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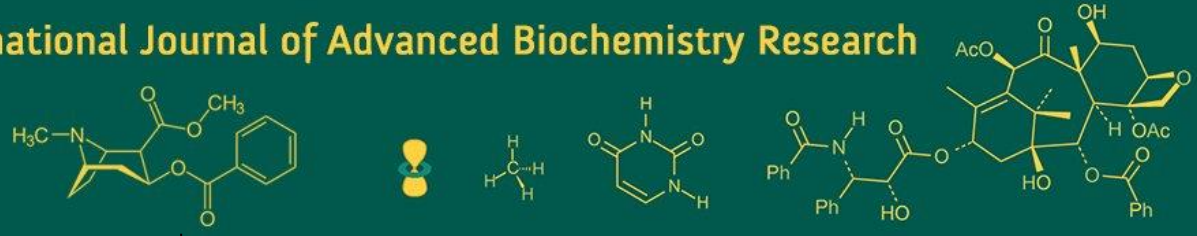

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Effect of aqueous leaf extract of *Macaranga barteri* on baker's yeast-induced pyrexia in wistar albino rats

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Abstract
This study was aimed at evaluating the anti-pyretic activity of the aqueous leaf extract of *Macaranga barteri* in Baker's yeast-induced pyrexia in wistar rats. Rats were divided into five groups of four rats/group. Group 1 received distilled water while groups 2-5 received subcutaneous injection 20% baker's yeast solution for 17hours before treatment. Rats in groups 3, 4, and 5 were treated with 250 and 500 mg/kg b.w extract and paracetamol respectively hourly. Rats were sacrificed and biochemical and heamatological analyses were done on blood. Qualitative phytochemical analysis revealed the presence of alkaloids, phenolic compounds, tannins, saponins, quinines and steroids. Result showed non-significant ($p \geq 0.05$) reduction in rectal temperature at 1, 2 and 3 hours in groups 3 and 2 and 3 hours in group 4 and 1 hour in group 5. Non-significant increase ($p \geq 0.05$) in WBC, lymphocytes, basophil and ESR values and reduction in neutrophil, eosinophil and monocyte when negative control was compared to normal control and significant reductions($p \leq 0.05$) of WBC count in groups 3, 4, and 5, Monocyte count in 4 and 5 and ESR in 3, 4, and 5 when compared to normal and negative control values. CRP and PTG S1 concentrations showed non significantly increased ($p \geq 0.05$) while IL-6 concentration significantly increased ($p \leq 0.05$) when negative control values were compared to control values and non-significant reduction ($p \geq 0.05$) in groups 3, 4 and 5 for CRP and groups 3 and 5 for PTG S1 and significant reduction ($p \leq 0.05$) in groups 3, 4 and 5 in IL-6 concentrations when compared to negative control. Aqueous leaf extract of *Macaranga barteri* demonstrated antipyretic potential hence could serve as antipyretic agent.

Keywords: *Macaranga barteri*, paracetamol, Baker's yeast, phytochemical

Introduction
A condition of abnormally high body temperature is known as pyrexia, sometimes known as fever. It is a feature of numerous medical conditions. For instance, fever is seen in a variety of pathologic conditions, including cancer, infections, malaria, coronary artery blockage, and several blood disorders, while being most frequently linked to infections. In addition, it might be brought on by environmental factors like heat exhaustion or heat stroke, or by physiological stressors like heavy exercise or ovulation. The temperature of the deeper parts of the head and trunk normally varies by little more than 1-2 °F per day, and it never rises above 99 °F (37.22 °C) in the mouth or 99.6 °F (37.55 °C) in the rectum. Individuals who have fever may fluctuate 5-9 °F above normal on a daily basis. It indicates that fever is the body's protective response to an infectious illness. One of the immune system's reactions to bacterial or viral invasions that result in tissue damage is the production of pyrogens, which cause the body to produce cytokines such as interleukins, tumor necrosis factor, and interferon. This process then increases the synthesis of prostaglandin E2 (PGE2) in the vicinity of the pre-optic hypothalamus. By encouraging heat production and reducing heat loss, this raises body temperature. i-pyretic medications, which are used to treat fever, function by preventing the expression of COX-2 (Cyclooxygenase-2), which lowers the production of PGE2, the main mediator of fever [1]. It is said that a wide variety of synthetic medications, primarily NSAIDs (non-steroidal anti-inflammatory medicines), steroidal, and immunodepresant medications, are used to treat inflammation. These medications are thought to be extremely dangerous for long-term use and do not come without negative effects [2]. Therefore, traditional medicine has been used as a substitute in the majority of the world's poorest nations.

Many societies view it as the best primary healthcare system, since more than 60% of people worldwide and over 80% of people in underdeveloped nations rely only on medicinal plants for their medical needs [3]. This is because of several factors, including affordability and ease of use. A plant that is considered medicinal is *Macaranga barteri*. *Macaranga barteri* is a common shrub or tree found in Equatorial Guinea, Southern Nigeria, Ghana, Liberia, and the Ivory Coast. While the Akan tribe in Ghana refers to it as "opam-kokoo," the Yoruba tribe in Nigeria refers to it as "aarasa" and "owariwa." Nigerians have long employed the bark and leaves as a vermifuge, either in powder form or in a decoction [4]. The plant is used in the Democratic Republic of the Congo as a worm expellant and medication to lower fever [5], which is why this study was created to look into the plant's potential as an antipyretic using an aqueous leaf extract. It is used to treat bronchitis and cough in combination with other *Macaranga* spp. [5]. Although its leaves have anti-gonorrhea properties in Sierra Leone, they are also commonly used as an aperient and anti-anemic tonic in Ivory Coast [5]. It has also been documented that *M. barteri* leaf extract has pharmacological significance as an antioxidant and antibacterial agent [4, 6]. *M. barteri* contains a lot of phenolic compounds, which have been identified as the main components linked to its anti-inflammatory effect [7].

Materials and Methods

Plant materials (source)

Fresh *Macaranga barteri* leaves were obtained in April 2021 from the University of Port Harcourt Teaching Hospital (UPTH), Rivers State's Savannah area. Dr. Ekeke, Chimezie of the Department of Plant Science and Biotechnology, University of Port Harcourt, Rivers State, identified and verified the leaves, and the voucher specimen and number (UPH/P/258) were deposited at the Herbarium for reference.

Extraction

The leaves of *Macaranga barteri* were air-dried for a period of two weeks away from direct sunlight, after which it was pulverized into coarse powder using a grinding Mill machine. After weighing and dissolving the ground leaf sample in 100 g/L of deionized water, the mixture was homogenized using a glass stirring rod and allowed to stand for a full day. It was then filtered with Whatman No. 1 filter paper. In order to evaporate the leaf extract's moisture content, the filtrate (extract) was subsequently dried in a crucible over a water bath at a moderate heat of 60 °C.

Experimental animals

Wistar albino female rats (100-150 g) were purchased from the Faculty of Basic Medical sciences, University of Port Harcourt and housed in clean cages with access to feed (commercial feeds) and water Ad Libitum. They were fasted for 12 hours prior to the experiment. All experimental protocols were in compliance with Department of Biochemistry Research Ethics Committee, University of Port Harcourt, (approval number UPH/BCHREC/2022/007) on research in animals as well as internationally accepted principles for laboratory animal use and care.

Drugs and Chemicals: Chemicals and drugs used in this work are: Baker's yeast (STK Industries Limited, Lagos), 0.9% Normal saline solution Paracetamol (Emzor Pharmaceutical Industries, Lagos), Chloroform (British Drug House (BDH), England).

Acute Oral Toxicity Test

Acute oral toxicity for the aqueous leaf extract of *Macaranga barteri* was adopted from [8] and doses used in this research were decided from this publication.

Qualitative Phytochemical Analysis

The freshly prepared crude extract was qualitatively tested for the presence of phytochemicals such as; Alkaloids, saponins, coumarins, steroids, tannins, flavonoids, proteins, phenolics, cardiac glycosides and anthraquinones.

Alkaloid: In a bath of boiling water, the aqueous extract of the plant sample's crude dry powder was evaporated until it was completely dry. 2M HCl was used to dissolve the residue. Following filtration of the combination, the filtrate was split into three equal pieces. Wagner's reagent was applied in an equal amount to one area, Mayer's reagent to another, and a few drops of Dragondroff's reagent to still another. The corresponding alkaloids were shown to be present by the creamy, orange, and brown precipitates.

Saponin: The foaming test was used to detect saponin. After vigorously shaking the plant's dry powder with distilled water and letting it stand for ten minutes, the saponin content of the powder was categorized as follows: A steady froth that lasted longer than 15 minutes indicated the presence of saponin, whereas no froth indicated the absence of saponin [9].

Coumarin: After 1 milliliter of plant extract was placed in a test tube and exposed to 3-4 drops of 1% potassium hydroxide solution (made by combining 1 gram of KOH with ethanol), the presence of coumarin was shown by the emergence of a yellow color.

Tannins (Ferric Chloride test): 0.5 g of plant extract was stirred with distilled water and filtered. Two drops of 5% Ferric Chloride solution was added to the filtrate. Formation of a blue black, green blue green precipitates were taken for evidence of tannins [10].

Quinine: Dilute sodium hydroxide was added to the test sample (plant leaves extract) which was in a test tube. Formation of blue green or red color indicates the presence of quinine (shindo's test).

Flavonoid: To 1 ml of extract, a few drops of 10% sodium hydroxide were added. The appearance of an intensive yellow color in the test tube which became colorless on addition of a few drops of dilute sulphuric acid, indicated the presence of flavonoids [10].

Protein (million reagent): Few drops of million's reagent was added to the sample in the test tube and the resultant mixture was heated for two minutes, formation of red precipitate indicates the presence of protein.

Phenolic compound: 0.5 g of plant extract was stirred with distilled water and filtered. 2-3, drops of 1% neural Ferric Chloride solution was added, (obtained by adding dilute

ammonia until precipitate just began to form and filtered). The appearance of violet color with ferric ion indicated the presence of phenolic compounds (Shindo's test).

Steroids: The presence of steroids was ascertained by the Liebermann-Burchard reaction. Drops of chloroform, 3-4 drops of acetic anhydride and 4 drops of concentrated sulphuric acid were added down the side. The presence of steroids was indicated by the appearance of purple color that changed to blue or green color was detected.

Cardiac glycosides: Cardiac glycosides was determined by the Keller-kiiani test. The crude dry powder of the plant was treated with 1 ml of Ferric chloride reagent (mixture of 1 volume of 5% $FeCl_3$ solution and 99 ml volume of glacial acetic acid). Few drops of concentrated sulfuric acid was added. The presence of cardiac glycosides was indicative by the production of greenish blue color in the test tube within a few minutes [11].

Anthraquinone: To the test sample in a test tube 10% potassium hydroxide solution was added in drops. A blue red coloration indicated the presence of anthraquinone (Bontrager's test).

Anti-pyretic Evaluation

The anti-pyretic activity of aqueous leaf extract of *Macaranga barteri* was evaluated using baker's yeast-induced pyrexia. The rats were randomly divided into five groups of four rats each. Groups III, IV, and V were treated with 250 and 500 mg/kg aqueous leaf extract and the later with 500 mg/kg paracetamol. Group I served as normal control and received distilled water only while groups III, IV, and V were induced with 20% baker's yeast solution 17 hours before commencement of treatment and induction of pyrexia was confirmed by 0.5 °C rise in temperature. The animals with a raised temperature of less than 0.5 °C were no included. Group II was induced pyrexia without treatment serving as negative control group. The temperature of each rats were taken before induction (basal temperature) and also 30 minutes after treatments at hourly intervals for three hours. Rats were sacrificed hourly by heart puncture and blood samples were collected into EDTA and heparinized sample bottles for biochemical and hematological analyses.

Collection and Preparation of Blood Sample

Blood in heparin sample bottles collected through heart puncture were put in centrifuge and spun at 4 °C and 1500 rpm for 15 minutes to separate serum for biochemical analysis.

Biochemical Analysis

The concentrations of PGE2, IL-6 and High-Sensitive C-Reactive Protein (HS-CRP) in the serum of wistar rats were quantified by commercially available enzyme-linked immunosorbent assay (ELISA) kits at a wavelength of 450 nm according to the instructions provided by the manufacturer.

Hematological Analysis

Hematological analysis of blood samples was determined using Sysmex XN-2000 Hematological Analyser (Zhejiang Xinke Medical Technology Co., Ltd, China).

Statistical Analysis

Data were expressed as mean±SD using SPSS by window 22 USA. The values were analyzed by one-way ANOVA followed by multiple comparisons by Turkey and values were considered significantly different at $p<0.05$ confidence level.

Results

Result of Qualitative phytochemical constituents of aqueous leaf extract of *Macaranga barteri*

Qualitative phytochemical analysis of *aqueous leaf extract of Macaranga barteri* from Table 1 revealed the presence of alkaloids, phenolic compounds, tannins, saponins, quinines and steroids.

Table 1: Qualitative phytochemical constituents of aqueous leaf extract of *Macaranga barteri*

Phytochemicals	Inference
Anthraquinones	-
Alkaloids	+
Phenolic compounds	+
Tannins	+
Flavonoids	-
Saponins	+
Quinines	+
Coumarins	-
Proteins	-
Cardiac glycosides	-
Steroids	+

(+) indicates presence and (-) indicates absence

Result of Anti-pyretic Effect of Aqueous Leaf Extract of *Macaranga barteri* on Baker's Yeast-induced Pyrexia in Wistar Rats

The extract and paracetamol treatment groups showed non-significant ($p\geq0.05$) reduction in rectal temperature at 1, 2, and 3 hours in groups 3 and 2 and 3 hours in group 4 and 1 hour in group 5 indicating antipyretic effect

Table 2: Effect of aqueous leaf extract of *Macaranga barteri* on heamatological indices of baker's yeast-induced pyrexia in wistar rats.

Group (°C)	Treatment (°C)1hour	Initial Rectal Temperature 3 hours	Induced temp. after 17 hours	Rectal temperature (°C) after drug administration		
1	Normal Control (Distilled H_2O only)	37.60±0.52 [a]	37.60±0.52 [a]	37.60±0.52 [a]	37.60±0.52 [a]	37.60±0.52 [a]
2	Control (-ve20% baker's yeast)	37.53±0.40 [a]	38.38±0.11 [a]	38.50±0.18 [a]	38.50±0.24 [a]	38.53±0.26[a]
3	20% baker's yeast + 250 mg/kg b.w *Macaranga barteri*	37.45±0.30 [a]	38.20±0.15 [a]	37.50±0.20 [a]	37.68±0.25 [a]	37.90±0.23 [a]
4	20% baker's yeast + 500 mg/kg b.w *Macaranga barteri*	37.80±0.04 [a]	38.13±0.10 [a]	38.08±0.29 [a]	37.45±0.31 [a]	37.50±0.31 [a]
5	20% baker's yeast 500 mg/kg b.w Paracetamol	37.65±0.46 [a]	38.50±0.70 [a]	37.88±0.14 [a]	38.05±0.52 [a]	38.85±0.30[a]

Values are reported as mean ± standard error of mean (M±SEM) (n=5). Values with similar different superscript letters indicate statistically significant differences ($p\leq0.05$) down the column while those with similar superscript show non-significant differences ($p\geq0.05$) down the column and between groups.

Result of the effect of aqueous leaf extract of *Macaranga barteri* on heamatological indices of baker's yeast-induced pyrexia in wistar rats: Result of Table 3 showed non-significant increase in WBC, lymphocytes, basophil and ESR values and reduction in neutrophil, eosinophil and monocyte when negative control group is compared to normal control. The effect of aqueous leave extract of *Macaranga barteri* on hematological indices of baker's yeast induced pyrexia in wistar albino rats in Table 3 revealed significant reductions of WBC count in groups 3, 4, and 5, monocyte count in 4 and 5 and ESR in 3, 4, and 5 when compared to normal and negative control values indicating ameliorative effect of the extract against baker's yeast induced pyrexia.

Table 3: Effect of aqueous leave extract of *Macaranga barteri* on hematological indices of baker's yeast induced pyrexia in wistar albino rats.

Groups	Treatment	WBC ($x10^9$)	Lymphocyte (%)	Neutrophil (%)	Eosinophil (%)	Monocyte (%)	Basophil (%)	ESR (mm/hour)
1	Normal control (water only)	8.93±1.44 [a]	51.25± 0.25	37.00±1.22 [a]	5.00±0.00 [a]	6.00±1.08 [a]	0.75±0.25 [a]	0.75±0.25 [a]
2	Negative control (20% baker's yeast)	10.83±2.05 [a]	59.00±6.42	35.25±4.29 [a]	2.00±0.91 [b]	5.25±1.44 [a]	1.25±0.75 [a]	1.25±0.75 [a]
3	250 mg/kg b.w *Macaranga barteri* + 20% baker's yeast	3.33±0.92 [b]	74.00±5.10 [a]	13.33±1.64 [b]	2.75±0.63 [b]	6.75±2.06 [a]	0.00±0.00	5.25±1.65 [b]
4	500 mg/kg b.w *Macaranga barteri* + 20% baker's yeast	5.10±1.38 [b]	71.25±6.81	28.36±6.02 [a]	4.00±1.35 [a]	1.75±1.03 [b]	0.00±0.00	2.75±1.03c
5	500 mg/kg b.w paracetamol + 20% baker's yeast	3.85±0.97 [b]	76.33±3.66 [a]	18.00±2.12 [b]	2.00±0.71 [b]	3.25±1.03 [b]	0.00±0.00	2.25±0.25 [c]

Values are reported as mean ± standard error of mean (M±SEM) (n=5). Values with different superscript letters indicate statistically significant differences ($p \leq 0.05$) down the column while those with similar superscript show non-significant differences ($p \geq 0.05$) down the column.

Result of the effect of aqueous leave extract of *Macaranga barteri* on biochemical parameters of baker's yeast induced pyrexia in wistar albino rat

CRP and PTG S1 concentrations non significantly increased while IL-6 concentration significantly increased when negative control values were compared to control values in Table 4. Treatment with aqueous extract and paracetamol revealed non-significant reduction in groups 3, 4 and 5 for CRP and groups 3 and 5 for PTG S1 and significant reduction in groups 3, 4 and 5 in IL-6 concentrations when compared to negative control

Table 4: Result of the effect of aqueous leave extract of *Macaranga barteri* on biochemical parameters of baker's yeast induced pyrexia in wistar albino rat

Groups	Treatments	CRP	IL_6	PTG S1
1	Normal Control (Distilled H_2O only)	0.19±0.02 [a]	3.32±0.39 [a]	0.23±0.27a
2	Negative Control (20% baker's yeast	1.19±0.19 [a]	44.63±18.45 [b]	1.71±0.40a
3	250 mg/kg bw *Macaranga barteri* + 20% baker's yeast	0.98±0.98 [a]	13.56±2.73 [c]	1.14±0.23a
4	500 mg/kg bw *Macaranga barteri* + 20% baker's yeast	0.93±0.30 [a]	24.56±8.40 [d]	2.81±1.30b
5	500 mg/kg bw Paracetamol + 20% baker's yeast	1.07±0.56 [a]	18.60±3.59 [d c]	1.38±0.50 [a]

Values are reported as mean ± standard error of mean (M±SEM) (n=5). Values with different superscript letters indicate statistically significant differences ($p \leq 0.05$) down the column while similar superscript show non-significant differences ($p \geq 0.05$) down the column when compared with the control and between groups.

Discussion and Conclusion

Alkaloids, phenolic chemicals, tannins, saponins, quinines, and steroids were found in the aqueous leaf extract of *Macaranga barteri* from Table 1 based on a qualitative phytochemical investigation. In their research on phytochemical screening of *M. barteri* stem bark and leaves, [8, 12] found the presence of tannins, alkaloids, flavonoids, and sterol, respectively. Secondary metabolites mediate the biological advantages of plants, including their analgesic, antipyretic, and anti-inflammatory properties [13]. It has been demonstrated that a number of these phytochemicals have antipyretic properties in the test animals [14]. Large amounts of steroids are present in many plants and have the capacity to display properties including antifungal, antiviral, antileukemic, hypnotic, antipyretic, and muscle-relaxant effects [15]. Many medicinal plants have been shown to have antipyretic properties due to the presence of steroids, tannins, triterpenoids, flavonoids, and glycosides [16-18]. Additionally, [19, 20] linked the antipyretic activity of *Vernonia amygdalina's* leaf, root saponin fraction, and ethanolic leaf extract to the presence of these substances.

Table 2 shows the antipyretic activity of *Macaranga barteri* aqueous leaf extract on baker's yeast-induced pyrexia in wistar rats. There was a non-significant ($p \geq 0.05$) decrease in rectal temperature at 1, 2, and 3 hours in groups 3 and 2 and 3 hours in group 4 and 1 hour in group 5 indicating an antipyretic effect for the extract and paracetamol treatment groups. After 18 hours of induction, the subcutaneous injection of yeast significantly raised the rectal temperature in every group, suggesting yeast-induced pyrexia. By introducing exogenous pyrogens through subcutaneous injection of baker's yeast suspension, which binds to the immunological binding protein, endogenous pyrogens, such as interleukins IL-1β, IL-6, interferon (IF-α), and tumor necrosis factor (TNF), also known as cytokines, are produced [21].

These pyrogenic cytokines cause the release of local prostaglandins, primarily prostaglandin E2 (PGE2), when they enter the bloodstream and go to the preoptic hypothalamic anterior area (POA). The build-up of PGE2 in the preoptic region of the hypothalamus alters the activity of heat-sensitive neurons in the preoptic hypothalamic anterior area (POA). PGE2 then sends a warming signal to the

effector, causing the body to produce more heat, dissipate less heat, and raise the hypothalamic thermal set point above normal [22-24]. The majority of antipyretic medications lower body temperature by preventing PGE2 from being produced [25]. It has been documented that alkaloids prevent prostaglandin production [26].

The effect of *Macaranga barteri's* aqueous leaf extract on the hematological indices of baker's yeast-induced pyrexia in wistar albino rats was shown in Table 3, where the extract significantly reduced the WBC count in groups 3, 4, and 5, the monocyte counts in groups 4 and 5, and the ESR in groups 3, 4, and 5. These results indicate that the extract has an ameliorative effect against baker's yeast-induced pyrexia. White blood cell count and its indices are crucial for immune function. Leukocytes, or white blood cells, give the body immunity against the infiltration of antigens. Particularly reacting to the antigens, lymphocytes create immunologic memory [27]. Bacteria, waste products from cells, and foreign objects are attacked and destroyed by neutrophils and monocytes [28]. When negative control values were compared to control values in Table 4, the concentrations of CRP and PTG S1 increased non-significantly, but the concentration of IL-6 increased considerably. When compared to the negative control, groups 3, 4, and 5 that received aqueous extract plus paracetamol treatment showed non-significant decreases in CRP and PTG S1 concentrations as well as substantial decreases in IL-6 concentrations. Exogenous cytokines including TNFα, IL-1, IL-6, and interferons are released in reaction to exogenous pyrogens, which causes pyrexia to be induced. Results from research using animal models showed that after yeast-induced pyrexia, levels of TNF-α and IL-6 rose [29, 30]. According to this finding, the antipyretic effect of medications might be assessed using the amounts of these variables. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) are among the pyrogenic cytokines that are released when a host is infected with exogenous pyrogens, since these infections trigger a series of immunological responses [31, 32].

The rats body temperature rises above the set point of 37.5-38.3 °C in the anus or rectum as a result of these pyrogenic cytokines, which also cause the creation of PGE2, which sends signals to the hypothalamus. Interleukin-6 (IL-6), one of the main pyrogenic cytokines in this study, increased considerably following baker's yeast injection along with a non-significant increase in PGE2 concentrations. Through signals involving the activator of transcription 3 (STAT3) pathway, IL-6 binds to IL-6 receptors on brain endothelial cells, inducing the production of prostaglandin synthase COX-2 [33]. Rats that were made pyretic by baker's yeast and treated with aqueous extract and paracetamol in the same way showed non-significant reductions in PTG S1 concentration in groups 3 and 5, as well as substantial reductions in IL-6 concentration in groups 3, 4, and 5, in comparison to the negative control. Most antipyretic drugs work by preventing PGE2 from being synthesized, which lowers body temperature [25]. Therefore, by blocking the STAT3 signaling pathway, the aqueous leaf extract of *Macaranga barteri* may have inhibited PGE2 production.

Conclusion

Aqueous leaf extract of *Macaranga barteri* demonstrated antipyretic potential hence could serve as antipyretic agent.

References

1. Murakami M. Lipid mediators in life science. Exp Anim. 2011;60(1):7-20.
2. Lana's A. Nonsteroidal anti-inflammatory drugs and cyclooxygenase inhibition on the gastrointestinal tract: A trip from peptic ulcer to colon Cancer. Am J Med Sci. 2009;338:96-106.
3. Shrestha Prasanna M, Dhillion Shivcharn S. Medicinal plant diversity and use in the highlands of Dolakha district, Nepal. J Ethnopharmacol. 2003;86(1):81-96.
4. Adesegun SA, Elechi NA, Coker HAB. Antioxidant power of *Macaranga barteri* leaf. Am J Food Technol. 2007;2(6):543-549.
5. Burkill HM. The useful plants of West Tropical Africa. London: Royal Botanic Gardens, Kew; c1994. p. 636.
6. Uduak AE, Ajibesin KK. Antimicrobial activities of some Euphorbiaceae plants used in the traditional medicine of Akwa Ibom state of Nigeria. Ethnobot Leaf. 2010;14:654-64.
7. Ngoumfo RM, Ngounou GE, Tchamadeu CV, Qadir MI, Mbazoa CD, Begum A, *et al*. Inhibitory Effect of *Macaranga barteri*, a polyoxygenated Ellagittannin from *Macaranga barteri*, on Human Neutrophil Respiratory Burst Activity. Phytochemistry. 2008;61:867-872.
8. Ehile E, Goze N, Yapo A, Ehoian E. Acute Toxicity and Gastric Anti-Ulcer Activity of an Aqueous Extract of the Leaves of *Macaranga barteri* MüellArg (Euphorbiaceae) On Rats Models. (Electronic Version) Of Medicinal Plants Research. 2018;12(9):96-105.
9. Kapoor LD, Singh A, Kapoor L, Srinivastava SN. Survey of Indian plants for saponins, alkaloids and flavonoids. Lloydia. 1969;32:297–304.
10. Trease GE, Evans WC. Pharmacognosy. 13th ed. London: ELBS/Bailliere Tindall; 1989. p. 345-6, 535-6, 772-3.
11. Ajaiyeoba EO. Phytochemical and antibacterial properties of Parkiabi oglobosa and Parkiabi colour leaf extracts. Afr J Biomed Res. 2002;5:125-129.
12. Asante-Kwatia E, Jibira Y, Mensah AY, Osei-Sarfoh D. *Macaranga barteri* stem bark extract exerts anti-inflammatory and anti-hyperalgesia activity in murine models. Discovery Phytomedicine. 2019;6(3):130-137. DOI:10.15562/phytomedicine.2019.104
13. Kifayatullah M, Rahim H, Jan NU, Chishti KA, Ullah I, Abbas S. *In vivo* analgesic, antipyretic and anti-inflammatory activities of ethanol extract of *Pericampylus glaucus* in experimental animals. Sains Malays. 2019;48(3):629-635.
14. Okokon JE, Nwafor PA. Antiinflammatory, analgesic and antipyretic activities of ethanolic root extract of *Crotonzam besicus*. Pak J Pharmaceut Sci. 2010;23:383-390.
15. Kokpol U, Chittawong V, Mills HD. Chemical constituents of the roots of *Acanthus illicifolius*. J Nat Prod. 1984;49:355-356.
16. Niazi J, Gupta V, Chakarborty P, Kumar P. Antiinflammatory and antipyretic activity of *Aleuritis moluccana* leaves. Asian J Pharm Clin Res. 2010;3:35-37.
17. Safari V, *et al*. Antipyretic, antiinflammatory and antinociceptive activities of aqueous bark extract of *Acaciani lotica* (L.) delile in albino mice. Pain Manage Med. 2016;2(113):2.

18. Gaichu DM, *et al*. Phytochemical screening and antipyretic activities of dichloromethane-methanolic leaf and stem bark extracts of *Ximenia americana* in rat models. J Herbmed Pharmacol. 2017;6.
19. Adiukwu P, *et al*. Anti-Inflammatory and anti-pyretic activity of the leaf, root and saponin fraction from *Vernonia amygdalina*. Br J Pharmacol Toxicol. 2013;4(2):33-40.
20. Tijjani MA, *et al*. Phytochemical analysis, analgesic and antipyretic properties of ethanolic leaf extract of *Vernonia amygdalina* Del. J Herbmed Pharmacol. 2017;6.
21. Saper CB, Breder CD. The neurologic basis of fever. N Engl J Med. 1994;330(26):1880-1886.
22. Dalal S, Zhukovsky DS. Pathophysiology and management of fever. J Support D.-B. Asante *et al*. Biomedicine & Pharmacotherapy. 2019;111:1187–1203.
23. Ganguly A, *et al*. *In-vivo* anti-inflammatory and anti-pyretic activities of *Manilkara zapota* leaves in albino Wistar rats. Asian Pac J Trop Dis. 2013;3(4):301.
24. Lin X, Kong J, Wu Q, Yang Y. Effect of TLR4/MyD88 signaling pathway on expression of IL-1_ and TNF-_ in synovial fibroblasts from temporomandibular joint exposed to lipopolysaccharide. Mediators of Inflammation. 2015;2015:329405.
25. Luo C, He ML, Bohlin L. Is COX-2 a perpetrator or a protector? Selective COX-2 inhibitors remain controversial. Acta Pharmacol Sin. 2005;26(8):926.
26. Niazi J, Gupta V, Chakarborty P, Kumar P. Antiinflammatory and antipyretic activity of *Aleuritis moluccana* leaves. Asian Journal of Pharmaceutical Clinical Research. 2010;3: 35-37.
27. Klein J, Horejí V. Immunology. Malden MA: Blackwell Scientific; c1997.
28. Dacie SIV, Lewis SM. Practical haematology; c1991.
29. Pasin JS, Ferreira AP, Saraiva AL, Ratzlaff V, Andrighetto R, Tomazetti J, *et al*. Diacerein decreases TNF-alpha and IL-1beta levels in peritoneal fluid and prevents Baker's yeast-induced fever in young rats. Inflamm Res. 2010;59:189-196. DOI: 10.1007/s00011-009-0085-8.
30. Dangarembizi R, Erlwanger KH, Rummel C, Roth J, Madziva MT, Harden LM. Brewer's yeast is a potent inducer of fever, sickness behavior and inflammation within the brain. Brain Behav Immun. 2018;68:211-223. DOI: 10.1016/j.bbi.2017.10.019.
31. Conti B, Tabarean I, Andrei C, Bartfai T. Cytokines and fever. Front Biosci. 2004;9(12):1433-1449. DOI:10.2741/1341.
32. Prajitha N, Athira SS, Mohanan PV. Comprehensive biology of antipyretic pathways. Cytokine. 2019;116:120-127. DOI:10.1016/j.cyto.2019.01.008.
33. Eskilsson A, Mirrasekhian E, Dufour S, Schwaninger M, Engblom D, Blomqvist A. Immune-induced fever is mediated by IL-6 receptors on brain endothelial cells coupled to STAT3-dependent induction of brain endothelial prostaglandin synthesis. J Neurosci. 2014;34(48):15957-15961. DOI:10.1523/JNEUROSCI.3520-14.2014.