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Antipyretic Activity of Aqueous Extract of *Daniellia oliveri* Leaves (Rolfe, Hutch Et Dalz) (Fabaceae)

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Abstract **Original Research Article**

The pharmacological study of the aqueous extract of *Daniellia oliveri* (Fabaceae) leaves revealed antipyretic properties .This dose-dependent reduction in brewer's yeast-induced hyperthermia in rats is similar to that of lysine acetylsalicylate. Qualitative phytochemical screening shows that the aqueous leaf extract of *Daniellia oliveri* contains polyphenols, flavonoids, saponosides, quinone substances, alkaloids, catechic and gallic tannins, sterols, polyterpenes and cardiodic heterosides. The oral LD_{50} of the aqueous extract of *Daniellia oliveri* leaves conducted according to OECD guideline 423 [1], is greater than 5000 mg/kg B.W, making this plant a substance of low toxicity, thus justifying its traditional use in painful ailments.

Keywords: Daniellia oliveri (Rolfe, Hutch et Dalz); Antipyretic; Lysine acetylsalicylate; Flavonoids.

INTRODUCTION

Daniellia oliveri (Fabaceae) is a plant described by Rolfe R.A., Hutchison J. and Dalziel J.M. in 1954 [2]. It is the most widespread plant in wooded savannahs, but in the Sudano- Guinean zone it is dominant in dry forests. It is a large tree reaching 25 metres in height witha conical crown and in generally spindle shape. The trunk is straight with light grey bark and the foliage is paripinnate. The secondary-veined leaflets connect before the margin, with a long bud often containing the young, rolled leaf, which is reddish-brown in colour, as is the young foliage. Its leathery, flattened pods carry a seed that remains attached to the wing of the pod by a small filament [3]. In Côte Ivoire, it is called slim, sanan respectively in Sénoufo and Malinké [4].

This plant is used in traditional medicine for various treatments: the roots are indicated against tuberculosis., the leaves are used to treat burns, headaches, glaucoma, toothache and gastrointestinal disorders, and to treat epilepsy in Mali [5], the leafy branches treat angina and liver failure. Our work aims to highlight the pharmacological activities of the aqueous extract of *Daniellia oliveri* in order to provide a scientific basis for the traditional use of this plant. The present study aims to justify the use of *Daniellia oliveri* as an antipyretic.

MATERIALS AND METHODS

Material

Plant material

Young leaves of *Daniellia oliveri* (Fabaceae) were collected in March 2017 during the dry season, in the region of Korhogo (Côte d'Ivoire). The leaves were dried at room temperature about 30 ± 2 °C in the shade. Finally, the dried leaves were ground into a powder from which the aqueous extract was made.

Animal Material

It consists of mice and rats for the study of antipyretic activity and acute toxicity. The mice are taken from *Mus musculus* species, and of the Swiss strain, weighing between 25 and 30 g, aged from 55 to 70 days. The rats belong to the species *Rattus norvegicus*. They are of the Wistar strain, weighing between 150 g and 180 g and aged from 60 to 70 days. These animals were obtained from the animal house of Ecole Normale Supérieure (ENS) in Abidjan.

The average temperature of the animal house was 28° ± 3°C with a relative humidity of 70%.The

photoperiod was 12/24. The animals have free access to water and food.

The animals have free access to water and food. All the experimental protocols are conducted following the European directive of November 24, 1986 (86/609/EEC) and the decree of April 19, 1988, [6] relating to the use of experimental animals in research.

Chemical products

- Distilled water used for extraction and for dilutions ;
- Physiological NaCl 9‰ solution for dilution of *Daniellia Oliveri* leaf lyophilisate and lysine acetylsalicylate;
- Lysine acetylsalicylate (Aspegic®, Sanofi France) used as the reference antipyretic molecule;
- Brewer's yeast (Gayelord-Hauser, France) to induce hyperthermia in rats.

Equipment

- A precision balance (Mettler toledo®, Switzerland Gfl 2102®,) for weighing the aqueous extract of *Daniellia oliveri*, lysine acetylsalicylate and brewer's yeast;
- An infrared thermometer brand Thermoscope S LBS Médical model HT-F03A (France) to measure the body temperatures of the rats;

A freeze-dryer (SERIAL) is used to freeze-dry the aqueous decoction of *Daniellia oliveri* leaves.

Methods

Preparation of the aqueous extract of *Daniellia oliveri* leaves

The aqueous extract of *Daniellia oliveri* leaves is obtained from 250 g of *Daniellia oliveri* leaf powder mixed with 3 litres of distilled water. This mixture is boiled for 30 minutes to obtain about 2 litres of decoctate. The solution is then filtered through cotton wool and Wattman paper (1mm). The filtrate is freeze-dried.

At the end of this operation, we obtain about 40 g of dark brown lyophilisate with a yield of 16.36%.

Methods for studying antipyretic activity

The method used is identical to that used by Teotino *et al*., 1963 [7]. The rats were divided into batches of 7 and fasted 16 hours before the experiment. Each batch was injected subcutaneously in the dorsolateral region with a 20% aqueous suspension of brewer's yeast at a rate of 1ml/100g of body weight. Sixteen hours after fasting, the pyrogenic effect of the brewer's yeast leads to an increase in the body temperature of the rats.

The different concentrations of the aqueous extract of Daniellia oliveri and lysine acetylsalicylate are prepared from stock solutions of concentrations equal to 10 mg/ml and 20 mg/ml respectively. The dissolutions are made with 9‰ isotonic NaCl solution.

Rats in the same batch are injected intraperitoneally with the same solution at a given concentration:

- Lot 1: (control lot) the 9‰ NaCl physiological fluid.
- Lot 2: the aqueous extract of *Daniellia oliveri* at 25 mg/kg B.P ;
- Lot 3: Aqueous extract of Daniellia oliveri at 100 mg/kg B.P;
- Lot 4: Lysine acetylsalicylate at 100 mg/kg bw.

Body temperatures were recorded 30 minutes; 1; 2; 3; 4 hours after administration of the aqueous extract of *Daniellia oliveri* leaves and the reference molecule.

Phytochemical Screening

This qualitative study allowed us to determine the groups of chemical constituents of pharmacological interest present in the aqueous extract of *Daniellia oliveri* leaves, namely sterols, polyterpenes, polyphenols, flavonoids, tannins, quinone compounds, saponosides, alkaloids and cardiotonic compounds. The protocols used are identical to those carried out by the analytical techniques described in the work of [8-10].

Sterols and Polyterpenes Research

This is done using the Liberman reaction. To detect sterols and polyterpenes, 5 ml of the solution of the aqueous extract of *Daniellia oliveri* is evaporated to dryness, without carbonising the residue, in a capsule on a sand bath. The residue is then dissolved hot in 1 ml of acetic anhydride and carefully added to 0.5 ml of concentrated sulphuric acid along the wall of the test tube containing the solution. The appearance of a purple or violet ring, turning blue and then green, indicates a positive reaction. A control test is carried out with a chloroform solution of cholesterol.

Search for polyphenols

The ferric chloride reaction was used for detection. In a test tube containing 2 ml of the aqueous solution of the aqueous extract of *Daniellia oliveri*, a drop of the 2% alcoholic solution of ferric chloride was added. The appearance of a blackish blue or green coloration indicates the presence of polyphenolic derivatives.

Research into flavonoid

The so-called cyanidin reaction was used. In a capsule, 2 ml of the aqueous solution of the aqueous extract of *Daniellia oliveri* is evaporated to dryness and the residue is taken up with 5 ml of hydrochloric alcohol. The solution is poured into a test tube and 2 to 3 magnesium chips are added. The pinkish-orange or

purplish colouring obtained indicates the presence of flavonoids.

Alkaloid research

Dragendorff (potassium iodobismuthate reagent) and Bouchardat (iodine reagent) reagents are used to characterise alkaloids. We start with the dry evaporation of 6 ml of solution of the aqueous extract of *Daniellia oliveri* in a capsule. The residue is taken up with 6 ml of 60° alcohol. The alcoholic solution obtained is divided into 2 test tubes. In the first tube, two drops of Dragendorff reagent (potassium iodobismuthate reagent) are added. The appearance of a reddish-brown precipitate indicates a positive reaction.

In the second tube, two drops of Bouchardat reagent (iodine reagent) are added. The appearance of a reddish-brown precipitate indicates a positive reaction. In both tests, a control test is performed with quinine.

Research into tannins

Tannins are identified using the Stiasny reaction.

- **Detection of catechic tannins**

Five (5) ml of the solution of the aqueous extract of *Daniellia oliveri* is evaporated to dryness in a capsule, then fifteen (15) ml of Stiasny's reagent (concentrated formalin 30% - HCL) is added to the residue obtained. The mixture is kept in a water bath at 80°C for thirty (30) minutes, then cooled. The observation of a precipitate in large flakes characterises the presence of catechic tannins. Catechin is used as a control.

- **Detection of gallic tannins**

The previous solution is filtered through a filter paper. Then sodium acetate is added to the filtrate. Three drops of 2% FeCl3 were added, which caused the appearance of an intense blue-black colour, indicating the presence of gallic tannins. A control test was carried out with gallic acid.

Research into saponosides

Saponosides are detected by the foam test. An aqueous solution of the aqueous extract of *Daniellia oliveri* is placed in a test tube and five (5) ml of distilled water is added. The test tube is then shaken vigorously.

The formation of a stable foam (height greater than 1 cm), persisting for one hour, indicates the presence of saponosides.

Detection of quinone compounds

The Borntraeger reagent is used to detect quinone substances. For this purpose, two (2) ml of the aqueous solution of *Daniellia oliveri* is evaporated to dryness in a capsule. The residue obtained is triturated in five (5) ml of hydrochloric acid and placed in a boiling water bath for 30 minutes. After cooling, the hydrolysate is extracted with two (2) ml of chloroform in a test tube. Finally, the chloroform phase is collected in another test tube and 0.5 ml of half diluted ammonia (Borntraeger's reagent) is added.

The appearance of a red to violet coloration indicates the presence of quinones. A control is made with vitamin E.

Study of acute toxicity

We determined the acute toxicity by the intraperitoneal route and by the oral route.

Study of acute toxicity by the intraperitoneal route
Method

The mice were divided into 5 batches of 10 healthy mice. Each batch contained an equal number of males and females. The different concentrations of the aqueous extracts of *Daniellia oliveri* are prepared from a 60 mg/ml stock solution and injected intraperitoneally. 0.1 ml per 10 g of body weight. Mice of the same batch are injected intraperitoneally with a solution of a given concentration. During this experiment, the general behaviour of the mice in the cage, changes in the rhythm of respiratory movements and the appearance of any death are observed for 24 hours.

Expressions of Results

The $_{LD50}$ expressed in mg/kg body weight (bw) is determined by the graphical method of Miller and Tainter (1944) [11] and the calculation method of Dragstedt and Lang (1957) [12].

- **Graphical method or Miller and Tainter's method (1944)**

The percentages of dead mice in each batch are recorded and converted into probit units. The doses corresponding to these percentages are determined in mg/kg CP. The curve expressing the mortality of the mice (in probit units) as a function of the logarithm of the dose administered (in mg/kg B.W is drawn. Linearisation of this semi-log curve allows the determination of the LD_{50} which is the abscissa corresponding to 50% mortality.

- **Calculation method or Dragstedt and Lang method (1957)**

This method is based on the following postulate:

- Any animal that has survived a dose given to it will survive any dose lower than that.
- Any animal that has succumbed to a dose that would have been given to it will succumb to any dose above it.

Thus, for each dose, the percentage mortality M(%) is calculated by summing all deaths observed at lower doses and all survivors observed at higher doses.

$$M(\%) = \frac{\text{Cumulative number of deaths}}{\text{Cumulative number of living + cumulative number of dead}} \times 100$$

$$\text{The } LD_{50} \text{ is calculated by extrapolation: } LD50 = \frac{50\,(X2\text{-}X1) + (X1Y2\text{-}X2Y1)}{Y2\text{-}Y1}$$

X2: Upper dose framing the LD_{50}
X1 : Lower dose framing the LD_{50}
Y2 : Percentage of mortality corresponding to X2
Y1 : Percentage of mortality corresponding to X1

Acute oral toxicity study

The acute oral toxicity test was carried out according to the Organisation for Economic Co-operation and Development (OECD) guideline 423 [1]. Fasting vigorous mice weighing between 20 g and 25 g were randomly divided into 3 groups of 10 and each mouse received 1 ml of a single dose, evaluated as mg/kg body weight (mg/kg bw) of the aqueous extract of *Daniellia oliveri*. A batch of mice each receiving 1 ml of distilled water is examined in parallel as a control. For the initial dose, one of four levels is chosen: 5, 50, 300 and 2000 mg/kg bw. The level chosen is the one at which mortality can be expected to occur in some of the treated animals.

The dose of 2000 mg/kg bw is the one chosen from these predefined doses. Exceptionally, an additional maximum pre-determined dose of 5000 mg/kg bw was used. Animals were observed during the first few hours after treatment to record immediate deaths and once a day for 14 days. The weight of each animal was determined shortly before administration of distilled water and aqueous extract of *Daniellia oliveri* twice weekly over a period of two 2 weeks.

Statistical Analysis

The curves and statistical analysis were carried out using GraphPad Prism 7 software (San Diego, California, USA). The statistical difference between the results was carried out using the analysis of variances (ANOVA), followed by the Tukey-Kramer multiple comparison test, with a significance level of $P < 0.05$. All values are presented as mean ± SEM (Standard Error on the Mean).

RESULTS

Phytochemical study

The phytochemical screening shows that the chemical groups identified in the leaves of *Daniellia oliveri* are water extractable. The main chemical constituents identified are listed in Table I. They consist of polyphenols, flavonoids of the flavone type, saponosides, alkaloids, quinone substances, polyterpenes, cardiodic heterosides and catechic and gallic tannins.

Acute toxicity study

The acute toxicity study of the aqueous extract of Daniellia oliveri administered intraperitoneally yielded an LD_{50} value of 436.51 mg/kg bw by the graphical method of Miller and Tainter (1994) (Figure 1). The acute oral toxicity study conducted according to the Organisation for Economic Co-operation and Development guideline 423 [1], showed that oral administration of the aqueous extract of *Daniellia oliveri* has an LD_{50} of more than 5000 mg/kg bw.

Table I: Phytochemical screening of the aqueous extract of *Daniellia oliveri* leaves

Flavonoids		+
Saponosides		+
Polyphenol		+
Alkaloids	**Dragendorff** **Bouchardat** **Valsen-Mayer**	+ + +
Coumarins		-
Quinonic compound		+
Cardiotonic heterosides		+
Sterols and polyterpenes		+
Tanins	**Gallic**	+
	Catechins	+

The sign (+) means that the reaction is positive.
The sign (-) means that the reaction is negative.

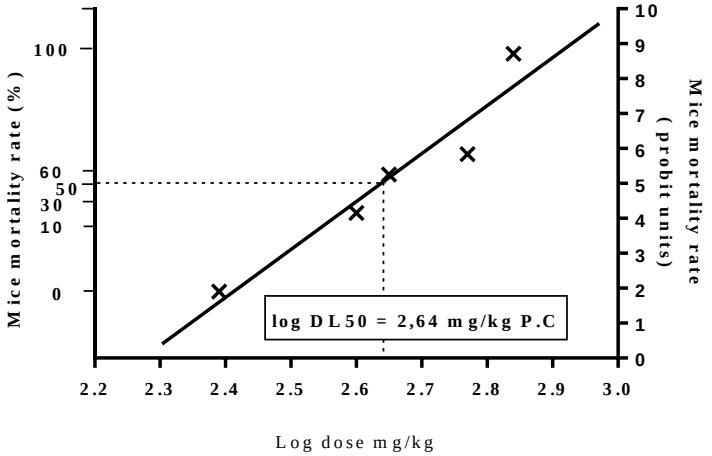

Figure 1: Toxicity curve of aqueous extract of *Daniellia oliveri* leaves with mice, by the graphic method of Miller and Tainter (1994)

Effects of the aqueous extract of *Daniellia oliveri* leaves of lysine acetylsalicylate on Fever

Figure 2 shows the percentage decrease in hyperthermia as a function of the dose of aqueous extract of *Daniellia oliveri* leaves and lysine acetylsalicylate.

For doses between 25 mg/kg bw and 100 mg/kg bw, the aqueous extract of *Daniellia oliveri* leads to a decrease in brewer's yeast-induced hyperthermia. This decrease is significant 30 minutes after the injection. It reaches its maximum two (2) hours after the injection of *Daniellia oliveri*, for the doses of 25, 50 and 100 mg/kg B.P., the percentages of inhibition are respectively equal to 48.67± 6.63%, 60.19 ± 6.21% and 84.81 ± 6.7%.

The effects of aqueous extract of *Daniellia oliveri* at 25mg/kg B.P. are similar to those of lysine acetylsalicylate at 100 mg/kg B.W. However, at this dose of 100 mg/kg B.W., the decrease in hyperthermia induced by lysine acetylsalicylate is maximal after three (3) hours while that induced by *Daniellia oliveri* decreases sharply in the same time interval.

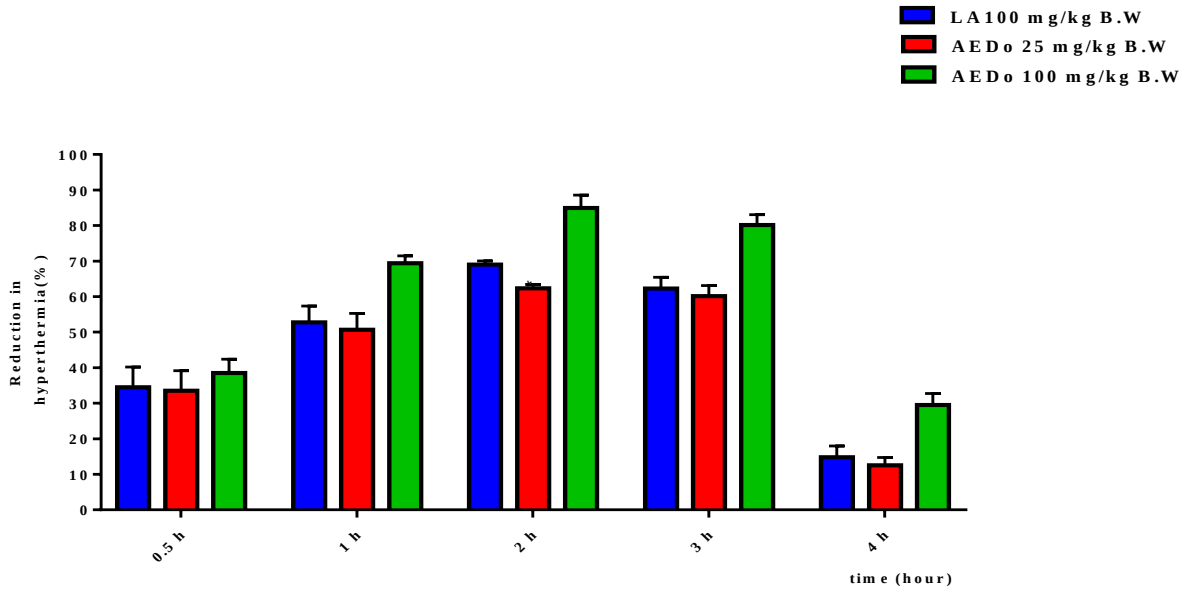

Figure 2: Reduction in hyperthermia induced in rats as a function of time and dose of aqueous extract of *Daniellia oliveri* leaves and lysine acetylsalicylate

Values represent the percentage (mean ± SEM, n = 7) reduction in hyperthermia induced by Daniellia oliveri at 25 and 100 mg/kg B.W. hyperthermia induced by Daniellia oliveri at 25 and 100 mg/kg B.W. The higher the dose of aqueous extract of Daniellia oliveri, the stronger and more sustained the reduction of hyperthermia. At the dose of 100 mg/kg B.W., the

effects of aqueous extract of Daniellia oliveri are greater than those of lysine acetylsalicylat

DISCUSSION

Our study aims to evaluate the antipyretic activity of aqueous extract of *Daniellia oliveri*, a plant used in traditional medicine for the treatment of various diseases. For this study, we injected rats in the dorsolateral region with a 20% suspension of brewer's yeast, which causes hyperthermia in the animals.

Aqueous extract of *Daniellia oliveri* administered at doses ranging from 25 to 100mg/kg bw, significantly reduced the brewer's yeast-induced hyperthermia in rats. Two (2) hours after injection of aqueous extract of Daniellia oliveri, for doses of 25, 50 and 100 mg/kg bw the respective percentages of reduction are 48.67± 6.63 %, 60.19 ± 6.21 % and 84.81 ± 6.7%.

From our results, we can state that this extract produces a significant decrease in body temperature, similar to lysine acetylsalicylate, the reference antipyretic molecule. Similar results were obtained by [13-16], who worked respectively on the essential oil of *Lippia multiflora*; *Borassus aethiopum*; *Ximenia american and Pterocarpus erinaceus.* However, our results are contrary to the research work of [17, 18]. Indeed, [17], showed that extracts of *Danielle olivieri* stem bark using hexane, ethyl acetate and methanol as extraction solvent did not record any antipyretic activity in rats. Lompo and colleagues found that *Kaya senegalensis* extracts induced hypothermia in rats. The antipyretic properties of the aqueous extract of *Daniellia oliveri* are thought to be due to interference with the biosynthesis of prostaglandins [19]. Indeed, the aqueous extract of *Daniellia oliveri* inhibits the release of cytokines and prostaglandins [20]. The saponosides present in *Daniellia oliveri* are thought to be the cause of this inhibition [21, 22]. By inhibiting their release, *Daniellia oliveri* corrects the disruption caused by prostaglandins at the level of the hypothalamic thermostat, thus bringing the body temperature back to normal. Phytochemical screening revealed the presence of polyphenols, flavone-type flavonoids, saponosides, alkaloids, quinone substances, polyterpenes, cardiodic heterosides and catechic and gallic tannins. The effectiveness of *Daniellia oliveri* in abolishing fever is thought to be due to its high saponoside content.

The acute intraperitoneal toxicity study yielded an $_{LD50}$ value of 436.51 mg/kg B.W and 437.5 mg/kg B.W by the graphical method of Miller and Tainter (1994) and the calculation of Dragsted and Land (1957), respectively. According to the classification of [23], the aqueous extract of the leaves of *Daniellia oliveri* administered intraperitoneally is toxic but only slightly toxic by the oral route according to the OECD guideline 423 [1]. However, this plant should be used with caution in humans.

CONCLUSION

The aqueous extract of *Daniellia oliveri* leaves showed antipyretic activity similar to that of lysine acetylsalicylate. Thus this plant deserves special attention for its antipyretic properties.

Intraperitoneal administration of high doses of the aqueous extract of *Daniellia oliveri* leaves to mice is toxic. On the other hand, this plant is weakly toxic by the oral route.

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