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Antimalarial and Antipyretic Activities of Cornsilk Extract and Fractions of Zea Mays

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ABSTRACT

To evaluate the antiplasmodial and antipyretic activities of *Z. mays* L. (Family- Poacae) cornsilk extract and fractions, to ascertain the folkloric claim of its antimalarial and antipyretic activities. The cornsilk extract (170–510 mg/kg) and fractions (hexane, dichloromethane, ethyl acetate and methanol; 340 mg/kg) were investigated for suppressive, prophylactic, and curative antiplasmodial activities against chloroquine-sensitive *Plasmodium berghei* infections in Swiss albino mice and for antipyretic activity against D-amphetamine, 2,4-dinitrophenol and yeast-induced pyrexia. chloroquine (5 mg/kg) and pyrimethamine (1.2 mg/kg) were used as positive controls for antiplasmodial models and Acetyl salicylic acid, ASA,(100 mg/kg) was used as standard for antipyretic models. Thin films made from tail blood of each mouse were used to assess the level of parasitaemia of the mice. The extract/fractions progressively reduced parasitaemia induced by chloroquine-sensitive *P. berghei* infection in prophylactic (46.16–86.80%), suppressive (48.59–71.95%), and curative (22.4–82.34%) models in mice. These reductions were statistically significant (p<0.01–0.001). They also improved significantly (p<0.01–0.001) the mean survival time (MST) from 18.91 to 23.66 d in suppressive, 17.33 to 28.00 in prophylactic and 20.25 to 26.75 d in curative models relative to control (13.75 d). The activities of extract/fractions were comparable to that of the standard drugs used (pyrimethamine) in prophylactic model only. The extract exerted prominent inhibition of pyrexia on amphetamine, dinitrophenol and yeast-induced pyrexia (5 h). Inhibition was significant (p<0.05–0.001) from 2 to 5 h post-administration of extract and in a dose-dependent fashion. The plant may possess antiplasmodial and antipyretic effects which may in part be mediated through the chemical constituents of the plant.

Keywords: *Zea mays*, cornsilk, antimalarial, antipyretic, antiplasmodial

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INTRODUCTION

Zea mays L.(Poacae) also known as maize or corn, is an annual grass plant cultivated through Nigeria primarily for human consumption and as animal feed. The plant is tall with a fibrous root system and has long narrow leaves on opposite side of the stem and bears ears that are enclosed in modified leaves known as husks.[1] Besides its nutritive values, maize grains, leaves, cornsilks, stalk, and inflorescence are also used in ethnomedicine for the treatment of several ailments. The corn silk is used as an antidiabetic or diuretic, and decoction of the silk is consumed for the treatment of urinary troubles and gallstones.[2] Corn silk was used in many parts of the world for the treatment of cystitis, gout, kidney stones, malaria, prostate hypertrophy, nephritis and heart disorders.[3]

Secondary metabolites like flavonoids, saponins, alkaloids, tannins, chlorogenic acid, allantoin, and phytosterols as well as flavonoids such as maysin, apigmaysin, 3-methoxymaysine and ax-4-OH-maysin have also been identified from corn silk.[4] Biological activities include; antioxidative stress,[5,6] a and kaliuresis effect,[7] hyperglycemic effect,[8] nephroprotective activity,[9] anti- fatigue,[10] anti-depressant activity,[11] anti-hyperlipidemic activity,[12] anti-diabetic effects.[13,14] Anti-inflammatory activity,[15] Antioxidant,[16,17,18,19] anticancer,[20] α- amylase inhibitory,[21] antidiabetic and hypolipidemic activities.[22,23] We report in this study the antimalarial and antipyretic activities of the cornsilk extract and fractions of *Zea mays*.

MATERIALS AND METHODS

Collection and identification of plant material

The cornsilk extract of *Zea mays* L. (Family-Poacae) were collected from farms in the Uyo area of Akwa Ibom State, Nigeria in May, 2018. The plant was identified by a taxonomist in the Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria. A voucher specimen of the plant (FPH, 614) was deposited in the Faculty of Pharmacy's herbarium at the University of Uyo.

Extraction

The cornsilk were washed and shade dried for two weeks. The dried cornsilk were pulverized

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to powder using electric grinder. The powdered cornsilk were divided into two parts (1.5 kg each). One part was macerated in ethanol for 72 hours, while the remaining part was successively and gradiently macerated for 72 hours in each of, n-hexane, dichloromethane, ethyl acetate and n-butanol respectively, which is along their polarity to give the corresponding gradient extract for each solvent. The liquid filtrate of each extract and fraction was concentrated and evaporated to dryness in *vacuo* 40°C using a rotary evaporator. The extract and fraction were stored in a refrigerator at -4°C, until used for the proposed experiments.

Microorganism (parasite)

Chloroquine-sensitive strain of *Plasmodium berghei berghei* were obtained from the National Institute of Medical Research (NIMER), Yaba Lagos, Nigeria and maintained by subpassage in mice.

Parasite inoculation

Each mice used in the experiment were inoculated intraperitoneally with 0.2 mL of infected blood containing about 1 x 10^7 *P. berghei berghei* parasitized erythrocytes. The inoculum consisted of 5 x 10^7 *P.berghei berghei* erythrocytes per milliliter. This was prepared by determining both the percentage parasitemia and the erythrocytes count of the donor mouse and diluting the blood with isotonic saline in proportions indicated by both determinations.[24]

Experimental animals

Male and female swiss albino rats (125-150 g) and mice, (18-25 g), were obtained from the University of Uyo's animal house. They were kept in standard cages and acclimatized for a period of 10 days before use in the experiments. The mice were fed on standard pelleted diet and water *ad libitum*. All animals were kept at room temperature in cross ventilated rooms. The care and use of animals were conducted in accordance with the National Institute of Health Guide for the Care and Use of laboratory Animals (NIH Publication, 1996). Approval for the study was obtained from the University of Uyo's Animal Ethics Committee.

Determination of median lethal dose (LD_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice by intraperitoneal (i.p) route using the method of Lorke[25] as reported by Okokon et al.[26] This involved intraperitoneal administration of different doses of the extract (100– 1000 mg/kg) to groups of three mice each. The animals were observed for manifestation of physical signs of toxicity such as writhing, decreased motor activity, decreased body/ limb tone, and decreased respiration and death. The number of deaths in each group within 24 h was recorded. The LD_{50} value was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b). $LD_{50} = \sqrt{ab}$

Drug administration

The extract, fractions, chloroquine and pyrimethamine that were used in the study were administered orally with the aid of a stainless metallic feeding cannula.

Evaluation of the in vivo antimalarial activities of cornsilk extract and fractions of *Zea mays*:

Evaluation of suppressive activities of the cornsilk extract and fractions of Zea mays (4-day test)

This test was used to evaluate the schizontocidal activity of the crude extract and fractions as well as chloroquine against early *P. berghei berghei* infection in mice. This was done using the method of Knight and Peters[27] as described by Okokon et al.[28] Fifty-four mice were randomly divided into nine groups of six mice each. On the first day (D_0), the fifty-four mice were infected with the parasite and randomly divided into various groups. These were administered the crude extract, fractions, chloroquine and distilled water. The mice in group 1-3 were given 170 mg/kg, 340 mg/kg and 510 mg/kg of crude extract respectively, while groups 4, 5, 6, 7 were administered 340 mg/kg of n-hexane, dichloromethane, ethyl acetate, and n-butanol fractions respectively, group 8 was given 5 mg/kg of chloroquine (positive control) and group 9 given 10 mL/kg of distilled water (negative control) for four consecutive days (D_0-D_3) between 8am to 9am. On the fifth day (D_4), thin films were made from the tail blood. The films were stained with Giemsa stain to reveal parasitized erythrocytes out of 500 in a random field of the microscope. The average suppression of parasitemia was calculated as follows: (average % parasitemia positive control – average % parasitemia negative control) / (average % parasitemia negative control).

The mean survival time of the mice in each treatment group was determined over a period of 29 days (D_0-D_{28}), as follows:

(No. of days survived) / (total No. of days (29) × 100

Evaluation of prophylactic or repository activities of the cornsilk extract and fractions of Zea mays

This was evaluated using the method of Peters[29] as described by Imoh *et al.,*[30] The mice were randomly divided into nine groups of six mice

per group. Groups 1-3 were given 170, 340, and 510 mg/kg of crude extract respectively, groups 4, 5, 6, and 7 were given 340 mg/kg of n-hexane, ethyl acetate, dichloromethane, and n-butanol fractions respectively, group 8 was given 1.2 mg/kg of pyrimethamine (positive control) and group 9 given 10 mL/kg of distilled water (negative control). Administration of the extract and fractions continued for three consecutive days (D_0-D_2). On the fourth day (D_3), the mice were inoculated with *P. berghei berghei*. The parasitemia level was assessed by blood smears 72 hours later. The mean survival time of the animals were calculated over a period of 29 days.

Evaluation of the curative activities of the cornsilk extract and fractions of Zea mays

This test was used to evaluate the schizontocidal activity of the extract, fractions and chloroquine in established plasmodial infection. This was conducted according to the method of Ryley and Peters[31] as described by Okokon et al.[32] *P. berghei berghei* was injected intraperitoneally into another fifty four mice on the first day *(D_0)*. Seventy two hours later (D_3), the mice were divided into nine groups of six mice per group. Groups 1-3 were given different doses of extract, 170, 340, and 510 mg/kg respectively, groups 4-7 were given 340 mg/kg of n-hexane, ethyl acetate, dichloromethane, and n-butanol fractions respectively, group 8 was given 5 mg/kg chloroquine (positive control) and group 9 was given 10 mL/kg distilled water (negative control). The crude extract, fractions and chloroquine were administered once daily for 5 days. Giemsa stained thin smears were prepared from tail blood samples collected on each day of treatment to monitor the parasitemia level. The mean survival time (MST) of the mice in each group was determined over a period of 29 days (D_0-D_{28}).

Evaluation of antipyretic activity

Evaluation of antipyretic activity of the cornsilk extract on D-amphetamine-induced pyrexia

Adult albino rats (130 – 150 g) of both sexes fasted for 24 hours but allowed water *ad libitum* were used for the experiment. They were randomized into groups of 6 rats each. Amphetamine (5 mg/kg, i.p) was administered to the animals after obtaining basal temperatures. Hyperthermia developed 0.5 h following amphetamine administration. Different doses of extract (170, 340 and 510 mg/kg i.p), aspirin (100 mg/kg) and distilled water (10 mL/kg, orally) were administered respectively to the treatment and control groups of animals. Rectal temperatures of the animals were obtained at an hour interval for 5 h.[33,34]

Effect of cornsilk extract on 2,4-Dinitrophenol (DNP)-induced pyrexia

Adult albino rats of both sexes fasted for 24 h but allowed water *ad libitum* were used for the experiment. They were randomized into groups of six rats each. DNP (10 mg/kg, i.p.) was administered to the rats after obtaining the basal rectal temperatures. Hyperthermia developed within 30 min of DNP administration. Different doses of extract (170, 340, and 510 mg/kg i.p.), aspirin (100 mg/kg), and distilled water (10 mL/kg, orally) were administered to the treatment and control groups of animals. Rectal temperatures of the animals were obtained at 1 h intervals for 5 h.[34]

Effect of cornsilk extract on yeast-induced pyrexia

Adult albino rats (125 – 130 g) of both sexes fasted for 24 hours but allowed water *ad libitum* were used for the experiment. They were randomized into groups of 6 rats each. At zero hour, the basal temperature of the rats was taken using digital clinical thermometer. Thereafter, each animal was administered subcutaneously with 20% W/V aqueous suspension of yeast at a volume of 10 mL/kg.[34] At suitable intervals beginning one hour after yeast injection, rectal temperature of animals were taken, animals with increase of 1°C were selected and grouped for the study. The extract understudy was administered i.p. after the pyrogen at doses of 170, 340 and 510 mg/kg to respective groups of rats. The control group received distilled water (10 mL/kg) and the reference group administered with ASA (100 mg/kg) both orally. The rectal temperature of the groups was taken at 1h interval for 5h.

Statistical analysis

Data obtained from this work were analyzed statistically using ANOVA (One- way) followed by a post test (Turkey-Kramer multiple comparison test). Differences between means were considered significant at 5% level of significance, that is $p \leq 0.05$.

RESULTS

Determination of median lethal dose (LD_{50})

The median lethal dose (LD_{50}) value was calculated to be 1732.05 mg/kg. The physical signs of toxicity included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping, convulsion and coma which was followed by death.

Table 1 **Suppressive activities of cornsilk extract and fractions during early *Plasmodium berghei berghei* infection in mice**

Treatment	Dose (mg/kg)	Parasitaemia	Chemosuppression (%)	MST
Control	-	35.66 ±1.20	-	13.00 ±0.66
extract	170	15.0±5.00[a]	57.93	18.91±0.35
	340	12.0±4.00[a]	66.34	22.06±1.33
	510	10.0±3.05[b]	71.95	23.66±0.68
n-hexane	340	18.33 ±1.20[a]	48.59	14.50 ±1.52
Dichloromethane	340	14.00± 1.20[b]	60.74	17.66 ±1.33[a]
Ethyl acetate	340	12.66± 3.93[b]	64.49	21.0 ±2.64[a]
Methanol	340	10.0 ± 5.00[b]	71.95	22.66±1.33[b]
Chloroquine	5	2.13 ± 2.02[c]	94.02	30.00 ±0.00[c]

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6

Table 2 **Prophylactic activities of cornsilk extract and fractions**

Treatment	Dose (mg/kg)	Parasitaemia	Chemosuppression (%)	MST
Control	-	17.66 ±1.45	-	13.0 ±0.57
Extract	170	9.33±1.45[a]	46.16	23.60±3.28[a]
	340	7.60±1.20[b]	56.96	24.60±2.18[a]
	510	7.0±2.30[b]	60.36	25.60±0.57
n-hexane	340	4.0 ±1.52[c]	77.34	28.00 ±1.52[b]
Dichloromethane	340	3.0± 1.52[c]	83.01	17.33 ±0.33
Ethyl acetate	340	3.0± 0.57[c]	83.01	24.60 ±2.90[a]
Methanol	340	2.33± 1.33[c]	86.80	26.66 ±1.20[b]
Pyrimethamine	1.2	2.66 ± 1.33[c]	84.93	25.04 ±0.29

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6

Table 3 **Mean survival time of mice treated with cornsilk extract and fractions during established *Plasmodium berghei berghei* infection**

Treatment	Dose (mg/kg)	Mean Survival Time (Days)
Control	-	13.75 ±1.43
Extract	170	20.50±1.55[a]
	340	21.25±1.03[a]
	510	22.50±0.50[b]
n-hexane	340	24.25 ±1.20[a]
Dichloromethane	340	20.25±1.37[b]
Ethyl acetate	340	26.75± 1.97[c]
Methanol	340	22.75 ± 0.75[b]
Chloroquine	5	30.00± 0.00[c]

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6.

Suppressive activities of ethanol cornsilk extract and fractions of *Z. mays*

The extract and its fractions exerted dose-dependent reductions in parasitaemia of the treated mice in various groups. These reductions were statistically significant relative to the control (p<0.001). The methanol fraction demonstrated the highest suppressive activity (71.95%) and m.s.t value of 22.66 d although less than that of the standard, Chloroquine, 5 mg/kg (94.02%) (Table 1).

Table 4 **Antipyretic effect of cornsilk extract on D-amphetamine-induced pyrexia**

Treatment/ Dose(mg/kg)	TIME INTERVALS (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	35.57±0.46	36.97±0.44	36.20±0.61	36.65±0.72	36.93±0.74	37.15±0.71	37.25±0.70	37.20±0.70
Extract 170	34.67±0.08	35.82±0.52	35.77±0.32	35.87±0.25[a]	35.22±0.44[a]	35.12±0.22[b]	34.52±0.19[a]	34.77±0.28[b]
Extract 340	35.30±0.33	36.42±0.28	36.02±0.49	36.25±0.50	35.10±0.33[a]	34.87±0.30[a]	33.80±0.30[b]	33.90±0.36[c]
Extract 510	34.65±0.24	35.87±0.38	35.60±0.45	35.62±0.10	34.82±0.24[a]	34.60±0.38[b]	33.97±0.31[b]	33.67±0.22[c]
ASA 100	34.77±0.14	35.72±0.47	34.87±0.18	34.72±0.20	34.75±0.18[a]	34.17±0.19[c]	33.95±0.02[c]	33.65±0.06[c]

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6.

Table 5 **Antipyretic effect of cornsilk extract on Dinitrophenol-induced pyrexia**

Treatment/ Dose(mg/kg)	TIME INTERVALS (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	34.92±0.34	36.55±0.46	36.07±0.49	36.55±0.67	36.27±0.51	35.57±0.23	36.07±0.41	36.17±0.41
Extract 170	34.40±0.14	36.72±0.34	36.90±0.81	36.70±0.58	36.20±0.56	35.37±0.42	33.85±0.25[c]	33.32±0.45[b]
Extract 340	34.95±0.13	35.97±0.54	36.00±0.56	35.75±0.45	34.93±0.33	34.00±0.35[b]	33.76±0.34[c]	33.23±0.50[b]
Extract 510	35.00±0.20	36.27±0.22	35.97±0.41	36.72±0.56	35.32±0.49	35.32±0.28	33.82±0.11[c]	33.07±0.43[c]
ASA 100	34.52±0.13	36.07±0.37	35.82±0.35	35.50±0.12	34.97±0.18	34.57±0.07	33.30±0.17[c]	32.80±0.20[c]

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6.

Table 6 **Antipyretic effect of cornsilk extract on yeast-induced pyrexia**

Treatment/ Dose(mg/kg)	TIME INTERVALS (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	35.95±0.29	37.17±0.31	37.87±0.74	37.82±0.10	37.75±0.68	37.70±0.37	37.77±0.29	37.50±0.23
Extract 170	35.60±0.60	37.00±0.37	36.95±0.38	36.95±0.40	36.25±0.42	36.02±0.42[a]	36.27±0.39[a]	36.30±0.54
Extract 340	35.75±0.51	37.10±0.55	36.20±0.73	36.37±0.17	36.32±0.39	36.02±0.59[a]	36.37±0.45[a]	36.10±0.61[a]
Extract 510	35.12±0.55	37.22±0.40	36.10±0.14	36.40±0.23	36.60±0.35	36.00±0.47[b]	36.00±0.45[b]	35.32±0.34[b]
ASA 100	35.20±0.31	37.12±0.49	36.67±0.51	36.22±0.21	36.40±0.60	36.17±0.31[b]	35.35±0.49[c]	35.30±0.27[c]

Values are expressed as mean ± SEM. Significance relative to control. [a]p<0.05; bp<0.01; cp<0.001. n = 6.

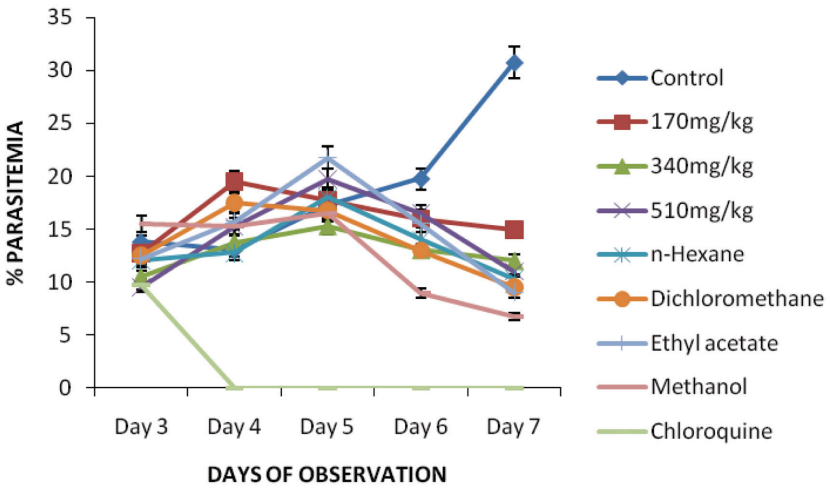

Figure 1 Curative activities of Cornsilk extract and fractions during established *Plasmodium berghei* infection in mice.

Prophylactic/repository activities of ethanol cornsilk extract and fractions of *Z. mays*

The ethanol cornsilk extract showed dose-dependent reductions of parasitaemia in the extract-treated groups. These reductions were statistically significant relative to the control (p<0.01– 0.001). The methanol fraction showed the most prominent prophylactic activity (86.80%) and m.s.t value of 26.66 d which was significant (p<0.001) when compared with control but was comparable to that exhibited by the standard drug, pyrimethamine, 1.2 mg/kg (Table 2).

Antiplasmodial effect of ethanol cornsilk extract and fractions of *Z. mays* on established infection

There were progressive dose-dependent reductions of parasitaemia in all the extract/fraction-treated

groups relative to control. These reductions were statistically significant relative to the control (p<0.001; Figure 1). The methanol fraction had the highest activity with chemosuppressive effect of 84.93%, this was lower compared with that of the standard, chloroquine,100%.

The cornsilk extract and fractions demonstrated significant (p<0.05-0.001) protective potentials on the mice as was seen in the mean survival time of the animals. The groups treated with ethyl acetate fraction had a longer mean survival time, 26.75 ± 1.97 d followed by those of methanol fraction treated mice, 22.75 ± 0.75 d. These were less than that of the standard drug, chloroquine (30.00 ± 0.00 d; Table 3).

Effect of ethanol cornsilk extract on D-amphetamine induced pyrexia

The antipyretic effect of the extract on amphetamine- induced pyrexia is shown in Table 4. Cornsilk extract (170-510 mg/kg), in the presence of the pyrogen, caused significant (p<0.05 – 0.001) reductions in the temperatures of the extract-treated rats when compared with the control. These effects were pronounced at the 4 h and 5 h post treatment with the extract. The antipyretic effects of the extract were comparable with that of the standard drug, ASA,100 mg/kg (Table 4).

Effect of ethanol cornsilk extract on 2,4-dinitronitrophenol (DNP)-induced pyrexia in rats

The cornsilk extract (170-510 mg/kg) demonstrated significant (p<0.05–0.001) dose-dependent lowering of temperature in DNP-induced pyretic rats. The antipyretic effect was, however, pronounced (p<0.05–0.001) at the 5 h in all the extract-treated groups. The effect of the highest dose (510 mg/kg) was comparable to that of the standard drug, ASA, 100 mg/kg (Table 5).

Effect of cornsilk extract of on yeast-induced pyrexia in rats

Ethanol cornsilk extract of *Z. mays* (170-510 mg/kg) caused significant (p>0.05-0.001) reduction of rat body temperature of rats elevated by the administration of yeast. The effect of the extract was pronounced at the 5 h. The antipyretic effects of the extract was not comparable to that of the standard, ASA,100 mg/kg (Table 6).

DISCUSSION

The cornsilk tea is used traditionally by the Ibibios of Southern Nigeria and other parts of the world as a malarial remedy and febrifuge.[35] This work was designed to evaluate the antimalarial and antipyretic activities of the cornsilk extract and fractions of *Zea mays*. The median lethal dose (LD_{50}) value was calculated to be 1732.05 mg/kg which shows that the cornsilk extract is slightly toxic.[36] The antimalarial activity of the cornsilk extract and fractions was evaluated against rodent malaria parasite, *Plasmodium berghei berghei* infection in mice using standard in vivo models. The extract and fractions were found to significantly reduced parasitemia in suppressive, prophylactic and curative models in a dose-dependent fashion with the methanol fraction exerting the highest antimalarial activity. The extract and fractions also prolonged the MST of the mice considerably suggesting that they were potentially able to offer significant degree of protection to the mice. This activity could have resulted from plasmodicidal or plasmodistatic activity of the extract and fractions.

The observation that the extract and fractions showed considerable *in vivo* activity suggest also the involvement of antioxidant activity which maybe due to the activities of phytochemical compounds present in the cornsilk extract and fractions.

Besides, the cornsilk fractions have been observed in this study to exhibit pronounced antioxidant activity[16,17,18] and the cornsilk extract has been known to be rich in flavonoids[15] which are known for significant antioxidant activity. Antioxidant potentials of some plant and natural products especially flavonoids have been found to promote schizonticidal activity by modulating the cellular signalling pathway[37] and this has been suggested to be responsible for antiplasmodial activity of compounds such as quercetin[38] as elevated free radicals levels which are common features of malaria disease are implicated in severe malaria complications. This also could be one of the modes of action of this extract as it contains phenolics and flavonoids with antioxidant activity. Moreso, flavones glycosides with antioxidative activity have been reported in cornsilk extract,[39] which further confirms the antioxidative potentials. These may in part contribute to the strong antimalarial and antioxidant activities of the cornsilk extract.

Other mechanisms of antiplasmodial activity have been proposed for flavonoids besides antioxidant activity. Flavonoids are known to exert antiplasmodial activity by chelating with nucleic acid base pairing of the parasite,[40] thereby producing plasmocidal effect. Other modes of action include modulation of host immunity to tackle disease and inhibition of plasmodial enoyl-ACP reductase (FAB I enzyme)—a key regulator of type II fatty synthases (FAS-II) in *P. falciparum*.[41,42] Flavonoids may also bind the parasite's serinethreonine kinase with high affinity and affect its development.[43] These compounds (flavonoids) present in this plant extract and in particular the methanol fraction may

in part have contributed to the plasmocidal activity of this extract/fraction and therefore explained the mechanism of antiplasmodial effect of the extract.

On antipyretic activity, the extract inhibited significantly amphetamine, dinitrophenol and yeast-induced pyrexia. The cornsilk extract (170-510 mg/kg) showed considerable dose-dependent reduction in the elevated temperatures of the extract-treated rats in the three models (amphetamine, DNP and yeast-induced pyrexia) evaluated. The antipyretic effect was sustained throughout the duration of the work with the effect being quite comparable to ASA (100 mg/kg). Pyrexia (fever) is the body's response to tissue damage, inflammation, malignancy or graft rejection that results in the formation of large amounts of cytokines, interleukin, interferon and TNF-α, and increasing PGE2 to trigger the hypothalamus and then cause fever.

In the brain, amphetamine causes the release of biogenic amines that are stored in nerve terminals leading to increases in the cAMP level, resulting in prostaglandins synthesis from arachidonic acids in neurons through hydrolysis of phospholipids. This results in hyperthermia.[44] DNP causes hyperthermia by uncoupling oxidative phosphorylation resulting in calcium release from mitochondrial stores and preventing calcium reuptake. This leads to increased intracellular calcium level, muscle contraction and hyperthermia.[45] The extract through its components may have caused stimulation of the sarcoplasmic reticulum Ca2+-ATPase thus promoting calcium reuptake into the sarcoplasmic reticulum, muscle contraction and hypothermia.[46] Yeast induced pyrexia which is pathogenic and caused by PGE2 production, which then resets the thermoregulatory center in the hypothalamus to a higher level.[47]

Antipyretics lower elevated body temperature by suppressing cyclooxygenase actions and decreasing PGE2 levels in the hypothalamus.[48] Temperature regulation involves a delicate balance between heat production and loss, and the hypothalamic thermostat.[48] Cyclooxygenase (COX2) activity leads to the synthesis of PGE2 which is an imperative mediator of fever within the hypothalamus and most NSAIDs antipyretic activity results from suppression of prostaglandin synthetase in the hypothalamus. The resultant antipyretic effects could be due to reduced PGE2 levels in the hypothalamus acting on COX2, or through increased production of substances such as vasopressin and arginine that reduce temperature.[49] Another possible antipyretic mechanism of the extract is the mediation of the vasodilation of superficial blood vessels which causes improved heat loss from resetting of hypothalamic thermostat.[49] The extract may have caused hypothermia by acting through any of these mechanisms.

Flavonoids such as baicalin exhibit antipyretic activity by inhibiting tumour necrosis factor,[47] and related compounds also suppress arachidonic acid peroxidation, resulting in decreased prostaglandin levels and fever reduction.[50] The phytochemical constituents of this extract which include flavonoids and other phenolic compounds[4] may be responsible for its antipyretic effect through any or all mechanisms described here.

The results of this study demonstrated that cornsilk extract of *Zea mays* possibly possesses considerable antiplasmodial and antipyretic properties. These confirm its use to treat malaria and fever in folkloric medicine. Therefore, it would be interesting if the active principle is isolated, identified, and characterized.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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REFERENCES

1. Simmonds NW. Evolution of Crop Plants. Longman. London. 1979; pp. 128-129.
2. Foster S, Duke JA. Field Guide 10 Medical Plants: Eastern and Central North America. Houghton MifAin, Boston 1990.
3. Hashim P. Corn silk (*Stigma maydis*) in healthcare: A phytochemical and pharmacological review. *Molecules* 2012; 17: 9697-9715.
4. El-Ghorab A, El-Massry KF and Shibamoto T. Chemical composition of the volatile extract and antioxidant activities of the volatile and nonvolatile extracts of Egyptian corn silk (*Zea mays* L.). *J Agr Food Chem* 2007; 55: 9124–9127.
5. Bai H, Hai C, Xi M, Liang X, Liu R. Protective Effect of Maize Silks (*Maydis stigma*) ethanol extract on Radiation-Induced Oxidative Stress in Mice. *Plant Foods for Human Nutr* 2010; 65: 271–276.
6. Hu QI, Deng ZI. Protective effects of flavonoids from corn silk on oxidative stress induced by exhaustive exercise in mice. *Afr J Biotech* 2011; 10: 3163–3167.
7. Velazquez DVO, Xavier HS, Batista JEM and Castro-Chaves CD. *Zea mays* L. extracts modify glomerular function and potassium urinary excretion in conscious rats. *Phytomedicine* 2005; 12: 363–369.
8. Guo J, Liu T, Han L and Liu Y. The effects of corn silk on glycaemic metabolism. *Nutr Metab* 2009; 6: 47.
9. Sepehri G, Derakhshanfar A, Zade FY. Protective effects of corn silk extract administration on gentamicin-induced nephrotoxicity in rat. *Comp Clin Pathol* 2011; 20: 89–94.
10. Hu QL, Zhang LJ, Li YN, Ding YJ, Li FL. Purification and anti-fatigue activity of flavonoids from corn silk. *Int J Phys Sci* 2010; 5: 321–326.
11. Ebrahimzadeh MA, Mahmoudi M, Ahangar N, Ehteshami S, Ansaroudi F. Antidepressant activity of corn silk. *Pharmacologyonline,* 2009; 3: 647–652.

12. Kaup SR, Arunkumar N, Bernhardt LK, Vasari RG, Shetty SS. Antihyperlipedemic activity of Cynodondactylon extract in high-cholesterol diet fed Wistar rats, *Genomic Medicine, Biomarkers, and Health Sci* 2011; 3: 98–102.
13. Zhao W, Yin Y, Yu Z, Liu J and Chen F. Comparison of anti-diabetic effects of polysaccharides from corn silk on normal and hyperglycemia rats. *International Journal of Biological Macromolecules,* 2012; 50: 1133–1137.
14. Sani UM. Anti-diabetic potential of methanol extract of cooked corn silk (*Stigma maydis)* on alloxan-induced diabetes in albino mice *The Pharm Chem J*. 2016; 3(4):68-72.
15. Wang GQ, Xu T, Bu XM, Liu BY. Anti-inflammation effects of corn silk in a rat model of carrageenin-induced pleurisy. *Inflammation* 2011; 35: 822–827.
16. Alam EA. Evaluation of antioxidant and antibacterial activities of Egyptian *Maydis stigma* (*Zea mays* hairs) rich in some bioactive constituents. *J Amer Sci* 2011; 7: 726–729.
17. Liu J, Wang C, Wang Z, Zhang C, Lu S.. The antioxidant and free-radical scavenging activities of extract and fractions from corn silk (*Zea mays* L.) and related flavone glycosides. *Food Chem* 2011; 126: 261–269.
18. Kan A, Orhan I, Coksari G, Sener B. In-vitro neuroprotective properties of the *Maydis stigma* extracts from four corn varieties. *Int J Food Sci Nutr* 2011; 63: 1–4.
19. Dong J, Cai L, Zhu X, Huang X, Yin T, Fang H, Ding Z. (2014). Antioxidant activities and phenolic compounds of cornhusk, corncob and *Stigma maydis. J Brazilian Chem Soc*. 2014; 25: 1956-1964.
20. Tian J, Chen H, Chen S, Xing L and Wang Y. Comparative studies on the constituents, antioxidant and anticancer activities of extracts from different varieties of corn silk. *Food and Function* 2013; 4(10): 1526-1534.
21. Chen S, Chen H, Tian J. Chemical modification, antioxidant and alpha amylase inhibitory activities of corn silk polysaccharides. *Carbohydrate Polymers,* 2013; 98(1): 428-437.
22. Ghada M, Eltohami MS, Nazik MM, Rawan BA, Rania EH, Azhari HN, Adurahman HN, Jessinta S. Hypoglycemic and hypolipidemic effect of methanol extract of corn silk (*Zea mays*)in Streptozotocin-induced Diabetic Rats. *Int J Eng Res Tech* 2013; 2 (10): 668 -672.
23. Zhang Y, Wu L, Ma Z, Cheng J, Liu J. Antidiabetic, antioxidant and antihyperlipidemic activities of flavonoids from corn silk on STZ-induced diabetic mice. *Molecules* 2016; 21(1):1-11.
24. Odetola A, Basir O. Evaluation of Antimalarial Properties of Some Nigerian Medicinal Plants. In Sofowora A, ed. Proceedings of African Bioscience Network, Federal Ministry of Science and Technology, Nigerian Society of Phrmacology and Drug Research and Production unit, University of Ife organized Workshop, Ife. 1980; pp. 275 – 283.
25. Lorke D. A new approach to practical acute toxicity testing. *Arch Toxicol* 1983; 54: 275-287.
26. Okokon JE, Nelson E, Sunday M. Antidepressant activity of ethanol husk extract of *Zea mays*. *Adv Herbal Med* 2016; 2(4):22-28.
27. Knight DJ, Peters W. The antimalarial action of *N*-benzylox- ydihydrotriazines and the studies on its mode of action. *Ann Trop Med Parasitol* 1980; 74:393–404.
28. Okokon JE, Mohanakrishnan D, Dinkar Sahal, Okokon PJ. Antimalarial and antiplasmodial activities of leaf extract and fractions of *Zea mays*. *J Herbs, Spices and Medicinal Plants*. 2017; 23(4): 334 – 346.
29. Peters W. Drug resistance in *Plasmodium berghei*. *Exp. Parasitology*.1985; 17:80-89.
30. Imoh SJ, Ettebong EO., Okokon JE. In vivo antiplasmodial activities of ethanolic leaf extract and fractions of *Helleria latifolia*. *J Med Plants Stud* 2017; 5(4): 118 – 122.
31. Ryley JF, Peters W. The antimalarial activity of some quinolone esters. *Ann Trop Med Parasitol* 1970; 84:209–222.
32. Okokon JE, Mohanakrishnan D, Sahal D, Okokon PJ. Antimalarial and antiplasmodial activities of leaf extract and fractions of *Zea mays*. *Journal of Herbs, Spices and Medicinal Plants*. 2017; 23(4): 334 – 346.
33. Blackhouse N, Delporte C, Negrete R, Munoz O, Ruiz R. Anti inflammatory and antipyretic activities of *Maytenus boaria*. *Int J Pharmacog* 1994; 32: 239-244.
34. Udobang J, Okokon JE, Bassey AL. Antimalarial and antipyretic activities of ethanol extract and fractions of *Setaria megaphylla* root. *J Coastal Life Med*. 2017; 5(7): 309 - 316.
35. Hashim P. Corn silk (*Stigma maydis*) in healthcare: A phytochemical and pharmacological review. *Molecules* 2012; 17: 9697-9715.
36. Homburger F. *In vivo* testing in the study of toxicity and safety evaluation. In: Marquis J, ed. *A Guide to General Toxicology*. 2nd ed. New York: Karger, 1989, 268–93.
37. Al-Adhroey AH, Nor ZM, Al-Mekhlafi HM, Amran, A.A., Mahmud, R. Antimalarial activity of Methanolic leaf extract of *Piper beetle* L. *Molecules* 2011;16: 107-118.
38. Ganesh D, Fuehrer H, Starzengrüber P, Swoboda P, Khan WA. Antiplasmodial activity of flavonol quercetin and its analogues in *Plasmodium falciparum*: Evidence from clinical isolates in Bangladesh and standardized parasite clones. *Parasitol Res* 2012; 110:2289–2295.
39. Ren S. Antioxidative activity of five flavones glycosides from corn silk (*Stigma maydis*). *Czech J Food Sci* 2013; 31(2): 148-155.
40. Liu KC, Yang SL, Roberts MF, Elford BC, Phillipson JD. Antimalarial activity of *Artemisia annua* flavonoids from whole plants and cell cultures. *Plants Cell* 1992; 11(12): 637-40.
41. Kirmizibekmez H, Calis I, Perozzo R, Brun R, Donmez A, Linden, A. Inhibiting activities of the secondary metabolites of *Phlomis brunneogaleata* against parasitic protozoa and plasmodial enoyl-ACP reductase, a crucial enzyme in fatty acid biosynthesis. *Planta Med*. 2004; 70:711.
42. Teffo LS, Aderogba M, Eloff J. Antibacterial and antioxidant activities of four Kaempferol methyl ethers isolated from *Dodonaea viscosa* Jacq. var. *angustifolia* leaf extracts. *South Afr J Bot* 2010; 76(1):25–29.
43. Ferreira JF, Luthria DL, Sasaki T, Heyerick A. Flavonoids from *Artemisia annua* L. as antioxidants and their potential synergism with artemisinin against malaria and cancer. *Molecules* 2010; 15(5):3135–3170.
44. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: *Gilman and Goodman's The Pharmacological Basis of therapeutics*. 11th ed. McGraw, New York, 2006.
45. Kumar S, Baker K, Seger D. Dinitrophenol-induced hyperthermia resolving with dantrolene administration. Abstract of North American Congress of Clinical Toxicology. *Clin Toxicol* 2002; 40:599–673.
46. Autry JM, Thomas DD, Espinoza-Fonseca LM. Sarcolipin promotes uncoupling of the SERCA Ca2+ pump by inducing a structural rearrangement in the energy-transduction domain. *Biochem* 2016; 55(44): 6083-6086.
47. Vasundra Devi PA, Divya Priya S. Antipyretic activity of ethanol and aqueous extract of root of *Asparagus racemosus* in yeast induced pyrexia. *Asian J Pharm Clin Res* 2013; 6(3): 190-193.
48. Rajani GP, Deepak G, Sowjanya K, Sahithi B. Screening of antipyretic activity of aerial parts of *Nelumbo nucifera* gaertn in yeast-induced pyrexia. *Pharmacologyonline* 2011; 1: 1120-1124.
49. Khan IA, Aziz A, Munawar SM, Manzoor Z, Sarwar HS, Afzal A. Study on antipyretic activity of *Rumex vesicarius* leaves extract in albino rabbits. *Vet World* 2014; 7(1): 44-48.
50. Taiwe GS, Bum EN, Dimo T, Talla E, Weiss N, Idiki N. Antipyretic and antinociceptive effects of *Nauclea latifolia* roots decoction and possible mechanisms of action. *Pharm Biol* 2001; 49(1): 15-25.