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Anti-Pyretic Activity of Aqueous Extract of *Pseudocedrela Kotschyi* (Schweinf.) Harms stem bark (Meliaceae)

Coulibaly Sirabana[1], Soro Tianga Yaya[1*], Mian Jean Claude[1], Ehoussou N'douffou Célestin[1]

1. Laboratory of Biology and health; Animal Physiology, Phytotherapy and Pharmacology Specialty: Felix Houphouët Boigny University, Abidjan, Ivory Coast.

ABSTRACT

The bark of *Pseudocedrela kotschyi* is traditionally used by people in sub-Saharan regions to treat fever. The main objective of this study is to determine the antipyretic activity, phytochemical constituents with pharmacological potential, and toxicity of the aqueous extract of *Pseudocedrela kotschyi* stem bark. The comparative study of the aqueous extract of *Pseudocedrela kotschyi* stem bark with lysine acetylsalicylate on brewer's yeast-induced hyperthermia in rats revealed the antipyretic properties of this extract. The standard methods used for the qualitative analysis of phytochemical constituents revealed the presence of alkaloids, flavonoids, catechic tannins, saponosides, polyphenols, quinones, terpenoids, oses and holosides while coumarins and gall tannins are absent. The toxicological study of the aqueous extract of stem bark of *Pseudocedrela kotschyi* determined an LD 50 of 240 mg/kg BW. According to the classification of Diezi (1989), this plant is moderately toxic by the intraperitoneal route. These results justify traditional use of *Pseudocedrela kotschyi* bark against fever.

Keywords: *Pseudocedrela kotschyi*-Lysine acetylsalicylate-Antipyretic.

*Corresponding Author Email: tiangaso@yahoo.fr
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INTRODUCTION

Fever refers to the body's temperature that is higher than the normal range due to an increase in set-point temperature in the hypothalamus[1]. It is a common sign in medicine that shows body temperature elevation above the standard range of 36.5-37.5 °C[2, 3]. Increased prostaglandin E2 (PGE2) biosynthesis in the hypothalamic pre-optic region alters the neuron firing rate, leading to fever induction

Fever is managed using synthetic drugs such as aspirin, paracetamol among others. Synthetic drugs are associated with many side effects. Herbal medicines form alternative therapy since they possess fewer side effects and are readily available.

Pseudocedrela kotschyi (Schweinf.) Harms (Meliaceae) or dryland cedar[4] is a tree that can reach a height of 20 m with grayish, cracked bark[5]. The leaves are alternate, pinnately compound, without stipules, and clustered towards the tips of the twigs. The hermaphrodite flowers are white, fragrant, and puberulent with a 4 mm pedicel, a 1 mm calyx with 5 small lobes, a 2.5 mm twisted corolla, and a 2.5 mm staminal column. The fruits, consisting of erect, oblanceolate capsules opening at the apex into 5 valves, contain 6 cm long-winged seeds that are attached to a 5-angled axis[6]**.**

Pseudocedrela Kotschyi is one of the largest trees in Savannah. It is irregularly distributed in the Sudanian shrub and woodland savannas. Where it exists, it forms stands because of its ability to suckle[6]**.**

Pseudocedrela Kotschyi is used in sub-Saharan regions to cure several diseases[7]**.** This plant cures toothache, stomachache, malaria, scabies and yaws. It is also used in traditional medicine in Ivory Coast to lower fever.

The present study aims to evaluate the antipyretic properties of the aqueous extract of *Pseudocedrela kotschyi* in order to verify whether its ethnopharmacological use is justified.

MATERIALS AND METHOD

Plant material

We used the lyophilisate of the infused stem bark of *Pseudocedrela kotschyi* (Meliaceae).The stem barks are collected in June 2018, in North of Ivory Coast, in the Dikodougou prefecture. The plant was authenticated at the National Floristic Center (CNF) of the University Felix Houphouët-Boigny from herbarium n°8664.

The harvested bark is dried in the shade at room temperature (25° to 28°C). Once dried, they are ground to obtain a powder that is used to prepare our aqueous extract.

Animal material

Rats, *Rattus norvegicus*, male, of Wistar strain, weighing between 180 g and 250 g, are used for the evaluation of antipyretic activity.

They are raised in the animal house of the Ecole Normale Supérieur (ENS) (Abidjan, Ivory Coast), where the average temperature is 28°± 3°C. The relative humidity is 70% and the photoperiod of 12 hours of light and 12 hours of darkness. The animals have free access to water and food.

The mice, *Mus musculus*, female and male, of Swiss strain, from the animal house facility of the Ecole Normale Supérieur (ENS) (Abidjan, Ivory Coast), weighting between 20 g and 30 g are used to study acute toxicity.

They are raised under the same conditions as rats.

All the experimental procedures and protocols used in this study are conducted in accordance with the European directive of November 24, 1986 (86/609/EEC) and the decree of April 19, 1988[8] relating to the use of experimental animals in research.

Extract, solvents and chemical reagents

- Freeze-dried aqueous extract of *Pseudocedrela kotschyi* stem bark is used in our experiments to reduce brewer's yeast-induced hyperthermia in rats.
- Distilled water is used for extraction.
- The 9 ‰ NaCl solution is used to dilute the lyophilisate of *Pseudocedrela kotschyi* bark and lysine acetylsalicylate.
- Lysine acetylsalicylate has been used as a reference antipyretic.
- The 20% aqueous suspension of brewer's yeast is used to induce hyperthermia in rats.

Equipment

- A magnetic stirrer (type RCT basic Kika Labortecknik) is used to stir the infusion of *Pseudocedrela kotschyi* stem barks.
- A freeze dryer (serial type) is used to freeze dry the infusion of *Pseudocedrela kotschyi* stem barks.
- An infrared thermometer is used to take the body temperature of rats.

Preparation of the aqueous extract of *Pseudocedrela kotschyi*

One hundred and fifty (150) grams of *Pseudocedrela kotschyi* stem barks powder is taken and put into a 5-liter beaker. Three liters of distilled water heated to 100° C are added. This mixture is stirred for 24 hours with a magnetic stirrer. The solution is then filtered on hydrophilic cotton and Whatman's No 3 qualifying filter papers. The filtrate obtained is freeze-dried using a freeze-dryer (type SERIAL). The lyophilisate is a light brown powder of 20% yield.

Study of antipyretic activity

The evaluation of the antipyretic activity of the aqueous extract of *Pseudocedrela kotschyi* was performed according to the method described by Teotino et al[9].

Sixteen hours before the test, the rats were injected subcutaneously in the dorsolateral region with a 20% aqueous suspension of brewer's yeast at a rate of 1ml per 100 g of body weight. The animals were fasted for twenty-four hours. and divided into 4 groups. The batches were made homogeneous as to the level of hyperthermia just before the intraperitoneal injection of the substances.

Batch 1: 9 ‰ physiological NaCl solution at 0.1 ml/10 g (Control).

Batch 2: lysine acetylsalicylate = 200 mg/kg body weight (BW) [AL 100 mg/kg].

Batch 3: Aqueous extract of *Pseudocedrela kotschyi* = 150 mg/kg BW

Batch 4: Aqueous extract of *Pseudocedrela kotschyi* = 200 mg/kg BW

Body temperature was taken 30 min, 1, 2, 3, and 4 hours after administration of the substances using an infrared thermometer.

Phytochemical screening

Phytochemical screening of the aqueous extract of *Pseudocedrela kotschyi* was carried out in order to identify chemical constituents of pharmacological interest such as sterols, terpenoids, polyphenols, flavonoids, tannins, quinone compounds, saponosides, alkaloids, coumarins, cardiotonic heterosides, reducing compounds, oses and holosides via qualitative analysis techniques described in literature[10, 11, 12, 13]**.** These techniques are based either on formation of insoluble complexes using precipitation reactions, or on the formation of colored complexes using staining reactions (conjugation, or unsaturation in a molecule).

Research of sterols and polyterpenes

For the detection of sterols and polyterpenes, we use Liebermann reaction. Five (5) ml of each extractive solution are evaporated to dryness in a capsule on a sand bath. The residue is dissolved while hot in 1 ml of acetic anhydride ($C_4 H_6O_3$) The resulting solution is inverted into a test tube. One (1) to two (2) ml of concentrated sulfuric acid (H_2SO_4) are added, without shaking, with a pipette to the bottom of the test tube. At interphase, a purple or violet ring appears which turns blue and then green indicating that the reaction is positive.

Research of polyphenols

The reaction with ferric chloride ($FeCl_3$) was used to characterize the polyphenols. In a test tube, a few drops of $FeCl_3$ at 2% are added to 2 ml of each aqueous extract. The appearance of a dark blue-black or green coloration indicates the presence of polyphenolic derivatives.

Research of flavonoids

Flavonoids which are a large family of compounds abundant in plants are highlighted by the cyanidin reaction.

Two (2) ml of each extractive solution are evaporated to dryness in a capsule. The residue is introduced in a test tube to which are added 5 ml of hydrochloric alcohol diluted to half, 1 ml of iso amyl alcohol, and 2 to 3 magnesium chips. A crepitation reaction occurs for a few minutes. The appearance of a pinkish-orange or purplish coloration indicates the presence of flavonoids.

Research of tannins

Gallic tannins and catechic tannins are highlighted by the Stiasny reaction. This reagent is prepared by mixing 10 ml of 30% formalin with 5 ml of concentrated hydrochloric acid.

Highlighting catechic tannins

Five (5) ml of each extractive solution previously evaporated to dryness in a capsule are introduced into a test tube. 1.5 ml of Stiasny's reagent is added. The mixture is heated in a water bath at 80°C for 30 minutes. After cooling, the observation of a precipitate in large light brown flakes indicates the presence of catechic tannins.

Highlighting Gallic tannins

Five (5) ml of each extractive solution previously evaporated to dryness in a capsule are introduced into a test tube. 1.5 ml of Stiasny's reagent is added. The mixture is filtered and saturated with 5 g of sodium acetate (CH_3 COONa). Two drops of a 1% iron (III) chloride solution ($FeCl_3$) are then added. The appearance of a blue-black coloration indicates the presence of Gallic tannins.

Research of quinone compounds

The Bornstraëgen reagent (ammonia diluted 2 times) allows the detection of free or combined quinone substances.

Two (2) ml of each extractive solution are evaporated to dryness in a capsule. One (1) g of each extract dissolved in 5 ml of HCl, diluted to 1/5. The solution is poured into a test tube and kept in a boiling water bath for 30 min. After complete cooling, 20 ml of chloroform ($CHCl_3$) are added. The chloroform phase is then recovered. To this organic phase, 0.5 ml of ammonia NH_4 OH at 50% are added. The appearance of a red to purple hue indicates the presence of quinones.

Research of saponosides

This research is based on the property of aqueous solutions containing saponosides to give persistent foam upon agitation. Fifteen (15) ml of aqueous solution are introduced into a test tube. The stoppered tube is shaken vertically for about ten seconds. It is left to stand for ten

minutes. If the foam formed has a height greater than 1 cm, then there is the presence of saponosides.

Alkaloid research

The characterization of alkaloids was carried out using BUCHARDAT's reagent (iodo-iodide reagent) and Dragendorff's reagent (potassium iodo-bismuthate reagent). After dry evaporation in a capsule, 4 ml of each solution, the residue is taken up in 4 ml of 60% ethanol. The solution obtained is divided into 2 test tubes. In the first tube, 2 drops of DRAGENDORFF reagent are added. The appearance of an orange precipitate indicates the presence of alkaloids. In the second tube, 2 drops of BURCHARDAT reagent are added. The appearance of a brown red precipitate indicates the presence of alkaloids.

Research of coumarins

5 ml of each solution are evaporated to dryness. The residue obtained is placed in a test tube in the presence of a few drops of water. The tube is then covered with paper soaked in diluted NaOH and boiled. Any yellow fluorescence indicates the presence of coumarins after examination under UV at 365 nm.

Research of reducing compounds

We introduce 2 ml of our extract in a test tube, to which we add 1 ml of Fehling's liquor (1 ml of reagent A and 1 ml of reagent B). The whole is brought to the boiling water bath for 8 min. A brick red precipitate indicates the presence of reducing compounds.

Reagent A is a copper sulfate solution that is obtained by dissolving 40 g of copper sulfate ($CuSO_4$) in 900. mL of distilled water. The mixture is heated to dissolve the salt and made up to 1 L.

Reagent B is a double tartrate solution that is obtained by dissolving 200 g of Seignette salt (sodium and potassium double tartrate) and 150 g of soda in 1 L of distilled water.

Research of oses and holosides

A 10% decoction is prepared by boiling plant powder (10 g) in distilled water (100 ml) for 15 minutes. Five ml of this 10% decoction are evaporated to dryness in a capsule. Five drops of concentrated H_2SO_4 and 3 drops of ethanol saturated with thymol are then added to this residue. A positive reaction results in a red coloration.

Study of acute toxicity

Method of study

After an adaptation period of 15 days, the mice were placed in cages, weighed, marked and fasted 18 hours before their use to prevent any digestive food interaction and 3 hours after

administration of the product. We used 6 batches of 10 female and male mice, to which we administered increasing doses of lyophilized total aqueous extract of *Pseudocedrela kotschyi* diluted in a 9 ‰ isotonic Nacl chloride solution intraperitoneally (I.P). These different doses were injected at a rate of 0.1 ml per 10 g body weight. Each batch of mice receives a single dose. These different doses are used to determine the percentage of mortality, ranging from 0 to 100% during 24 hours of time.

Animals are observed and manifestations of toxicity such as increased activity, salivation, convulsions, coma and death are noted. These observations are made regularly for up to 24 hours.

Expression of results

The LD50 expressed in mg/ kg body weight (BW.) is determined by the graphical method[14] and by the calculation method[15].

Graphical method or Miller and Tainter method

The percentages of dead mice in each batch are recorded and converted to probit units. Doses corresponding to these percentages are determined in mg/kg body weight. The curve, expressing the mortality of the mice (in probit units) as a function of the logarithm of the administered dose (in mg/kg of body weight), is drawn. The linearization of this semi-log curve allows determining the LD50 which is the abscissa of the point corresponding to 50% of mortality.

Calculation method or Dragstedt and Lang method

This method is based on the following premise:

- Any animal that has survived a dose given to it will survive any dose below that.
- Any animal that has succumbed to a dose given to it will succumb to any dose above that.

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

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

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

X2 : Upper dose limit for LD50

X1 : Lower limit of the LD50

Y2 : Percentage of mortality for X2

Y1 : Percentage of mortality for X1

Statistical and graphical analyzes

Statistical analyzes of values and graphical representations of data are performed using *GraphPad Prism 5 Demo software and CoStat version 6.400* (San Diego, California, USA). Comparison of temperature means between batches was done using Student's (t) test. When $p \leq 0.05$ the difference is said to be significant. The results are expressed as the mean ± error of the mean (ESM).

RESULTS AND DISCUSSION

During the acute toxicity study we observed frequent displacements followed by twisting of the body, acceleration of respiration and heart rate, and strong convulsions and agitations of mice.

The activity of the animals is reduced, their gait becomes slow, and death occurs from the 15th minute to the 6th hour for doses of 150 mg/kg BW and higher. After 24 hours, surviving animals returned to normal behavior similar to that of controls. The acute toxicity study of the aqueous extract of *Pseudocedrela kotschyi* by intraperitoneal route allowed to calculate the LD50 values in mice. This is 230.08 mg/kg BW and 240 mg/kg BW respectively by the graphical method (Table 1, Figure 1) and the calculation method**.** Below is the calculation of the LD50 according to Dragstedt and Lang.

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

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

$$LD50 = \frac{50(300-150) + (150x70-300x20)}{70-20} = 240 \text{ mg/kg BW.}$$

Table 1: Dose-dependent mortality rate of mice with aqueous extract of *Pseudocedrela kotschyi*

Lots	Number of mice	Dose in mg/kg BW	Number of dead mice	Mouse mortality rate (%)	Mouse mortality rate (probit units)	Log dose mg/kg
1	10	100	0	0	1,90	2,00
2	10	150	2	20	4,15	2,18
3	10	250	5	50	5,0	2,40
4	10	300	7	70	5,52	2,48
5	10	400	9	90	6,28	2,60
6	10	500	10	100	8,71	2,70

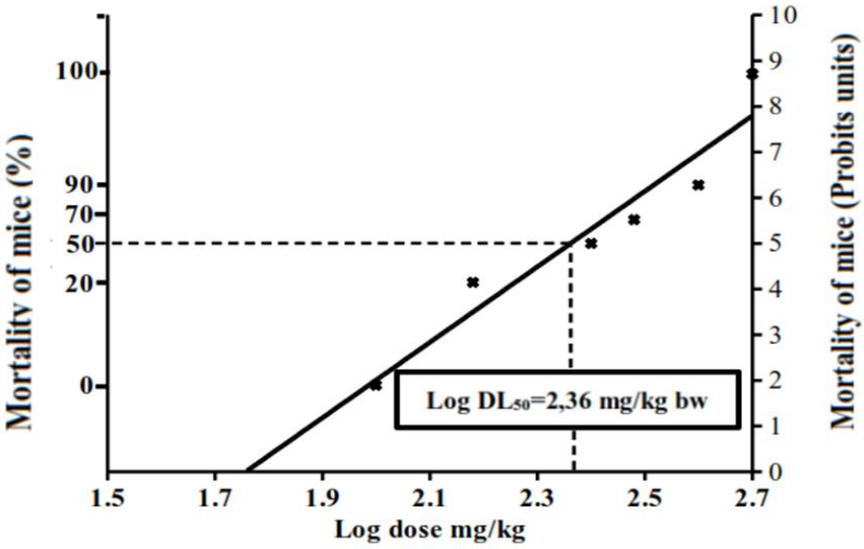

Figure 1: **Toxicity curve of aqueous extract of *Pseudocedrela kotschyi* in mice Log LD50=2.36 mg/kg BW, LD50=230.08 mg/kg BW**

These two values are quite close, which demonstrates the reliability of the determination methods.

According to Diezi's classification[16], a pharmacological substance with a LD50 of less than 5 mg/kg BW. is said to be very toxic. The one with LD50 between 5 and 50 mg/kg BW is extremely toxic, the one with LD50 belonging to the interval 50 and 500 mg/kg BW is considered as toxic. The substance with LD50 between 500 and 5000 mg/kg BW is weakly toxic, and the substance with LD50 above 5000 is non-toxic. According to this classification, the aqueous extract of *Pseudocedrela kotschyi* administered intraperitoneally is toxic. This result is different from that obtained by authors[17] who determined a LD50 of 775 mg/kg BW intraperitoneally of aqueous extracts of *Pseudocedrela kotschyi*.

This toxicity of the aqueous extract of *Pseudocedrela kotschyi* determined by intraperitoneal route is similar to that of the aqueous extract of the stem barks of *Ximenia americana*, *Tamarindus indica* which have a respective LD50 of 237.5 mg/kg BW[18] and 377±27 mg/kg BW[19]. This plant deserves to be used with caution in humans.

Table 2: **Chemical composition of the aqueous extract of *Pseudocedrela kotschyi* stem bark**

	Flavonoids	Alkaloids	Saponosids	Polyphenols	Coumarins	Terpenoids	Oses et holosides	Reducing compounds	Quinones	Tannins	
										Catchism	Gallic
Aqueous extract	+	+	+	+	-	+	+	+	+	+	-

+ = Presence of compound; - = absence of compound.

Phytochemical screening of the aqueous extract of *Pseudocedrela kotschyi* stem barks, by qualitative characterization reactions, revealed the presence of alkaloids, flavonoids, catechic tannins, saponosides, polyphenols, quinones, terpenoids, oses and holosides (Table 2).

These same chemical compounds were demonstrated by authors[20, 21, 22] with the methanolic extract of stem bark, aqueous extract of roots, and methanolic extract of *Pseudocedrela kotschyi* respectively.

Table 3: Temperature variation caused by aqueous extract of *Pseudocedrela kotschyi* (Pk) and lysine acetylsalicylate on hyperthermia induced in rats by brewer's yeast.

Products	Decrease in body température (°C)					
	Before treatment	0.5 h	1 h	2 h	3 h	4 h
Control (Nacl)	39.2 ± 0.04	-0.05± 0.03	-0.15± 0.06	-0.27± 0.09	-0.3± 0.07	-0.35± 0.09
Pk 200 mg/kg	39.2 ± 0.05	-1.65±0.01**	-1.8± 0.1**	-1.99±0.03**	-2.14±0.01***	-2.07±0.02***
Pk 150 mg/kg	39.23 ±0.03	-1.4± 0.01**	-1.52±0.03**	-1.69±0.01**	-1.79± 0.02**	-1.71± 0.02**
AL 200 mg/kg	39.25 ±0.02	-1.5± 0.02**	-1.6± 0.01**	-1.76±0.03**	-1.86± 0.03**	-1.77± 0.06**

Values represent mean ± SEM (standard error on mean percentage); n=7 for each group.

***p<0.01; ***p<0.001 compared to controls.*

The antipyretic activity was evaluated by injecting rats with 20 % brewer's yeast in the dorsolateral region. The results of effect of aqueous extract of lysine acetylsalicylate and all the doses of stem bark aqueous extract are depicted in Table 3.

Aqueous extract of lysine acetylsalicylate and all the doses of stem barks aqueous extract under study exhibited remarkable antipyretic activity. In control rats, the temperature level before treatment was 39.2 ± 0.04 while in non-control rats, the temperatures levels were 39.2 ± 0.05; 39.23 ± 0.04 and 39.25 ± 0.04. In control rats, these rates do not vary significantly ($p>0.05$) during the 4 hours of experimentation. On the other side, intraperitoneal injection of the aqueous extract of lysine acetylsalicylate at a dose of 150 mg/kg BW and aqueous extracts of *pseudocedrela kotschyi* stem barks at the doses of 150 mg/kg BW and 200 mg/kg BW at the rats induce a significant decrease ($p<0.001$) of hyperthermia during the 4 hours of experimentation.

Figure 2 represents the percentage reduction in hyperthermia induced by these substances. The maximum reduction for these different substances was obtained in the 3rd hour after their administration.

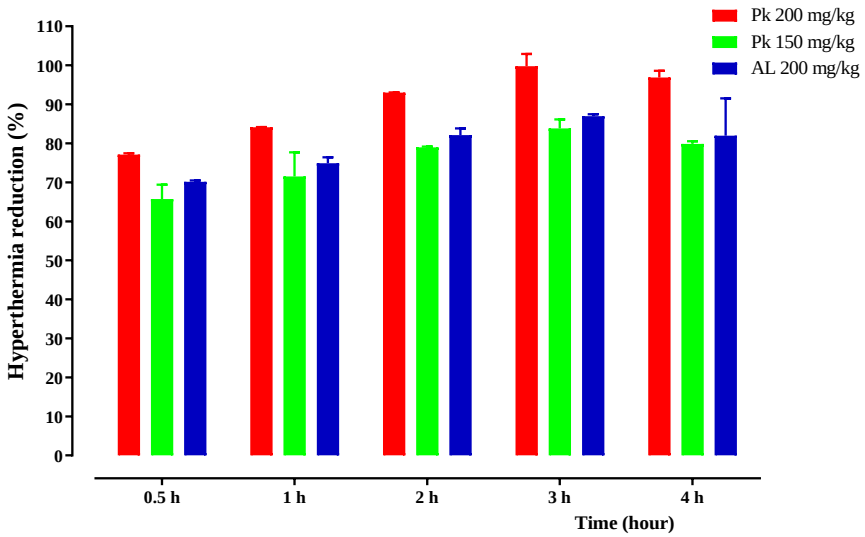

Figure 2: **Antipyretic activity: effect-time relationship of aqueous extract of *Pseudocedrela kotschyi* and lysine acetylsalicylate on brewer's yeast-induced hyperthermia in rats.**

Values represent the mean ± SEM (standard error on the mean percentage) percentage reduction in hyperthermia, after 0.5, 1, 2, 3, and 4 hours, induced by lysine acetylsalicylate at 200 mg/kg BW and by Pseudocedrela kotschyi at 150 and 200 mg/kg BW in rats, n=7 for each group.

The temperature decrease induced by aqueous extract of *Pseudocedrela kotschyi* at the doses of 150 mg/kg BW and 200 mg/kg BW at the 3rd hour is respectively to 82.72 ± 0.27 % and 99.07 ± 2.58 %. That induced by lysine acetylsalicylate at the 3rd hour is 98.41 ± 0.79 %.

The injection of 20 % brewer's yeast causes hyperthermia in rats. This rise in temperature is linked to the release of cytokines (TNF-α, IL1, IL6...) which, having reached the blood vessels, stimulates the biosynthesis of prostaglandins which are pyrogenic in the vicinity of the thermoregulatory hypothalamic center[23, 24, 25].

This clearly indicates that the aqueous extract of *Pseudocedrela kotschyi* stem barks would contain bioactive components that are capable of inhibiting prostaglandins biosynthesis[26, 27].

Some phytochemical components of the aqueous extract of *Pseudocedrela kotschyi* such as alkaloids, flavonoids, phenolic compounds, saponosides and terpenoids have antipyretic actions. Thus, they are able to inhibit the production of prostaglandins and or increase the synthesis of antipyretic components by inhibiting cyclooxygenases[4]. Alkaloids, tannins and terpenoids inhibit the synthesis of prostaglandins while flavonoids inhibit arachidonic acid peroxidation[28] and suppress tumor necrosis factor α[29]. This substance stimulates the synthesis of PGE2, which causes fever. The antipyretic activity of flavonoids results in the suppression of TNF α[29]. They

also lead to the reduction of the quantity of prostaglandins by inhibiting the peroxydation of arachidonic acid.

Previous studies have shown that alkaloids have antipyretic activity. Alkaloids isolated from *Hunteria zeylanica* have shown antipyretic activity in animal experiments[30].

Saponosides inhibit cyclooxygenase and phospholipase A2 which cause fever[31, 32, 33]. A previous study showed that the antipyretic activity of ethanolic extract of *Asparagens racemosus* is due to the presence of saponosides[5].

CONCLUSION

The results of this study show that the aqueous extract of *Pseudocedrela kotschyi* stem bark has antipyretic properties. These antipyretic properties are probably due to the presence of phytochemicals such as alkaloids, flavonoids, phenolic compounds, saponosides and terpenoids found in this aqueous extract. Intraperitoneal administration of the aqueous extract of *Pseudocedrela kotschyi* stem bark, at high doses is highly toxic to mice. The aqueous extract should therefore be used with caution. Further experiments using purified extracts are envisaged to identify precisely compounds responsible for this antipyretic activity and to understand their action mechanism.

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