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Anti-pyretic Activity of *Garcinia kola* Seed Extract

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Authors' contributions

All the authors collaborated in carrying out this work. The study was designed by the authors KDF, MOU and NLN who all jointly participated in the laboratory bench work, preparation and editing of the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Garcinia kola (Heckel) has been used in folk medicine for the treatment of several ailments. One of these is its use for the treatment of conditions involving pain and inflammation with accompanying pyrexia. Our objective is to evaluate the anti-pyretic property of *Garcinia kola* (Heckel) seed extract in albino Wistar rats. Twenty-five albino Wistar rats of both sexes, randomized into five groups were used. Group one served as the control and received only the vehicle, propylene glycol. Group two received paracetamol 150 mg/kg body weight orally while groups three to five received 500, 1000 and 1500 mg/kg body weight of the extract orally respectively. Pyrexia was induced using brewer's yeast. We found LD_{50}, determined by Lorke's method to be greater than 5000 mg/kg indicating the wide margin of safety of *Garcinia kola* (Heckel) seeds. The extract at doses of 500, 1000 and 1500 mg/kg respectively showed statistically significant (P<0.01) dose dependent reduction of brewer's yeast induced pyrexia in albino Wistar rats. The study shows that *Garcinia kola* (Heckel) seeds possess significant anti-pyretic activity, thus justifying its ethnomedicinal use.

Keywords: Garcinia kola; Inflammation; Brewer's yeast induced pyrexia.

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1. INTRODUCTION

Plant derived medicines have made large contributions to human health and well-being. Estimates show that plant materials are present in or serve as models for almost 50% of western drugs. Plant derived medicines have many benefits, being relatively safer and affordable [1].

Fever or pyrexia, is a common symptom of many illnesses and in children accounts for 19% to 30% paediatric emergency visits. Although it's a beneficial physiological response, fever often leads to irritability in children and anxiety in parents [2] with the cost-effectiveness and the availability of fever-reducing agents being a major factor in its treatment, thus the need for readily available, cheap and effective agents. Medicinal plants found in our environment are used by the population as cheaper alternatives to conventional orthodox medicines [3,4]. The World Health Organization estimates that almost 80% of African populations use herbal remedies [5]. One such plant used in treatment of conditions involving pyrexia is *Garcinia kola* (Heckel).

Garcinia kola (bitter kola) is a flowering plant of many species in the Clusiaceae or Guittiferae family. The tree grows to a height 12 metres in moist forests in most parts of West and Central Africa, its natural habitat being subtropical or tropical lowland forests [6]. In Nigeria, it is commonly called *Orogbo* by the Yorubas, *Namijin goro* by the Hausas (who use it as a local snack) and *Akuilu* in Igbo [7]. It is called 'male kola' because of its claimed aphrodisiac property [8] and referred to as a wonder plant because every part of it is of medicinal importance [9].

Garcinia kola seeds have been used in ethnomedicine as a purgative, anti-parasitic and anti-microbial agent [10]. Other uses include the treatment of diarrhoea, bronchitis, throat infections and liver disorders [11]. The masticated fruit pulp is used as an oral antiseptic and in the treatment of cuts and sore throats [12]. The roots and stem serve as bitter chewing sticks and used for oral hygiene. The powered bark is used in the treatment of malignant tumours, pyrexia and; as a bitter tonic and astringent [6]. Lartex from the stem bark is reported to be effective against parasitic skin diseases and applied topically for wound dressing [2]. Traditional medicine practitioners in Nigeria, particularly in the Ogoni area use a decoction of *Garcinia kola* stem bark for the treatment of dysmenorrhoea, fever, inflammation and burns. It is also used to treat conditions such as laryngitis, gonorrhoea and hepatitis [2,13].

Physiological and pharmacological effects such as anti-inflammatory property [5], antimicrobial activity [4,14], hepatoprotective, antioxidant, antifertility, haematological and anticancer effects [15] have been attributed to the plant. It is reportedly efficacious in patients with primary open angle glaucoma or ocular hypertension [16].

In this study, we set out to investigate the anti-pyretic activity of *Garcinia kola* with a view to establishing a basis for its use in conditions involving pyrexia of different causes.

2. MATERIALS AND METHODS

2.1 Collection, Identification and Preparation of Plant Material

Garcinia kola (Heckel) seeds were procured from local dealers in the Terminus market, Jos, Plateau state, North Central Nigeria, and authenticated at the Federal College of Forestry, Jos. The voucher specimen, Number FHJ 948 has been deposited at the college herbarium for reference. The seeds were first inspected for deterioration and the presence of foreign materials. The seeds were sun-dried for two days, manually peeled, size-reduced with a hand grater then dried to constant weight in a hot air oven maintained at 40℃.

2.2 Drugs and Reagents

Chemicals and reagents used included methanol and propylene glycol; and paracetamol syrup 125 mg/5 ml; Brewer's yeast, gum acacia and Normal Saline. All the chemicals and reagents used were of analytical grade. Paracetamol 125 mg/5 ml was obtained from Europharm Laboratories limited, Jos.

2.3 Preparation of Extract

Three hundred grams of the powder was extracted for 72 hours in a Soxhlet apparatus using 70% methanol [9]. This was dried to a constant weight in a boiling water bath to give a dark brown semi-solid extract with a rubbery texture free of the solvent and of yield 48.31%. The extract was packaged in an air-tight container and kept in a refrigerator until needed.

2.4 Thin layer Chromatography (TLC) Profiling/Fingerprinting

The extract was applied on silica gel pre-coated TLC plates with the aid of capillary tubes and developed in a TLC chamber using different solvent systems or mobile phases. The solvent systems used were chloroform: water (8:2), chloroform: methanol: water (7:3:1) and acetone: water: 25% ammonia (90:7:1). The developed TLC plates were air dried and observed under day light; and ultra violet light UV at 254 nm. The plates were later sprayed with different spraying reagents for the development of colour in separated bands. The spray reagents used were iodine vapour and 10% sulphuric acid. The movement of the various spots were expressed by the retention factor (R_f).

The R_f values were calculated for the different spots using the formula [17]:

$$R_f \text{ value} = \frac{\text{Distance travelled by the solute}}{\text{Distance travelled by the solvent front of the TLC plate}}$$

2.5 Experimental Animals

Adult albino rats of both sexes, body weight 125-230 gm obtained from the National Veterinary Research Institute, Vom, Plateau State, Nigeria were used for the study.

The animals were housed in disinfected metal cages padded with saw dust, placed on metal shelves in a well ventilated room at controlled temperature (25 ± 2℃) and maintained in a 12 hour dark-light cycle. The animals had free access to feed and clean tap water *ad libitum.*

The drinkers containing clean tap water for the animals were washed and refilled daily. The use of experimental animals was approved by the Ethical Committee, Department of Pharmacology, Faculty of Pharmaceutical Sciences of the University of Jos, Nigeria.

2.6 Acute Toxicity

The animals were allowed to acclimatize for a period of 7 days before the determination of LD_{50} [18] which was carried out according to the method of Lorke [19] as modified by Builders *et al* [20]. In this procedure, there were two phases. In phase one, nine rats divided into three groups of three rats per group received graded doses (10, 100 and 1000 mg/kg respectively) of the extract by the oral route. In phase two, a further nine rats in three groups of three rats each received graded doses (1500, 3000 and 5000 mg/kg respectively) of the extract by the oral route. Any acute toxic symptoms were observed and recorded systematically in 1, 2, 4, 6 and 24 hours after extract administration. The number of animals that survived or died in each group within 24 hours was observed recorded. The observation of acute toxic symptoms included but is not limited to skin changes, restlessness and aggressiveness, rubbing of nose and mouth on the floor of the cage, sensitivity to sound and pain, as well as respiratory movements and sedation. The acute toxic effect of the extract was assessed on the basis of mortality, which was expressed as LD_{50}. Finally the LD_{50} value was calculated as the geometric mean of the highest non-lethal dose (with no deaths) and the lowest lethal dose (where deaths occurred).

2.7 Induction of Pyrexia

The animals were allowed an acclimatization period of 7 days before the experiment for the evaluation of antipyretic activity was carried out [18]. A 20% suspension of dried brewer's yeast in 2% gum acacia prepared in normal saline was used as the pyrexia-inducing agent [21]. Initial rectal temperatures of the experimental animals were recorded with the aid of an clinical thermometer by inserting it 1.5cm deep into the rectum, and holding it in place for one minute [22]. This was done in order to ensure that the rats were normothermic before administering the brewer's yeast which was administered subcutaneously according to the body weights of the rats [23]. After 18 hours the rectal temperature of the rats were determined via the same procedure and recorded. Animals that showed a rise in body temperature of at least 0.6℃ [21] were eligible for carrying out further experiments.

2.8 Antipyretic Activity

Twenty-five experimental animals eligible for the experiment as earlier defined above, were randomly divided into 5 groups of 5 rats each. Group 1 received 5 ml/kg propylene glycol orally, as negative control. Group 2 received paracetamol 150 mg/kg body weight orally. Group 3, 4 and 5 received 500, 1000 and 1500 mg/kg body weight respectively of *Garcinia kola* (Heckel) seed extract orally suspended in propylene glycol. The rectal temperatures of the rats were recorded at 0, 1, 2, 3, 4 and 5 hours [14,24].

2.9 Statistical Analysis

The data values were expressed as mean $\pm$ standard error of mean and analyzed using one way ANOVA. *P* values lower than the appropriate levels of significance as designated were considered statistically significant.

3. RESULTS

The results for the various R_f values according to solvent systems, different spray reagents and colours of the spots are presented in Table 1. No peaks or spots were noticeable when the developed plates were viewed under daylight.

Summary of experimental procedure is presented in Table 2, results of oral LD_{50} is presented in Table 3 and the effect of oral administration of the seed extract on brewer's yeast induced pyrexia is presented in Table 4.

In the oral LD_{50} determination, none of the animals died. The absence of death at doses up to 5000 mg/kg body weight of the extract showed that the oral LD_{50} of the extracts of *Garcinia kola* is greater than 5000 mg/kg. Only slight sedation was noticed at the 5000 mg/kg dose.

4. DISCUSSION

The result of acute toxicity test, with oral LD_{50} being greater than 5000 mg/kg body weight shows it is safe. Even though sedation - probably due to an overwhelming concentration of the extract - was observed in the group administered 5000 mg/kg body weight, its use at this high dose for the purposes mention in literature would be rare.

At 500 mg/kg body weight dose of the extract there was significant antipyretic activity ($P < 0.05$) from 1hour after administration and ($P < 0.01$) from the second up to the fifth hour. The extract at doses of 1000 and 1500 mg/kg body weight respectively showed a significant decrease of body temperature in each group ($P < 0.01$) from the first hour after administration to the fifth hour. The control group showed no significant decrease in body temperature throughout the experiment as body temperatures of the group remained significantly elevated both before and after administration of 5 ml/kg body weight of propylene glycol, similar to the state when pyrexia was induced. The paracetamol group showed a significant decrease of body temperature from the first hour after administration up to the fifth hour ($P < 0.01$). This reduction in body temperature observed with paracetamol has been described as resulting from its property of being a non-selective Cyclooxygenase enzyme (COX) inhibitor [25].

Normal body temperature is regulated by centres in the hypothalamus that ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which leads to the set-point of body temperature being raised. Cyclooxygenase enzyme inhibitors which are often used as Non steroidal Anti-inflammatory drugs, NSAIDs, reset the thermostat. Once there has been a return to the normal set-point, the temperature regulating mechanisms (dilation of superficial blood vessels, sweating, etc.) then operate to reduce temperature. NSAIDs are thought to be anti-pyretic largely through inhibition of prostaglandin production in the hypothalamus [15, 26]. During an inflammatory reaction, bacterial endotoxins cause the release of a pyrogen, Interleukin-1 from macrophages. Interleukin-1 stimulates the generation of E-type prostaglandins (PGEs) in the hypothalamus, with resultant the elevation of the set-point for temperature. There is some evidence that prostaglandins are not the only mediators of fever; hence NSAIDs may have an additional anti-pyretic effect by mechanisms yet unknown even as they do not affect normal body temperature [26,27].

Table 1. R_f values of peaks from *Garcinia kola* seed extract obtained with different solvent and visualization systems

Solvent System	Visualization System, R_f value and colours of peaks					
Chloroform: Methanol (8:2)	UV (254nm)		Iodine Vapour		10% Sulphuric acid	
	R_f values	Colour	R_f values	Colour	R_f values	colour
	No peak seen		0.87	Brown	0.25	All Dark brown
			0.75	Brown	0.33	on a pinkish tail
					0.42	
					0.53	
					0.70	
					0.75	Dark Blue
Chloroform: Methanol: Water (7:3:1)	0.68	Yellow	0.68	Yellow	0.30	Dark brown
	0.89	Pink	0.89	Yellowish brown	0.50	Light pinkish
					0.54	Pink
					0.70	Dark orange
					0.77	Light brown
					0.92	Yellow
Acetone: Water: 25% Ammonia (90:7:3)	No peak seen		0.57	Brown	0.57	Orange
			0.62	Light orange	0.62	Orange
			0.92	Light pink	0.92	Light Brown

Table 2. Summary of experimental method

Groups	N	Induction of pyrexia (0 hour) in all groups	Treatment (18hours)
1	5	20ml/kg of 20% suspension of dried brewers' yeast prepared in 2% gum acacia	Propylene glycol 5ml/kg
2	5		Paracetamol 150mg/kg
3	5		Extract 500mg/kg
4	5		Extract 1000mg/kg
5	5		Extract 1500mg/kg

N = number of experimental animals per group

Table 3. Oral LD_{50} of *Garcinia kola* (Heckel) seed extract

Groups	N	Dose (mg/Kg body weight)	Mortality	Percentage Mortality	Other Symptoms
Phase I					
1	3	10	0	0 %	-
2	3	100	0	0 %	-
3	3	1000	0	0 %	-
Phase II					
1	3	1500	0	0 %	-
2	3	3000	0	0 %	-
3	3	5000	0	0 %	Sedation

N = number of experimental animals per group - = other symptoms not observable
The oral LD_{50} of Garcinia kola (Heckel) seed extract was found to be more than 5000 mg/kg body weight.

Table 4. Effect of *Garcinia kola* (Heckel) seed extract administered orally on brewer's yeast-induced pyrexia in albino Wistar rats

Group	Normal	Pyrexia	0 Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours
Propylene glycol 5 ml/kg	37.50 ± 0.09	38.20 ± 0.15	38.40 ± 0.15	38.43 ± 0.14	38.63 ± 0.09	38.63 ± 0.09	38.43 ± 0.09	38.30 ± 0.04
Paracetamol 150 mg/kg	37.40 ± 0.05	38.24 ± 0.09	38.28 ± 0.04	37.58 ± 0.07**	37.38 ± 0.04**	37.30 ± 0.05**	37.43 ± 0.04**	37.44 ± 0.05**
Extract 500 mg/kg	37.30 ± 0.05	38.30 ± 0.07	38.38 ± 0.07	37.98 ± 0.07*	37.60 ± 0.04**	37.56 ± 0.05**	37.62 ± 0.04**	37.80 ± 0.04**
Extract 1000 mg/kg	37.42 ± 0.04	38.32 ± 0.06	38.34 ± 0.05	37.76 ± 0.07**	37.54 ± 0.05**	37.30 ± 0.03**	37.62 ± 0.06**	37.70 ± 0.04**
Extract 1500 mg/kg	37.46 ± 0.04	38.30 ± 0.07	38.34 ± 0.05	37.38 ± 0.04**	37.34 ± 0.02**	37.36 ± 0.04**	37.44 ± 0.07**	37.34 ± 0.06**

*Values are rectal Temperatures (℃) and represented asMean ± standard error of mean (S.E.M) *P < 0.05; **P < 0.01 compared with control.*
Number of animals per group = 5

The time of onset of reduction of pyrexia in the extract and paracetamol groups was approximately 1 hour. This may have been due to the route of administration. In this experiment, paracetamol, the control and extract preparations were administered orally. This route comes with some general characteristics which may have a toll on onset of action, bioavailability, duration of action and certain other pharmacokinetic parameters. Typically, about 75% of a drug given orally is absorbed within 1-3 hours, but numerous factors alter this, some physiological and some to do with the formulation of the drug. The main factors that affect gastrointestinal absorption are gastrointestinal motility, splanchnic blood flow, physicochemical factors, and particle size and formulation [16]. From the results, body temperature of the animals started to show a marginal rise from the third hour post administration in both test and paracetamol groups. This may have been due to the decline in the peak plasma concentration of the agents administered. There was also a fall in body temperature after the fifth hour succeeding the rise observed in the fourth hour in the 1500 mg/kg body weight group. This fluctuation may have been due to the effect of the administered agent wearing off, and the body recovering its own ability to lower the set-point of body temperature in the hypothalamus, thus restoring body temperature to normal.

The anti-pyretic activity *Garcinia Kola* (Heckel) seed extract may be due to phytoactive constituents present in it. Many authors have documented these to include flavonoids, tannins, cardiac glycoside, steroids, saponins and reducing sugars [9,28]. The presence of these five groups of phytoactive constituents was confirmed by thin layer Chromatographic profiling (Table 1) wherein five distinctive peaks or spots of different R_f values could be seen especially when the spots were visualized after spraying with 10% sulphuric acid. Thus the versatility of chromatographic techniques especially thin layer chromatography in the initial qualitative evaluation of herbal products as has been highlighted by many reports [29,30] cannot be overemphasized. With particular reference to the antipyretic effect, flavonoids that are abundantly present in the seeds are known to inhibit prostaglandins which are involved in pyrexia [11]. Many experiments suggest that interleukin-1 causes fever by first inducing the formation of one of the prostaglandins, mainly prostaglandin E2, which acts in the hypothalamus to elicit the fever reaction. Therefore when prostaglandin formation is blocked by drugs or phytoactive constituents such as flavonoids, the fever is completely abrogated or reduced [23,4]. The anti-pyretic activity of the extract could also be as a result of vasodilation of superficial blood vessels leading to increased heat dissipation as a result of the resetting of temperature control centres in hypothalamus. It could also be through enhancement of the production of other anti-pyretic substances such as vasopressin and arginine by the body [23].

5. CONCLUSION

The results of this study show that *Garcinia kola* (Heckel) seed extract has significant antipyretic activity in experimental animals and provides a basis for the wide spread ethnomedicinal use of the seed and indeed the plant in the treatment of fevers and related conditions.

PATIENT CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed. All experiments and procedures have been examined and approved by the Animal Care and Use Committee, Faculty of Pharmaceutical Sciences, University of Jos.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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