to the plasma exudation and the decrease in the hepatic synthesis of albumin, a protein of the negative acute phase. It seems that this is the consequence of an orientation of the hepatocyte metabolism towards a preferential synthesis of positive total proteins of the inflammation such as CRP, haptoglobin, orosomucoid, fibrinogen and ceruloplasmin to the detriment of the proteins of the negative acute phase. (albumin, prealbumin and transferrin) [40].

This phenomenon would make it possible to counterbalance the increase in oncotic pressure due to positive proteins, and provide more amino acids for their elaboration [41,42]. In addition, the results of the NFS indicate that the rats treated with the different products showed no significant difference from healthy control rats, unlike the untreated feverish rats, which showed a significant difference ( $p < 0.001$ ). Indeed, during inflammatory processes, the activation of leukocyte cells induces the secretion of several pro-inflammatory mediators such as TNF- $\alpha$ , interleukins and prostaglandins (IL-1, IL-6) [43,44].

The results obtained in this activity give the plant antipyretic properties. The effect of this extract in this test is dose-dependent since at 800 mg / kg/bw, the extract appears to be active like aspirin.

## 5. CONCLUSION

The present study has shown that the aqueous extract of the bark of *D. benthamianus* is not toxic by the oral route and is also thought to have interesting antipyretic activities, similar to aspirin. Further analysis will allow us to quantify this antipyretic activity by precisely establishing the dose-response relationship and subsequently, to produce an improved traditional drug against fevers, after preclinical and clinical tests.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The animals were used under ethical and deontological conditions under the tutelage of our Supervisor.



## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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