Antipyretic Properties of Methanol Stem Bark Extracts of Acacia hockii De Wild and Kigelia africana (Lam) Benth in Wistar Rats

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Abstract
Synthetic antipyretic drugs are not readily accessible and have adverse side effects. Herbal medicines possess bioactive compounds that are safer and efficient in the management of various diseases and disorders. Acacia hockii and Kigelia africana are traditionally used to manage pyrexia among the Embu and Mbeere communities in Kenya but lack scientific data to validate their use. The present study evaluated for the antipyretic activity of the A. hockii and K. africana in rat models to scientifically validate their traditional use. The plant samples were collected with the help of local herbalists in Embu County, Kenya and transported to Kenyatta University for cleaning, air drying, milling, and extraction. Adult male Wistar rats were randomly divided into six groups of 5 animals each: normal control, positive control, negative control, and three experimental groups. The antipyretic effect was assessed using turpentine-induced pyrexia method. The antipyretic activities of the extracts were compared to reference drug aspirin. The stem bark extract of A. hockii reduced the raised rectal temperature by between 0.62-3.88% while the stem bark extract of K. africana reduced the elevated rectal temperature by between 0.06-3.07%. The reference drug aspirin reduced the rectal temperature of pyretic rats by between 0.63-3.1%. The qualitative phytochemical screening of the two extracts indicated the presence of flavonoids, alkaloids, saponins, terpenoids which are associated with the antipyretic activity. The present study demonstrated potent antipyretic activities of methanolic extracts of A. hockii and K. africana in a dose-dependent manner after the second hour of the treatment period, which supports their traditional use. The present study, therefore, recommends the ethnomedicinal use of K. africana and A. hockii in the management of pyrexia.

Keywords: Kigelia africana; Acacia hockii; Pyrexia; Turpentine; PGE₂

Introduction
Pyrexia, also known as fever [1], is a medical sign associated with the elevation of body temperature above the normal range (36.5-37.5°C), due to the cytokine-induced upward displacement of the thermoregulatory set-point of the hypothalamus [2]. The elevation of the body temperature occurs when prostaglandin E₂ (PGE₂) increases within the pre-optic region of the hypothalamus and changes the firing rate of neurons in the thermoregulatory center [3]. Symptoms of fever include shivering, sweating, headache, dehydration, muscle aches and general weakness [4].

The impacts of secondary infection, tissue damage, neoplasms or other diseased states induce fever. The infectious causes of pyrexia include viral, bacterial, parasitic infections, common cold, malaria, and meningitis among others while the non-infectious causes of fever include deep vein thrombosis, cancer, and side effects of medication among others [4]. Infected or damaged tissue produces cytokines such as interleukins 1 (β and α), tumor necrosis factor (β and α) and interleukin-6 which triggers the arachidonic acid pathway to initiate the synthesis of PGE₂ in the hypothalamus. The increased production of PGE₂ stimulates the hypothalamus to generate responses to raise the body temperature [5].

Most of the conventional antipyretic drugs such as ibuprofen, paracetamol, aspirin, and naproxen inhibit cyclooxygenase 2 (COX-2) expression [6]. The inhibition of COX-2 lowers the production of PGE₂ necessary for pyrexia induction. However, they are toxic to hepatic cells, glomeruli and heart muscle [7].

The World Health Organization estimates that 80% of populations in developing countries depend on herbal preparations for their health care [8]. The demand for ethnomedicine is raising due to the growing recognition of herbal medicine having fewer side effects, better compatibility with the human body, easily available and being comparatively affordable [9]. Herbal preparations have become the subject of extensive recent studies regarding whether their traditional uses can be scientifically validated [10].

Traditionally, A. hockii and K. africana are used in management of pyrexia among Embu community in Kenya, but lacks scientifically validated data [11]. This study was, therefore, designed to test for the antipyretic activity of the two extracts to act as a preliminary step towards the development of alternative antipyretic agents.

Materials and Method
Plant sample collection and preparation
Fresh stem bark of A. hockii and K. africana were collected in Embu County, Kenya with the help of traditional herbalist in September, 2015. Some of the information obtained from local herbalist included vernacular names, plant parts used in the management of various ailments and other cultural uses. The plant samples were provided to an acknowledged taxonomist in Kenyatta University for botanical authentication and a sample voucher deposited at National Museums.

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of Kenya herbarium. The plant samples were sorted out, cleaned with distilled water and transported to biochemistry and biotechnology laboratories at Kenyatta University. The plant samples were chopped into small pieces, and air dried at room temperature until dry. The dried plant samples were ground into homogenous fine powder using an electric mill.

**Extraction**

To 400 grams of plant sample powder, 2 litre of methanol was added, stirred for four hours and left for two days for the bioactive compounds to dissolve. The extract was filtered using Whatman’s No.1 filter paper and then the filtrate concentrated to dryness under reduced pressure using rotary evaporator at a maximum temperature of 64°C. The concentrate was then put in an airtight container and stored at 4°C until utilized.

**Laboratory animals**

Male Wistar rats aged 3 months and weighing between 140-160 grams were used in the present study. The animals were acquired from animal breeding and experimentation facility in Kenyatta University and were allowed to acclimatize for seven days before testing. The experimental animals were kept in the standard cages in animal experimental facility maintained under standard condition of an ambient temperature of 20-25°C with 12 hours darkness and 12 hours day light cycles. The male Wistar rats were provided water and fed on standard rodent pellets ad libitum [12].

**Evaluation of antipyretic activity**

The animals were fasted during the experiment but were given water ad libitum. Before fever induction, rats were weighed and their basal rectal temperature measured and recorded. Steam distilled turpentine (20 ml/kg bw) was injected intraperitoneally to induce pyrexia [13]. Rats whose rectal temperatures rose by 0.8°C after one hour were termed pyretic and used for studies. The extract was dissolved in Dimethyl Sulfoxide (DMSO) solvent and a vehicle normal saline (0.9% sodium chloride solution) added before treatment. The extracts and aspirin (0.5 ml) were administered intraperitoneally one hour after fever induction.

Thirty male Wistar rats were divided randomly into six groups of five rats each and treated as follows; normal control (Group I) was not induced with fever but administered DMSO. Negative control (Group II) was induced with fever and received DMSO. Positive control (Group III) was induced with fever and received aspirin (standard drug) at a dosage of 100 mg/kg body weight. Experimental groups (Group IV, V and VI) were induced with fever and received extract at a dose levels of 50 mg/kg, 100 mg/kg and 150 mg/kg body weight. This design is summarized in Table 1.

The rectal temperatures were taken by inserting a well-lubricated thermistor probe of a digital thermometer in the rectum [13]. The digital thermometer was calibrated against a mercury thermometer before recording rectal temperature. The mean temperature was measured at 15 minutes intervals for one hour prior to pyrexia induction, and this was termed as baseline temperature.

The rectal temperatures were measured and recorded at 1, 2, 3, and 4 hours after treatments. Rectal temperature at the first hour after turpentine administration and after treatments was compared and their percentage inhibition calculated using formula as follow [14];

\[
\text{Inhibition} \% = \frac{B - C_{r}}{B} \times 100
\]

Where,

- B = Rectal temperature at 1 hour after turpentine administration
- C_{r} = Rectal temperature after treatment

**Phytochemical screening**

The extracts were subjected to standard qualitative phytochemical screening to identify the absence or the presence of various phytochemicals according to methods as described by Harbone [15] and Kotake [16]. Some of the phytochemicals tested are associated with antipyretic properties and they include alkaloids, steroids, terpenoids, saponins and flavonoids [17]. Alkaloids were tested using Dragendroff’s test, sodium hydroxide test was used for flavonoids, Salkowski test was used for terpenoids, sulfuric acid steroid ring test was used for steroids and froth test was used for saponins.

**Data management and statistical analysis**

Recorded rectal temperature were tabulated on the spread sheet in Microsoft excel. The tabulated data was exported to Minitab statistical software version 17.0 (State College, Pennsylvania) for statistical analysis. Descriptive statistics was expressed as mean ± standard error of mean. One-way Analysis of Variance (ANOVA) was used to determine the significant difference between the means of different treatment groups followed by Tukey’s post hoc tests for pairwise comparison among the various treatment groups. The mean activity of the two extracts was compared using unpaired student t-test. The values of p ≤ 0.05 were considered significant. The data was presented in tables and graphs.

**Results**

**Antipyretic activity of stem extract of Acacia hockii de wild on turpentine-induced pyrexia**

The methanol stem bark extract of A. hockii demonstrated antipyretic effect on turpentine-induced pyrexia by lowering rectal temperature of pyretic rats (Figure 1; Table 2). In the first hour after treatment, only the group of rats treated with aspirin (reference drug) at the dosage of 100 mg/kg body weight showed antipyretic activity by reducing the elevated rectal temperature of pyretic rats by 1.7% (Figure 1; Table 2). However, the group of rats treated with extract at the dose levels of 50 mg/kg, 100 mg/kg and 150 mg/kg body weight never demonstrated antipyretic effects at this hour (Figure 1; Table 2). The antipyretic effects of the extract at all dose levels showed no significant difference and were comparable to the negative control (p>0.05; Table 2).

In the second hour after extract administration, the extract at the dosage of 100 mg/kg and 150 mg/kg body weight as well as the aspirin demonstrated antipyretic effect by reducing elevated rectal temperature by 0.68%, 0.72% and 2.47% respectively (Figure 1; Table 2). However, the group of rats treated with extract at the dose level of 50 mg/kg body

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**Table 1**: Treatment protocol for evaluation of antipyretic activities of methanolic extracts of Kigelia africana (Lam) benth and Acacia hockii de wild in male Wistar rats.

| Group  | Status     | Treatment                           |
|--------|------------|-------------------------------------|
| I      | Control    | DMSO                                |
| II     | Negative control | Turpentine+DMSO                    |
| III    | Positive control | Turpentine+100 mg/kg bw Aspirin   |
| IV     | Experimental group A | Turpentine+50 mg/kg bw extract+DMSO |
| V      | Experimental group B | Turpentine+100 mg/kg bw extract+DMSO |
| VI     | Experimental group C | Turpentine+150 mg/kg bw extract+DMSO |

Steam distilled turpentine, DMSO=4%
Antipyretic activity of stem bark Kigelia africana (Lam) bark on turpentine-induced pyrexia

The methanol stem bark extract of K. africana showed antipyretic activity on turpentine-induced pyrexia in male Wistar rats, which was demonstrated by decreased elevated rectal temperature after extract administration (Figure 2; Table 3). In the first hour after extract administration, the stem bark extract of K. africana at the dosage of 150 mg/kg body weight and aspirin (reference drug) at the dose level of 100 mg/kg body weight reduced elevated temperature of pyretic rats by 0.31% and 0.63% respectively (Figure 2; Table 3). However, the extract at the dosage of 50 mg/kg and 100 mg/kg body weight never demonstrated antipyretic activity at this hour (Figure 2; Table 3). The antipyretic activity of the extract at the dosage of 50 mg/kg, 100 mg/kg and 150 mg/kg demonstrated no significant difference and were comparable to aspirin and normal control (p>0.05; Table 3).

In the second hour after extract administration, the group of rats treated with extract at the dose levels of 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight demonstrated antipyretic activity by decreasing the raised rectal temperature by 0.06%, 0.11% and 1.20% respectively (Figure 2; Table 3). Similarly, the rats treated with aspirin (reference drug) showed antipyretic activity by lowering the elevated rectal temperature by 1.25% (Figure 2; Table 3). The antipyretic activity of extract at the dose level of 150 mg/kg body weight was significantly different from 50 mg/kg and 100 mg/kg body weight (p<0.05; Table 3).

Besides, the extract at the dosage of 150 mg/kg body weight was comparable to aspirin (p=0.05; Table 3).

In the third hour after treatment, the group of rats administered with extract at the dosage of 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight reduced elevated rectal temperature of pyretic rat by 0.58%, 1.00% and 1.83% respectively (Figure 2; Table 3). Similarly, the rats treated with aspirin reduced elevated rectal temperature by 1.30% (Figure 2; Table 3). The antipyretic activity of the extract at the dosage of 100 mg/kg and 150 mg/kg body weight showed no significant difference and were comparable to aspirin (p=0.05; Table 3). Besides, the antipyretic activity of the extract at the dosages 50 mg/kg and 100 mg/kg was not significantly different (p=0.005; Table 3).

In the fourth hour after extract administration, the group treated with extract at the dose levels of 50 mg/kg, 100 mg/kg and 150 mg/kg body weight lowered the elevated rectal temperatures by 1.61%, 2.41%, 3.88% and 3.1% respectively (Figure 1; Table 2). The antipyretic activity of the extract at the dose level of 150 mg/kg body weight was significantly different from the extract at the dose levels of 50 mg/kg and 100 mg/kg body weight (p<0.05; Table 2). The antipyretic activity of the extract at the dose of 100 mg/kg and 150 mg/kg body weight was comparable to aspirin (reference drug) (p>0.05; Table 2).

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and terpenoids, alkaloids, cardiac glycosides, flavonoids, phenolics, saponin, steroids, and the bark extracts of K. africana and A. hockii on turpentine-induced pyrexia in rats (Figures 1 and 2; Tables 2 and 3).

**Comparison between the antipyretic activities of Acacia hockii and Kigelia africana on turpentine-induced pyrexia**

In comparison, the antipyretic activity of the two extracts was not significantly different at the dose level of 50 mg/kg body weight in the 1, 2, 3 and 4 hours of the test period with p values of 0.75, 0.70, 0.93, and 0.56 respectively (p>0.05). Similarly, the antipyretic effect of the two extracts at the dose level of 100 mg/kg body weight was not significantly different in the 1,2,3 and 4 hours of the test period with p values of 0.28, 0.16, 0.42 and 0.08 respectively (p<0.05). The antipyretic activity of both extracts was best active at the dosage of 150 mg/kg in fourth hour after extract administration (Figure 3).

**Phytochemical screening**

The qualitative phytochemical screening of the methanolic stem bark extracts of K. africana and A. hockii indicated the presence of alkaloids, cardiac glycosides, flavonoids, phenolics, saponin, steroids, and terpenoids.

**Discussion**

Although there is a considerable progress in the treatment of diseases and disorders using modern therapeutic drugs, search for alternative medication continues due to the existing association of synthetic drugs with several limitations. The long-term use of NSAIDs in the management of pyrexia and inflammation may result in severe complications such as renal damage, cardiac abnormalities and gastric ulcers [18]. Herbal preparations possess a wealth of secondary metabolites that can manage various disease and disorders. In addition, herbal preparations have shown potent antipyretic activities in experimental animals [19].

The present study was designed to determine the antipyretic effects of methanol extracts of A. hockii and K. africana in male Wistar rats. Exogenous pyrogens such as Lipopolysaccharides (LPS), stem distilled turpentine, brewer’s yeast, Muramyl Dipeptide (MDP) and polysinosinic: polycytidylic acid (poly I: C) are used to induce pyrexia in experimental animals [20,21].

The exogenous pyrogens produce fever by their ability to stimulate the synthesis and release of endogenous pyrogens from the host phagocytic cells. Moreover, it is the circulating endogenous pyrogens rather than circulating exogenous pyrogens which act on the thermoregulatory center to raise the thermostatic set-point in the hypothalamus and produce fever [22]. Fever is mediated by the pyrogens which are synthesized and released by activated phagocytes in response to endogenous pyrogens. These mediators stimulate the synthesis of PGE2, which is the primary mediator of the well-coordinated fever response [23].

Turpentine is a fluid obtained by the distillation of resin from pine. Subcutaneous injection of steam distilled turpentine causes pyrexia by enhancing the production of PGE2, which ultimately increase the body temperature [24]. The turpentine-induced pyrexia has been established as a model for the study of fever response in experimental animals [25].

The present study demonstrated significant antipyretic activity of methanol stem bark extracts of A. hockii and K. africana on turpentine-induced pyrexia in rats [Figures 1 and 2; Tables 2 and 3]. These findings were in agreement with other study carried out on herbal preparation using experimental animals. The study carried out on dichloromethane: methanolic leaf and root bark extracts of Carissa edulis (Forssk.) Valh showed antipyretic activity on turpentine-induced pyrexia in rats [26]. Similarly, the root extract of Solanum incanum...
(Linnaeus) demonstrated antipyretic activity on lipopolysaccharides-induced pyrexia in male Wistar rats [27]. Besides, according to [28] the methanolic leaf extract of Vernonia cinerea showed antipyretic activity on brewer’s yeast induced pyrexia in Wistar rats.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, acetaminophen, diclofenac and ibuprofen are commonly used in the medication of fever [29]. The NSAIDs manage pyrexia through inhibition of the Cyclooxygenase (COX) enzyme that stimulates the production of PGE, responsible for fever induction [30]. Studies have established that at least two COX isoenzyme exist; COX-1 and COX-2. The COX-1 synthetize prostaglandins that protect the stomach and the kidney from damage while the COX-2 stimulate PGE production that contributes to fever induction [31]. It was therefore believed that the methanolic stem bark extracts of K. africana and A. hockii reduced the elevated rectal temperatures of rats by inhibiting the enzyme COX-2 responsible for the production of PGE.

The antipyretic activity of methanol stem bark extracts of K. africana and A. hockii demonstrated a dose-dependent response after the second hour of the test period, with the dose level of 150 mg/kg body weight producing greater antipyretic activity (Figures 1 and 2; Tables 2 and 3). These findings were consistent with the study carried out on the antipyretic activity of methanol extracts of aerial parts of Costus speciosus Koen in experimental animals [32]. Similarly, a study conducted on the antipyretic activity of ethyl acetate roots extracts of Ocimum sanctum demonstrated a dose dependent response in laboratory animals [33].

The aspirin (reference drug) achieved its maximum antipyretic activity in the third hour (Figures 1 and 2; Tables 2 and 3). Its activity decreased subsequently probably due to metabolism and elimination of the drug. The maximum antipyretic activity of the stem bark extracts of A. hockii and K. africana occurred in the fourth hour, indicating slow but steady passive diffusion of the bioactive compounds across the cell membrane [34]. The stem bark extracts of A. hockii and K. africana at the dose level of 150 mg/kg body weight were more active in the fourth hour of treatment compared to aspirin (reference drug) (Figures 1 and 2; Tables 2 and 3). These findings indicated that stem bark extracts of K. africana and A. hockii were able to inhibit the synthesis of prostaglandins more than the reference drug (aspirin). However, the aspirin showed a sudden decrease in elevated rectal temperatures as compared to the extracts of A. hockii and K. africana (Figures 1 and 2; Tables 2 and 3). The antipyretic activity of methanol stem bark extracts of K. africana and A. hockii could be due to the ability of herbal preparations to possess a wealth of secondary metabolites required in the management of various diseases and disorders [19]. The qualitative phytochemical screening of methanolic stem bark extracts of A. hockii and K. africana indicated the presence of alkaloids, flavonoids, steroids, saponins and terpenoids (Table 4). The presence of these bioactive constituents such as steroids, terpenoids, saponins, alkaloids and flavonoids have shown to exhibit antipyretic activity in experimental animals [35].

Flavonoids exhibit inhibition of arachidonic acid peroxidation, which results in the reduction of prostaglandins levels thus managing fever [36]. Flavonoids also inhibit the synthesis of tumor necrosis factor alpha which stimulates the production of PGE, necessary for fever induction [37]. Alkaloids, terpenoids and steroids inhibit the synthesis of prostaglandins synthase which stimulates the production of PGE [36]. Steroids have also been reported to inhibit the conversion of linoleic acid to arachidonic acid, a substrate required for PGE synthesis [38]. The antipyretic activity exhibited by methanolic stem bark extracts of K. africana and A. hockii was therefore believed to be associated with the presence of flavonoids, terpenoids, alkaloids and steroids in the extracts.

**Conclusion**

The methanolic stem bark extracts of K. africana and A. hockii demonstrated significant antipyretic effects on turpentine-induced pyrexia in rats. The antipyretic activity of the two extracts showed a dose-dependent response and were comparable to aspirin (reference drug). Besides, the extracts of K. africana and A. hockii at the dose level of 150 mg/kg body weight were more active in the fourth hour after treatment.

The extracts of K. africana and A. hockii could, therefore, can be an alternative bio-resource for generating antipyretic agents which are efficient and with less side effects. Besides, further studies should be carried out to elucidate the mechanism behind these effects. The present study, therefore, scientifically confirm and supports the ethnomedical use of K. africana and A. hockii in the management of pyrexia.

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