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Evaluation of Antipyretic Potential of *Pseudocedrela kotschyi* Schweint. Harms (Meliaceae)

G. C. Akuodor[1*], A. D. Essien[1], G.A. Essiet[1], Essien David-Oku[2], J. L. Akpan[3] and F.V. Udoh[1]

[1]Department of Pharmacology, College of Medical Sciences, University of Calabar, Nigeria.
[2]Department of Biochemistry, College of Medical Sciences, University of Calabar, Nigeria.
[3]Department of Pharmacology and Therapeutics, Ebonyi State, University, Abakaliki, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author GCA designed and managed the literature searches. Authors GCA, ADE and GAE carried out the antipyretic study. Author FVU wrote the protocol. Author JLA wrote the first draft of the manuscript. Author EDO performed the statistical analysis. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Pseudocedrela kotschyi is used in ethnomedicinal practice for the treatment of fever, pains and inflammation. The ethanol leaf extract of the plant was investigated for antipyretic potency in rats. Yeast and amphetamine induced hyperpyrexia were used to determine the antipyretic activity. The leaf extract (50, 100 and 150 mg/kg *i.p.*), exhibited significant ($P<0.05$) dose dependent effect on the tested experimental animal models of pyrexia. The LD_{50} was established to be 775 mg/kg, *i.p.* in mice. The results obtained suggest that the ethanol leaf extract may be a promising agent for the treatment of pyrexia.

Keywords: Pseudocedrela kotschyi; herbal medicine; ethanol extract; antipyretic activity; rats.

**Corresponding author: Email: goddyakuodor@yahoo.com;*

1. INTRODUCTION

Herbal products symbolizes safety in contrast to the synthetics that are regarded as unsafe to man and his environment [1]. *Pseudocedrela kotschyi* is a medicinal plant belonging to the family of meliaceae and is mainly found across West and Tropical Africa. It is a tree of up to 20 metres high with a wide crown fissured bark and fragrant white flowers [2]. In Togo, the bark is used as a febrifuge and for the treatment of gastrointestinal diseases and rheumatism [3]. The plant has also been reported to be used traditionally in the treatment of dysentery (Nigeria). The analgesic, anti-inflammatory [4], antiepileptic [5], antidiabetic [6], antimalaria [7,8], dental cleaning [9,10,11] and antibacterial [12], activities of various extracts of the plant have been scientifically investigated and reported.

The World Health Organization (WHO) has long recognized and drawn the attention of many countries to the everincreasing interest of the public in the use of medicinal plants and their products in the treatment of various diseases and ailments. These plants, which are abound in our environment enjoy wide acceptability by the population and serve as cheaper alternatives to orthodox medicine [13,14].

Pseudocedrela kotschyi is one of such medicinal plants whose therapeutic value no doubt has a folkloric background. The ethnomedicinal activity of the leaves of this plant suggest that the leaves might possess antipyretic activity and this stimulated our interest to study the effect of the leaf extract of this on experimental induced pyrexia conditions.

2. MATERIALS AND METHODS

2.1 Plant Collection

Fresh leaves of *Pseudocedrela kotschyi* were collected from Chaza suleja, Niger State, Nigeria in April 2010. The plant was identified and authenticated by Mallam Ibrahim Muazam and Mrs. Jemilat A. Ibrahim of the Department of Medicinal plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria, A voucher specimen (NIPRD/H/ 6542) was deposited in the herbarium of the institute for reference. The international plant name index is Meliaceae *Pseudocedrela kotschyi*-Bot. Jahrb. Syst. 22(1):154. 1895(19 Nov.1895 (IK).

2.2 Extraction

The air-dried leaves of *Pseudocedrela kotschyi* were ground to coarse powder in a mortar. Extraction was carried by dispensing 350 g the plant material in 1.5 L of 70% ethanol and shaking with shaker GFL 3017 MBH, Germany for 24 h. The filtrate was dried on a water bath given a dark brown solid with a yield of 37.5 g (10.71%w/w). The leaf extract was subsequently reconstituted in distilled water at appropriate concentration for the experiment.

2.3 Animals

Wister albino rats (180-200 g) of both sexes were used in this study. All the animals were obtained from animal facility centre, Department of Pharmacology and Toxicology, National Institute for Pharmaceutical Research and development (NIPRD), Abuja, Nigeria. The animals were kept in cages at room temperature and moisture, under naturally illuminated

environment of 12:12 h dark/light circle. They were fed with standard feed and had water *ad libitum*.

2.4 Phytochemical Test

Standard screening tests [15,13] for detecting the presence of different chemical constituents were employed. Secondary metabolites tested for include: flavonoids, tannins, saponins, alkaloids, glycosides, sterols, carbohydrates, reducing sugars, anthroquinones and terpenoids.

2.5 Test for Tannins

About 0.5 g of the extract was boiled in 10 ml of water in a test tube and then filtered. A few drops of 0.1% ferric chloride was added and observed for brownish green or a blue-black colouration.

2.6 Test for Saponins

To 0.5 g of the extract was added 5 ml of distilled water in a test tube. The solution was shaken vigorously and observed for a stable persistent froth. The frothing was mixed with 3 drops of olive oil and shaken vigorously after which it was observed for the formation of an emulsion.

2.7 Test for Terpenoids

To 0.5 g each of the extract was added 2 ml of chloroform. Concentrated H_2SO_4 (3 ml) was carefully added to form a lower layer. The formation of a reddish-violet colour in the chloroform layer indicates the presence of terpenoids.

2.8 Test for Flavonoids

Three methods were used to test for flavonoids. First, dilute ammonia (5 ml) was added to a portion of an aqueous filtrate of the extract. Concentrated H_2SO_4 (1 ml) was added. A Yellow colouration that disappears on standing indicates the presence of flavonoids. Second, a few drops of 1% aluminium solution were added to a portion of the filtrate. A yellow colouration indicates the presence of flavonoids. Third, a portion of the extract was heated with 10 ml of ethyl acetate over a steam bath for 3 min. The mixture was filtered and 4 ml of the filtrate was shaken with 1 ml of dilute ammonia solution. A yellow colouration indicates the presence of flavonoids.

2.9 Test for Alkaloids

0.5 g of the extract was diluted to 10 ml of acid alcohol, boiled and filtered. To 5 ml of the filtrate was added 2 ml of dilute ammonia. 5 ml of chloroform was added and shaken gently to extract alkaloidal base. The chloroform layer was extracted with 10 ml of acetic acid. This was divided into two portions. Mayer's reagent was added to one portion and Draggendorff's reagent to the other. The formation of a cream (with Mayer's reagent) or reddish brown precipitate (with Draggendorff's reagent) was regarded as positive for the presence of alkaloids.

2.10 Test for Steroids

To 0.5 g each of the extract was added 2 ml of chloroform. Concentrated H_2SO_4 (3 ml) was carefully added to forma layer. A reddish brown colour at the interface indicates the presence of steroidal ring.

2.11 Test for Carbohydrates

About 0.5 g of the extract was boiled in 10 ml of water in a test tube and then filtered. A few drops of concentrated sulphuric acid was added and allowed to form a lower layer. A purple ring at the interface of the liquids indicates the presence of carbohydrates.

2.12 Test for Reducing Sugars

The aqueous ethanol extract (0.5 g in 5 ml of water) was added to boiling Fehling's solution (A and B) in a test tube. The solution was observed for a colour reaction.

2.13 Test for Anthraquinones

0.5 g of the extract was boiled with 10 ml of sulphuric acid (H_2SO_4) and filtered while hot. The filtrate was shaken with 5 ml of chloroform. The chloroform layer was pipette into another test tube and 1ml of dilute ammonia was added. The resulting solution was observed for colour changes.

2.14 Test for Cardiac Glycosides

To 0.5 g of extract diluted to 5 ml in water was added 2 ml of glacial acetic acid containing one drop of ferric chloride solution. This was under layed with 1 ml of concentrated sulphuric acid. A brown ring at the interface indicated the presence of a deoxysugar characteristic of cardinolides. A violet ring may appear below the brown ring, while in the acetic acid layer a greenish ring may form just above the brown ring and gradually spread throughout this layer.

2.15 Acute Toxicity Study

The lethal dose (LD_{50}) of the ethanolic leaf extract was determined in mice intraperitoneally (i.p.) using the method described by Lorke [16] with slight modifications. Mice of both sexes were fasted overnight and the evaluation of the LD_{50} was done in two phases. In first phase, 3 groups of 3 mice per cage were treated with the extract at doses of 10, 100 and 1000 mg/kg, *i.p* in order to determine the range in which the LD_{50} falls. In the second phase, another group of four mice per cage were further treated with the extract at doses of 140, 225, 370 and 600 mg/kg. Animals were observed for 24 h after treatment for signs and symptoms of toxicity. The number of deaths in each group within 24 h was recorded and the final LD_{50} values were calculated as the geometric mean of the highest non-lethal dose (with no deaths) and the lowest lethal dose (where deaths occurred).

2.16 Yeast-Induced Pyrexia

The method described by AL-Ghamdi [17], Mukherjee et al. [18] was adopted with slight modification. Rats were divided into five groups of six rats each and were subcutaneously injected with 20 ml/kg of 15% yeast (Danbaoli, china) suspended in 0.5% methylcellulose solution to induce pyrexia, after measuring the basal rectal temperature of each rat using a clinical thermometer (Boots, Birmingham England). Rats that did not show a minimum increase of 0.5ºc in temperature 24 h after yeast injection were discarded. Then ethanolic leaf extract of *Pseudocedrela kotschyi* was intraperitoneally administered at doses of 50, 100 and 150 mg/kg to three groups of animals respectively. Distilled water (10 ml/kg *i.p.*) was administered to the control group. The standard drug, Aspirin (150 mg/kg *p.o*.) was administered to group five. The rectal temperature of each rat was again recorded at one hour interval, after drug administration.

2.17 D-Amphetamine-Induced Pyrexia

The method described by Berkan et al. [19] was adopted with slight modification. Rats were divided into five groups of six rats each and fasted for 24 h. Their basal rectal temperature was recorded prior to the induction of pyrexia by intraperitoneal injection of d-amphetamine, 10 mg/kg. Thirty minutes after d-amphetamine administration and confirmation of hyperthermia in the experimental animals, the extract (50, 100 and 150 mg/kg) was intraperitoneally administered to three groups of animals respectively. Distilled water (10 ml/kg *i.p.*) was administered to the control group. The standard drug, Aspirin (150 mg/kg *p.o.*) was administered to group five. The rectal temperature of each rat was again recorded at one hour interval, after drug administration.

2.18 Statistical Analysis

Results were expressed as mean ± S.E.M. The significance of difference between the controls and treated groups were determined using two-way analysis of variance (ANOVA), followed by student t-test. $P<0.05$ were considered to be statistically significant.

3. RESULTS

3.1 Phytochemical Screening

The phytochemical analysis of the crude extract gave a positive reaction for each of the following secondary metabolites: alkaloids, flavonoids, terpenes, steroids, tannins, saponins, glycosides, carbohydrates and reducing sugar.

3.2 Acute Toxicity Tests

The LD_{50} of the extract was established to be 775 mg/kg *i.p.* in mice. The signs of toxicity observed in mice were abdominal constriction and inactivity.

3.3 Yeast Induced Hyperthermia

Subcutaneous injection of yeast caused elevation of rectal temperature after 24 h of administration. The extract at doses of 50, 100, and 150 mg/kg produced a significant

(P<0.05) dose dependent inhibition of temperature elevation. The inhibitory effect started at 1 h post-therapy and was maintained for 4 h. The effect was comparable to that of the standard drug, Aspirin (Table 1).

3.4 D-Amphetamine Induced Hyperthermia

Intraperitoneal injection of d-amphetamine increased the rectal temperature after 30 minutes. The extract at doses of 50, 100 and 150 mg/kg produced a significant (P<0.05) dose dependent reduction of pyrexia. The reduction effect started at 2 h post-therapy and was maintained for 4 h. The effect was comparable to that of Aspirin, the standard drug (Table 2).

4. DISCUSSION

Fever usually results from secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased states. The infected tissue initiates the enhanced formation f pro-inflammatory mediators (cytokines like interleukin 1β, α β and TNF-α) which increase the synthesis of PGE_2 near pre-optic hypothalamus area thereby triggering the hypothalamus to elevate the body temperature [20].

For better characterization of the antipyretic activity of *P. kotschyi*, two models of pyresis including amphetamine-induced and brewer's yeast-induced fever were employed in this study. Antipyretics such as acetylsalicylate acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) reduce fever by depressing inflammatory messages at both peripheral sites of tissue inflammation and within central nervous system thermoregulatory sites. These agents suppress peripheral production of pyrogenic cytokines such as TNF-α and interleukin- 1β, while lowering the thermoregulatory set point by inhibiting central cyclooxygenase production of prostaglandin E_2 [21]. The ethanol leaf extract of *P. kotschyi* demonstrated effective antipyretic activity as evident in the blocking of temperature elevation in the yeast and amphetamine models. The antipyretic action of the extract may possibly be through inhibition of prostaglandin production, leading to suppression of elevated plasma level [22], especially since the extract had been shown to possess antinociceptive and anti-inflammatory activities [4].

The leaf extract at all doses employed in this study, significantly attenuated the fever induced by both brewer's yeast and amphetamine in rats. The onset of action was observed 1 h after administration and maintained throughout the 4 h duration of the study.

Table 1. Effect of *P. kotschyi* leaf extract on yeast-induced pyrexia in rats

Treatment	Dose (mg/kg)	Rectal temperature (ºC)					
		After yeast injection		After drug administration			
		0 h	24 h	1 h	2 h	3 h	4 h
Control		37.52±0.07	39.40±0.07	39.56±0.04	39.65±0.05	39.70±0.06	39.78±0.08
Aspirin	150	37.80±0.05	39.50±0.12	38.11±0.14	37.79±0.03	37.66±0.08	37.56±0.07*
P. kotschyi	50	37.65±0.09	39.63±0.11	37.97±0.12	37.80±0.43	37.72±0.07	37.64±0.08*
	100	37.60±0.12	39.23±0.38	37.85±0.36	37.74±0.53	37.64±0.08	37.54±0.10*
	150	37.30±0.05	39.25±0.04	37.61±0.04	37.49±0.04	37.32±0.05	37.22±0.04*

*Results given are mean ±S.E.M (n=6) *P<0.05 as compared to control*

Table 2. Effect of *P. kotschyi* leaf extract on amphetamine-induced pyrexia in rats

Treatment	Dose (mg/kg)	Rectal temperature (ºC)					
		After amphetamine injection		After drug administration			
		0 h	24 h	1 h	2 h	3 h	4 h
Control		36.94±0.16	37.58±0.18	37.67±0.21	38.12±0.14	38.27±0.18	38.32±0.22
Aspirin	150	36.81±0.10	37.60±0.12	37.20±0.04	36.98±0.06	36.86±0.09	36.74±0.11*
P.kotschyi	50	37.65±0.09	39.63±0.11	37.97±0.12	37.80±0.43	37.72±0.07	37.64±0.08*
	100	36.69±0.09	37.40±0.10	37.07±0.04	36.88±0.07	36.73±0.08	36.60±0.08*
	150	36.63±0.06	37.45±0.07	37.08±0.05	36.87±0.07	36.69±0.06	36.50±0.06*

*Results given are mean ± S.E.M (n=6) *P<0.05 as compared to control*

5. CONCLUSION

In conclusion, the result of the present study indicates that the ethanol leaf extract of *P. kotschyi* has remarkable antipyretic activity. However, more studies are required to identify the active components and precise mechanism of antipyretic action.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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