Int J Clin Exp Physiol. 2024;11(2):64-69.
https://www.ijcep.org

Original Article

Ameliorating Potentials of Methanol Extract of *Psorospemum fabrifugum* Leaves on Malaria and Yeast-Induced Fever in Wistar Mice

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ABSTRACT

Background and Aim: Malaria remains a significant global health concern, with fever being a hallmark symptom, while fever, often caused by various infections, poses additional health challenges. This study addresses the need to explore natural remedies for these conditions, focusing on the methanol extract of *Psorospermum febrifugum* leaves. The primary aim of this research is to investigate the effects of the extract on malaria-induced fever and yeast-induced fever in Wistar mice. Additionally, the study includes a phytochemical analysis and the acute toxicity test of the extract. **Methods:** Malaria parasitaemia (*Plasmodium berghei*) was obtained from a malaria infected mice gotten at Veterinary Medicine Department in University of Nigeria, Nsukka. The main study involved 45 Wistar mice weighing between 20 g and 32 g and was divided into two sets of animals. The first set was used for anti-malaria and the fever induced by plasmodium beighe inoculation, while the second group was for the antipyretic activity induced by yeast. **Results:** In the anti-malaria study, *Psorospermum febrifugum* leaves extract showed a dose dependent significant reduction of the parasitaemia count ($p < 0.05$) for the first, second and the third day of treatment. Within the three days of the study, the temperature check showed a dose-dependent significant difference ($p < 0.05$); the 400 mg/kg of the extract and the Arthemeter (standard drug) at 5 mg/kg, showed significant reduction against the negative control group. In the yeast-induced fever, after the single treatment, 200 mg/kg of the extract exhibited a significant reduction ($p < 0.05$) at 1 hr and 2 hr after treatment compared with the control, while the 400mg/kg of the extract showed significant reductions ($p < 0.05$) at 30 min, 1 hr, and 2 hr post-treatment. Paracetamol at 100 mg/kg also showed a statistical significant reduction ($p < 0.05$). **Conclusion:** The findings from this study suggest that the extract has potential as a treatment for malaria-induced fever due to its significant impact on parasitaemia levels. It also demonstrates antipyretic properties in yeast-induced fever, indicating its potential as an antipyretic agent for various infections.

Keywords: Parasthemia count, Plasmodium inoculation, Pyresis and Antipyresis.

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Received: 30-03-2024;
Revised: 18-05-2024;
Accepted: 27-06-2024

INTRODUCTION

Fever, a hallmark of many infectious and inflammatory conditions, is the body's response to harmful stimuli. The management of fever has been a fundamental aspect of medical care for centuries, and antipyretic agents play a pivotal role in alleviating its symptoms and associated discomfort.[1,2] Fever refers to the body's temperature that is higher than the normal range of 37°C due to an increase in set-point temperature in the hypothalamus.[3] Fever is orchestrated by the release of endogenous pyrogens, which stimulate the hypothalamus to raise the body's set point temperature.[4] The release of pro-inflammatory cytokines, such as interleukin-1β and interleukin-6, triggers this cascade, leading to an elevation in body temperature.[4,5] Increased Prostaglandin E2 (PGE2) biosynthesis in the hypothalamic pre-optic region

DOI: 10.5530/ijcep.2024.11.2.11

alters the neuron firing rate, leading to fever induction.[6] While fever is generally considered a protective mechanism, excessive or prolonged elevation in body temperature can lead to detrimental effects.[1] Two distinct fever-inducing conditions that warrant thorough investigation are malaria-induced fever, caused by Plasmodium parasites, and yeast-induced fever, often attributed to pathogenic yeast infections.[7]

Malaria, a mosquito-borne infectious disease caused by Plasmodium parasites, remains a significant global health burden, especially in tropical and subtropical regions. In 2019, an estimated 229 million cases and approximately 409,000 deaths were attributed to malaria worldwide, with sub-Saharan Africa bearing the highest disease burden.[8] Malaria infection is characterized by recurrent episodes of fever, often accompanied by additional symptoms such as chills, sweats, and fatigue.[8]

Conversely, yeast-induced fever is commonly associated with systemic infections caused by yeasts belonging to the Candida genus and other pathogenic species.[4] Such infections can lead to fever and septicaemia particularly in immune compromised individuals.[1] Yeast-induced fever presents unique challenges due to its multifaceted etiology and potential for severe complications.[7]

The primary class of antipyretic agents includes nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol). NSAIDs, like ibuprofen and aspirin exert their antipyretic effects by inhibiting prostaglandin synthesis through Cyclooxygenase (COX) enzyme inhibition.[5]

Table 1: Qualitative Phytochemical Analysis of Methanolic Extract of *Psorospermum febrifugum*.

Secondary Metabolite	Relative Abundance
Alkaloids	++
Steroids	+++
Saponins	+++
Tannins	+
Terpenoids	++
Carbohydrates	++
Proteins	++
Resins	+
Oil	++
Flavonoids	+++
Reducing sugar	++
Acidic compound	++
Glycosides	+++

+ indicates present in small quantity; ++ indicates moderately present; +++ indicates abundantly present.

Fever itself serves as a protective response to infections, and the indiscriminate use of antipyretics might hamper the body's immune defence mechanisms.[1] While antipyretic agents are widely used, their administration requires careful consideration. Additionally, some antipyretics have potential adverse effects, such as gastrointestinal bleeding associated with NSAID use.[9]

In recent years, there has been growing interest in natural remedies as potential antipyretic agents. Medicinal plants have been used for centuries in various cultures to manage fever.[10] Handling of human illnesses with traditional medicinal plants has been an integral part of traditional medicine for centuries nationwide. Significantly, herbal medicines play a valuable role in developed, as well as developing countries in improving primary healthcare for the reason that they have effective biological and medicinal properties with easy accessibility and low costs.[11]

Psorospermum febrifugum, an African plant traditionally employed for its reputed antipyretic properties, is of particular interest.[12] The leaves of *Psorospermum febrifugum* are known to contain various bioactive compounds that have demonstrated anti-inflammatory and antipyretic effects.[12]

This study aims to investigate the potential antipyretic effects of the methanol extract of *Psorospermum febrifugum* leaf in the context of both malaria-induced fever and yeast-induced fever using Wistar rats as an experimental model. By examining the impacts of the plant extract on these distinct fever-inducing conditions, this research seeks to contribute to our understanding of its potential therapeutic utility. The outcomes of this study could hold implications for the development of alternative or adjunctive antipyretic treatments for fever-related disorders.

MATERIALS AND METHODS

Ethical Approval

Ethics approval for this study was gotten from Research and Ethics committee, Department of Zoology, University of Nigeria, Nsukka, Enugu State.

Table 2: Grouping of yeast induced Wistar mice and treatment.

Group	Treatment
Group 1	Induced with fever and treated with 200 mg/kg of the extract.
Group 2	Induced with fever and treated with 400 mg/kg of the extract.
Group 3	Standard control (Induced with fever and treated with 100mg/kg of standard drug (Paracetamol).
Group 4	Negative control (Induced with fever and treated with 10 mL/kg of normal saline).

The route of administration (treatment) was via oral route with the aid of an oral cannula. Treatment lasted for 2 hr during which the body temperature of the mice was checked for 0 hr (18 hr after induction), 30 min, 1 hr and 2 hr with a rectal thermometer.

Drugs

The following drugs were used in the research; Artemetrin tablet 800 mg (A.C Drugs LTD Emene, Enugu State, Nigeria), Paracetamol tablet 500 mg (EMZOR Pharmaceutical industries, Lagos, Nigeria). They were purchased from a controlled pharmaceutical shop in Enugu state, Nigeria.

Chemicals and Solvents

Solvent for extraction and dissolution includes analytical grade of 95% Methanol (Archer Daniels Midland Co., USA).

Reagents

Reagents used for all the assays were commercial kits and products Randox, USA. They include Molisch's reagent, Fehlings solution I and II, Mayer's reagent, Drageudoff's reagent, Wagner's reagent, Picric acid solution (1%), 1.0 mL of Folin-Denis reagent and Million reagents.

Equipment and Materials

Soxhlet Extractor (Home Science Tool China, 98-1-1B model), UV Spectrophotometer (Gallen Komp England, 752s model), Crucible (Rotilabo, Germany); Weighing scale (Gallenkamp, England); Beakers (Pyrex, England) and Test tube (Pyrex, England), Syringes and Cannular (Wuxi Yushou medicals co. Ltd, China), Disposable latex gloves (AMMEX, USA); Stopwatch (Rolilink USA).

Table 3: Grouping of malarial induced Wistar mice and treatments.

Group	Treatment
Group 1	Inoculated with malaria parasite and treated with 100 mg/kg of the extract.
Group 2	Inoculated with malaria parasite and treated with 200 mg/kg of the extract.
Group 3	Inoculated with malaria parasite and treated with 400 mg/kg of the extract.
Group 4	Standard control (Inoculated with malaria parasite and treated with 5 mg/kg of the standard drug, Artemetrin).
Group 5	Negative control (Inoculated with malaria parasite and treated with 10 mL/kg of normal saline).

Treatment was administered orally via an oral cannula for 4 days, and body temperature and parasitemia levels were monitored daily. In the yeast-induced fever study, 20 Wistar mice were divided into four groups of 5 mice each, acclimatized for one week, and induced with fever, then treated as follows:

Qualitative Phytochemical Analysis

The phytochemical constituent of the plant (Table 1) was assayed using the method of Trease and Evans (1988).[13,14]

Acute Toxicity (LD_{50}) Determination

The protocol of Lorke's (1983) were used for this study.[15]

Procurement of Parasitaemia

Malaria parasitaemia (*Plasmodium berghei*) was obtained from a malaria infected mice gotten at Veterinary Medicine Department in University of Nigeria, Nsukka. Ten drops of the parasitized blood obtained with the aid of a capillary tube through the ocular region of the mice was diluted with 1 mL of normal saline. Thereafter, 0.2 mL of the diluted parasitized blood was used to passage each of the three mice that served as the host from where subsequent ones were passaged.

Experimental Animals and Design

The animals used for this study were Wistar mice of either sex weighing 20-32 g. A total of Forty-five (45) Wistar mice were obtained from the animal house of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka for the experimental studies. The animals were acclimatized for duration of 7 days under standard environmental condition with a 12 hr light/dark cycle maintained on regular feed (vital feed and water).[16] In the malaria-induced fever study, 25 Wistar mice were divided into five groups of 5 mice each. They were acclimatized for one week, inoculated with malaria parasite (Plasmodium berghei), and treated as given in Table 2.

Treatment was administered orally via an oral cannula for 4 days, and body temperature and parasitemia levels were monitored daily.

In the yeast-induced fever study, 20 Wistar mice were divided into four groups of 5 mice each, acclimatized for one week, and induced with fever, then treated as given in Table 3.

Table 4: Effect of the methanol extract of *Psorospermum febrifugum* on the weight of *Plasmodium berghei* infected Wistar mice.

Samples	Doses	Initial Weight (g)	AI Weight (g)	AT Weight (g)
Extract	100 mg/kg	19.3440±2.65647	20.3460±2.66539	20.3520±2.55883
Extract	200 mg/kg	22.7920±1.97550	23.4120±2.00250	24.4240±2.04122
Extract	400 mg/kg	20.7420±2.18779	22.8780±2.46801	22.3480±2.34544
Artemetrin	5 mg/kg	20.0680±3.60466	22.5240±35.80444	23.5660±3.15997
DW	10 mL/kg	20.4740±2.67143	22.3040±2.42440	22.7340±2.02005

Results are expressed in Means ± SD. AI: After induction; AT: After treatment; DW: Distilled water.

Anti Malarial Activity Test

The *in vivo* anti-malarial activity was assessed by the 4-day chemo suppressive standard test portrayed by Peters and Robinson.[17] A total of 25 Wistar mice inoculated with *Plasmodium berghei* were arbitrarily assigned into five groups with five mice in each group and their weights were measured using weighing scale (Gallenkamp, England). *Psorospermum febrifugum* leaf extract was prepared in three doses by dissolving in distilled water. Groups 1, 2 and 3 were treated with 100, 200, and 400 mg/kg of the *Psorospermum febrifugum* respectively, which served as test groups, and group 4 were treated with a standard drug. Artemetrin (A.C Drugs LTD, Emene, Enugu State, Nigeria) 5 mg/kg which served as positive control. Group 5 which served as negative control were given 10 mL/kg of distilled water. All treatments were administered safely to mice via an oral route using oral cannula and repeated for the next 3 days.

Mice received the drug for 4 days.[18] The Parasitemia level and the rectal temperature were determined daily starting from day three post infection to the seventh day. Thin blood smears were prepared from the tail of each mouse and applied on microscopic slides (Science lab, USA) and the blood was drawn equitably over a second slide to make thin blood film and allowed to dry at room temperature. They were fixed with absolute methanolic, stained with 10% Giemsa stain for 20 min, washed with distilled water and then air dried. Each slide was then studied under a compound microscope and data obtained were recorded and analyzed to determine percent parasitemia. The parasitemia was decided by checking the least of three areas per slide with 100 RBC per field. The smears were studied and counted by a laboratory scientist. The average percent parasitemia was then determined using the following formula.[18]

$$\% \text{ Parasitemia} = \frac{\text{Number of Parasitized Red Cells}}{\text{Total number of Red cells}} \times 100$$

Antipyretic Activity Test

Twenty mice of both genders were selected and randomized into four groups (n=5). The rectal temperature of each rat was checked using the rectal thermometer. The fever was stimulated in each mouse by administering 20% Brewer's yeast suspension (20 mL/kg) subcutaneously on the back of each mouse just under the nape of the neck. Following the yeast injection, food was withheld. 18 hr later, the rectal temperature was then measured and recorded for each of the animals by rectal thermometer immediately before (-18 hr) and 18 hr after (0 hr) Brewer's yeast injection. Prior to the experiment, Paracetamol (PCM) (100 mg/kg) was used as standard drug for comparing the antipyretic action of *Psorospermum febrifugum.*

The mice in the group 1 and 2 were administered *Psorospermum febrifugum* leaf extract (200 mg/kg and 400 mg/kg) respectively, whereas group 3 and 4 received standard antipyretic agent (paracetamol) (100 mg/kg) and distilled water (5 mL/kg) respectively. The rectal temperature of each mouse was taken before inducing the fever and at 0, 30 min, 1 hr and 2 hr after the treatment.

Table 5: Effect of methanol extract of *Psorospermum febrifugum* on Parasitaemia level of *Plasmodium berghei* induced Wistar mice.

Sample	Doses	Parasitaemia (%) Day 0	Parasitaemia (%) Day 1	Parasitaemia (%) Day 2	Parasitaemia (%) Day 3
Extract	100 mg/kg	28.40±1.28841	20.00±.31623*	15.20±.374 *	6.40±.5099*
Extract	200 mg/kg	28.80±1.65529	13.40±.97980*	6.20±.800 *	3.00±.4472*
Extract	400 mg/kg	30.20±2.28910	10.60±1.77764*	4.00±.894*	1.40±.6000*
Artemetrin	5 mg/kg	28.60±1.32665	14.40±.92736*	4.60±.927*	1.20±.5831*
NC (D.water)	10 mL/kg	28.80±1.35647	31.00±1.44914	31.60±1.25	33.60±1.69

NC: Negative control (distilled water). The mean difference is significant at $p < 0.05$ level.

Table 6: Effect of methanol extract of *Psorospermum febrifugum* on temperature of *Plasmodium berghei* induced Wister mice.

Sample	Doses	Day 0 Temp	Day 1 Temp	Day 2 Temp	Day 3 Temp
Extract	100 mg/kg	39.08±.20670	37.22±.64915	37.26±.52972	37.26±.57931
Extract	200 mg/kg	39.10±.36261	36.88±.47062	37.12±.40915	37.56±.45673
Extract	400 mg/kg	38.61±.10495	36.74±.43886	36.98±.64062	36.60±.40249*
Artemetrin	5 mg/kg	38.71±.30801	36.88±.32619	38.14±.32031	36.52±.35412*
NC	10 mL/kg	38.47±.22261	38.28±.20347	38.00±.38601	38.38±.28531

NC: Negative control (distilled water).

Table 7: Anti-pyretic effect of the methanol extract of *Psorospermum febrifugum* on Mice (Yeast Induced Fever).

Sample/Doses	0 Temp	30 min Temp	1 hr Temp	2 hr Temp
Extract. 200 mg/kg	38.74±.23579	36.30±1.074	36.2000±.62690*	38.86±.36688*
Extract. 400 mg/kg	38.46±.18260	35.15±.6739*	35.2000±.19149*	34.50±.67700*
Paracetamol 100 mg/kg	39.26±.37642	36.00±.4761	36.3250±.54981*	35.90±.89536
Negative control (distilled water) 10 mL/kg	38.90±.34740	38.34±.1879	38.8600±.36688	38.00±.29496

* The mean difference is significant at $p< 0.05$; Results are expressed in mean±SD.

Statistical Analysis of Data

Statistical analysis of the data obtained was carried out with the aid of SPSS software. Comparisons were performed using one-way ANOVA followed by Duncan and post-hoc test. Data was presented as mean ± standard deviation.

RESULTS

Percentage Yield

The percentage yield of the Methanol extract of *Psorospermum febrifugum* after extraction was 20 g representing 4%. It was calculated using the following formula:

[Weight of extract (g) / Weight of plant material (g)] × 100

Weight of extract= 20 g; Weight of plant material = 500 g;

Therefore,

$$\% \text{ yield} = 20 \text{ g}/500 \text{ g} \times 100 = 4\%.$$

Effect on Weight of Plasmodium berghei infected Wistar Mice

Table 4 shows that there was no statistical significant weight difference among all the tested groups compared with the negative control group (non-treated group).

Effect on Parasithemia Level of *Plasmodium berghei* induced Wistar Mice

Table 5 shows there were significant reduction in the parasitemia level of the *Plasmodium berghei* infected mice from day 1-3 with different doses of the extract (100 mg/kg, 200 mg/kg & 400 mg/kg) and the standard drug (Artemetrin 5 mg/kg) when compared with the negative control.

Effect on Temperature of *Plasmodium berghei* Induced Wistar Mice

Table 6 shows that there was statistically significant antipyretic effect on the third day of the sample administration and treatment with the statistical significant values of 0.027 and 0.020 for 400 mg/kg of the extract and the standard anti-malarial drug (Artemetrin) 5 mg/kg respectively when compared with the negative control.

Anti-Pyretic Effect of *Psorospermum Febrifugum* on Mice

Table 7 shows a dose-dependent statistically significant reduction in body temperature at the dose of 200 mg/kg and 400 mg/kg methanol extract of *Psorospermum febrifugum* and the standard drug (Paracetamol) 100 mg/kg at 0, 30 min, 1 hr and 2 hr when compared with the negative control group.

DISCUSSION

The study investigated the effect of the methanol extract of *psorospermum febrifugum* leaves on malaria induced fever and yeast induced fever. The weight difference in *Plasmodium berghei* induced Wistar mice was compared to the control group. The results indicated that there was no significant weight difference observed among these groups. This suggests that the administration of *Psorospermum febrifugum* leaf extract, as well as the standard drug Artemetrin, did not exert a noticeable impact on the overall body weight of the infected mice.The study further investigated the parasitemia level in the mice. The findings revealed a dose-dependent, statistically significant ($p<0.05$) reduction in parasitemia with the administration of different doses of the *Psorospermum febrifugum* leaf extract and the standard anti-malaria drug, Artemetrin, when compared to the negative control group. The dose-dependent reduction in parasitemia suggests that the higher the dosage, the more pronounced the anti-malaria effect.

The study evaluated the antipyretic effect of the *Psorospermum febrifugum* leaf extract on malaria-induced fever. On the third day of the extract administration, statistically significant antipyretic effects were observed. Both the 400 mg/kg dose of the extract and the anti-malaria standard drug, Artemetrin (5 mg/kg), displayed statistically significant values of $p = 0.027$ and 0.020, respectively when compared with negative control group. The significant reduction in body temperature suggests that the extract may have a direct impact on fever reduction, which could be attributed to its phytochemical composition.[19]

In the context of yeast-induced fever, the study showed dose-dependent, statistically significant reductions in body temperature at different time points (0, 30 min, 1 hr, and 2 hr) with the administration of 200 mg/kg and 400 mg/kg methanol extract of *Psorospermum febrifugum*, as well as the standard drug

Paracetamol (100 mg/kg), when compared to the negative control group. This finding suggests that the extract has an antipyretic effect on yeast-induced fever. The dose-dependency again indicates that higher doses of the extract result in more significant reductions in body temperature.

Considering the phytochemical analysis, the presence of various bioactive compounds such as alkaloids, flavonoids, tannins, and terpenoids in the *Psorospermum febrifugum* leaf extract was identified. This supports the phytochemical analysis carried out by[20,21] on *Psorospermum febrifugum* leaf extract. These phytochemicals are known for their potential therapeutic properties and may contribute to the observed antipyretic and anti-malaria effects. Alkaloids, for instance, can have antipyretic and anti-malaria properties, while flavonoids and tannins are associated with anti-inflammatory and antioxidant effects. Therefore, the results of this study suggest that the methanol extract of *Psorospermum febrifugum* leaves possesses promising anti-malaria and antipyretic properties.

LIMITATIONS OF THE STUDY

The dose used for this study might not be applicable for use in human treatment. Also, there was no significant difference in the weight of the mice which could be attributed to the short duration of study.

CONCLUSION

The findings from this study suggest that the extract has potential as a treatment for malaria-induced fever due to its significant impact on parasitaemia levels. It also demonstrates antipyretic properties in yeast-induced fever, indicating its potential as an antipyretic agent for various infections. These findings underscore the importance of exploring natural remedies with fewer side effects to improve fever management.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the effort of the laboratory technologists that offered their technical assistance in the course of the research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PGE2: Prostaglandins E2; **NSAIDS:** Non-Steroidal Anti-Inflammatory Drugs; **COX:** Cyclooxygenate; **PCM:** Paracetamol; **AI:** After Induction; **AT:** After Treatment; **DW:** Distilled Water; **SD:** Standard Deviation; **NC:** Negative Control.

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Cite this article: Richards NN, Augustine NO, Wike NY, Casmir CU, Godwin CU, Chidiogo NU. Ameliorating Potentials of Methanol Extract of *Psorospemum fabrifugum* Leaves on Malaria and Yeast-Induced Fever in Wistar Mice . Int J Clin Exp Physiol. 2024;11(2):64-9.