

ORION
SCHOLAR JOURNALS



(RESEARCH ARTICLE)



Effect of aqueous leaf extract of *Macaranga barterion* selected haematological and biochemical indices of carrageenan -induced paw edema in Wistar albino rats

Dikioye Emmanuel Peters*, Chimburuoma Goodness Amadib and Chukwuka Promise Ali

Department of Biochemistry, University of Port Harcourt, Choba, Rivers State, Nigeria.

International Journal of Scientific Research Updates, 2022, 04(02), 092–101

Publication history: Received on 04 August 2022; revised on 30 September 2022; accepted on 03 October 2022

Article DOI: <https://doi.org/10.53430/ijrsru.2022.4.2.0074>

Abstract

This research was designed to determine the anti-inflammatory and quantitative characterization of phenolic compounds in aqueous leaf extract of *Macaranga barteri* on carrageenan induced paw edema in wistar rats. Phenolic compound was characterized using GC-MS. Twenty wistar rats of both sexes weighing between 120-140g were grouped into 5 with four (4) rats per group. Group 1 served as the normal control which received distilled water, group 2 (negative control) rats received 1% carrageenan only, groups 3 and 4 were treated with aqueous leaf extract of *M. barteri*, group 5 was treated with diclofenac, 30 minutes after receiving 1% carrageenan, the changes in paw sizes were observed hourly for 3 hours. Rats were sacrificed and blood samples collected for haematological and biochemical analyses. Phenolic compounds detected were 2-nitro phenol (3.29 ppm) and 4-chloro-3-methyl-phenol (5.09ppm). Significant reduction in rat paws oedema was observed when rats in group 4 were compared with group 2 at 3 hours with percentage oedema inhibition of 46.91. Mean ESR of rats in groups 2, 3 and 5 significantly increased and group 4 none significantly reduced when compared to control. Non-significant differences in mean WBC, neutrophil and lymphocyte counts, significant reduction of mean eosinophil counts in groups 2 and 3 and non-significant increase in group 4 when compared to control. Significant increase in mean CRP concentration was observed when group 2 was compared to control group and a significant reduction in group 4 treated with 500mg/kg b.wt. When compared to group 2. Mean concentrations of Il-6 and prostaglandin significantly increased in all the groups when compared to control. Aqueous leaf extract of *M. barteri* demonstrated near average percentage paw oedema inhibition and mild anti-inflammatory potential at 500mg/kg b.wt.

Keywords: Anti- Inflammatory; Carrageenan; Phenolic; Haematological; Biochemical; Prostaglandin

1. Introduction

Inflammation is a local response of living mammalian tissues to injury. It is a body defense reaction in order to eliminate or limit the spread of injurious agent [1]. There are various components to an inflammatory reaction that can contribute to the associated symptoms and tissue injury.

Edema, leukocyte infiltration, and granuloma formation represent such components of inflammation, though, it is a defense mechanism. The complex events and mediators involved in the inflammatory reaction can induce or aggravate many reactions [2].

As it is well known, the probiotic bacteria are nonpathogenic and consumed as/with food for a long time.

*Corresponding author: Peters Dikioye Emmanuel
Department of Biochemistry, University of Port Harcourt, Choba, Rivers State, Nigeria.

Furthermore, inflammation is regarded as a defensive response that induces physiological adaptations to limit tissue damage and removes the pathogenic infections [3]. The conventional signs of acute inflammation are pain, heat, redness and swelling [4].

These symptoms are a result of various inflammatory mediators and chemical agents such as prostaglandins (PGs), histamine, serotonin, bradykinin, leukotrienes, and Nitric Oxide which are produced either locally or infiltrate in the area of insult. Macrophages play an important role in inflammation and are activated by various inflammatory mediators such as PGE₂, tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and interleukin-10 (IL-10).

Cyclooxygenase (COX) enzyme catalyzes the biosynthesis of PGs. There are at least two main isoforms, COX-1, and COX-2. Although both isoforms catalyze the same biochemical transformation, their expression is differentially regulated. COX-1 is a constitutive enzyme and augments the physiological role of prostaglandins (PGs) including maintaining the integrity of the GIT mucosa and adequate vascular homeostasis whereas, COX-2 is induced only after an inflammatory stimulus. Inhibition of COX enzyme is considered to be an important target in the discovery of anti-inflammatory and anti-nociceptive drugs.

Anti-inflammation is the property of a substance or treatment that reduces inflammation or swelling. Anti-inflammatory agents from plant sources have been extensively studied, and have shown promising results against inflammatory disorders due to their mild adverse effects [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most widely prescribed drugs to treat inflammatory and pain disorders. This class includes drugs such as celecoxib, rofecoxib, meloxicam, diclofenac, indomethacin, and ibuprofen [6].

NSAIDs exert its pharmacological activity via suppression of prostaglandin biosynthesis by inhibiting the enzyme cyclooxygenase (COX). It is well known that the gastrointestinal adverse effects associated with the long terms use of NSAIDs are due to inhibition of COX-1, and the adverse effects on the cardiovascular system are due to inhibition of COX-2 enzymes [7]. It has been observed that these drugs are associated with side effects.

The World Health Organisation (WHO) recommends medicinal plants that scientific evidence is established for their harmless and therapeutic efficacy [8]. Traditional medicine has been an alternative in most developing countries of the world. It is recognized as the preferred primary health care system in many communities, with over 60% of the world's population and about 80% in developing countries depending directly on medicinal plants for medicinal purposes [9]. *Macaranga barteri* is one of these medicinal plants with phytochemicals exhibiting medicinal properties.

Macaranga barteri Mull.Arg. is a shrub or tree 20m high by 1.30m girth, of forest, Secondary jungle and grassy savanna, common throughout the region from Guinea to Southern Nigeria, and Equatorial Guinea.

It is a common specie of the family Euphorbiaceae distributed in the arid forests and grassy savannahs of tropical Africa.

Macaranga barteri is endowed to possess numerous ethno medical uses. The leaf decoction of *Macaranga barteri* is being used to treat sexually transmitted infection, as a laxative and haematinic in Sierra Leone.

Together with other *Macaranga* species, it is also used to relieve persistent cough, bronchitis, stomatitis, gastric ulcer, dysentery, swelling and arthritis. In previous scientific reports, the leaf extract of *M. barteri* showed remarkable antimicrobial, antioxidant and anti-diabetic activity as well as the ability to protect the gastric mucosa against gastric injury [10].

1.1 Carrageenan

Carrageenan or (from Irish carraigín, "little rock") are a family of natural linear sulfated polysaccharides that are extracted from red edible seaweeds.

The most well-known and still most important red seaweed used for manufacturing the hydrophilic colloids to produce carrageenan is *Chondrus crispus* (Irish moss) which is a dark red parsley-like plant that grows attached to the rocks. Carrageenan are widely used in the food industry, for their gelling, thickening, and stabilizing properties. Carrageenan is used to induce inflammation. Inflammation models induced by carrageenan are frequently used acute inflammation models mainly because they are well researched and they exhibit a high degree of reproducibility. Carrageenan is a

strong chemical that functions in stimulating the release of inflammatory and pro-inflammatory mediators, including bradykinin, histamine, tachykinins, reactive oxygen, and nitrogen species.

Generally, animals are injected with a certain concentration (usually 1%) of the irritant substance carrageenan in one hind footpad, usually, half an hour or an hour after they are treated with the test compound while the other footpad is injected with saline as a control [11].

1.2 Phytochemicals in *Macaranga barteri* Exhibiting Anti-Inflammatory properties

Phytochemicals are compounds that are produced by plants ("phyto" means "plant"). They are found in fruits, vegetables, grains, beans, and other plants.

Some of these phytochemicals are believed to protect cells from damage that could lead to cancer.

Some scientists think that you could reduce your cancer risk by as much as 40% by eating more vegetables, fruits, and other plant foods that have certain phytochemicals in them. Some phytochemicals found in *Macaranga barteri* are; alkaloids, phenols, saponins, tannins, steroids, flavonoids.

2. Material and methods

2.1 Materials, Drugs and chemicals

Plant extract (*M. barteri*), Diclofenac from Novartis Indian limited, Bangalore, carrageenan.

2.2 Plant material

The leaves of *Macaranga barteri* were collected from the savannah area of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt. The plant was authenticated by an expert taxonomist of the Department of Plant Science and Biotechnology, University of Port Harcourt, and a specimen representing this collection has been deposited in the University Herbarium, for further reference (accession number UPH/P/258).

2.3 Experimental Animals

Twenty (20) adult wistar albino rats of both sexes weighing between 120 and 140 gram were used for this study. They were purchased from the Biochemistry Animal House, University of Port Harcourt, Choba. They were also acclimatized at the Biochemistry Animal House, acclimatization of the rat was carried out for fourteen days given free access to feed and water. 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.

2.4 Preparation of Plant Extract

The plant (*M. barteri*) was harvested from the farm, washed and shade dried, it was dried for about 2 weeks. After drying, the plant was ground into smaller particles, it was then taken for extraction in order to get the juice of the plant.

The volume of deionized water required was measured using a measuring cylinder and introduced into a glass jar, then using a digital weighing balance, the number of grams equivalent of the plant was measured and introduced into the glass jar which contained the already measured volume of deionized water. the solution was homogenized using a glass rod to stir. The macerated mixture was then covered and left to stand for 24hrs, after which it was sieved using the no.1 watman filter paper (maceration extracts the nutrient and active ingredients from the dried plant). The filtrated extract was then dried in a crucible over a water bath at a moderate temperature, so as to evaporate the moisture content of the extract.

2.5 Preparation of carrageenan

1% of carrageenan was measured using a weighing balance and put into a beaker, 100ml of distilled water was introduced into the beaker and the mixture was homogenized using a glass rod, a clear solution was formed.

2.6 Preparation of the reference drug (diclofenac)

50mg of diclofenac was dissolved in 100ml of distilled water.

2.7 Acute Toxicity

Acute toxicity describes the adverse effects of a substance that result either from a single exposure or multiple exposures in a short period of time (usually less than 24 hours). To be described as acute toxicity, the adverse effects should occur 14 days of the administration of the substance. The median acute (LD₅₀) toxicity value of AEMb was determined in the rats using the limit test to 5000mg/kg b.w [12].

2.8 Experimental Design

Twenty (20) wistar albino rats were used, they were separated into 5 groups (each group having 4 rats). The rats were grouped and induced as follows:

- Group 1: This is the normal control which was fed with water
- Group 2: This is the negative control, it was induced with 1% carrageenan
- Group 3: This group was treated with 250mg/kg body weight *Macaranga barteri*, after 30 minutes the rats were induced with 1% carrageenan.
- Group 4: This group was treated with 500mg/kg body weight *M. barteri* after 30 minutes they were induced with 1% carrageenan.
- Group 5: This is the positive control, the rats were treated with reference drug (diclofenac), after 30 minutes they were induced with 1% carrageenan.

Paw edema thickness was measured using digital vainer caliper and the percentage (%) inhibition of edema is calculated using the formula % inhibition = $1 - \frac{T_t - T_o}{T_o} \times 100$ Where T_t is the thickness of paw of rats given test extract at corresponding time and T_o is the paw thickness of rats of control group at the same time

2.9 Mode of treatment and induction

The mode of induction of carrageenan for group 2 was done using a 2ml syringe, 1.2ml carrageenan was injected under the skin of the right paw (subplantal). For groups 3 and 4, they were first induced with the plant extract (0.5ml *M. barteri*) using a syringe through the mouth (oral treatment), after 30mins, 1.2ml carrageenan was injected under the skin of the right paw.

2.10 Statistical analysis

Data were expressed as mean value \pm standard error of mean (M \pm SEM). A statistical significance comparison between groups was accomplished using the SPSS. The mean of each group was compared using one way ANOVA, post hoc and least significant difference. Differences were considered significant at $P \leq 0.05$.

2.11 Phytochemical screening of the plant extract

The freshly prepared crude extract was qualitatively tested for the identification of chemical constituents such as; alkaloids, saponins, coumarins, steroids, tannins, flavonoids, protein, phenolic compounds, cardiac glycosides and anthraquinones.

2.12 Procedure for the determination of phenolic compound in the plant extract

0.5g of plant extract was stirred with distilled water and filtered. 2-3 drops of 1% neutral ferric chloride solution was added (obtained by adding dilute ammonia until precipitate begins to form, the precipitate is filtered). The appearance of violet color with ferric ion indicates the presence of phenolic compounds. This process is carried out in shindo's test.

2.13 Procedure for the quantitative phytochemical characterization of phenolic compounds in aqueous leaf of *M. barteri*

2.13.1 GC-MS Determination of Phytochemical Characterization

Prior to analysis, the MS was auto tuned to perfluorotributylamine (PFTBA) using already established criteria to check the abundance of m/z 69, 219, 502 and other instrument optimal and sensitivity conditions. Determination of the levels of phytochemicals in the sample was carried out using GC-MS by operating MSD in scan mode to ensure all levels of detection of the target constituents. Agilent 7820A gas chromatography coupled to 5975C inert mass spectrometer (with triple axis detector) with electron impact source was used. The stationary phase of separation of the compounds was HP-5 capillary column coated with 5% phenyl methyl siloxane (30m length \times 0.32mm diameter \times 0.25 μ m film thickness) (Agilent technologies). The carrier gas was helium used at constant flow of 1.4871mL/min at an initial

nominal pressure of 1.4902 psi and average velocity of 44.22cm/sec. 1 μ L of the samples were injected in splitless mode at an injection temperature of 3000c. Purge flow to split vent was 15 mL/min at 0.75, in with a total flow of 16.654 mL/min; gas saver mode was switched off. The mass spectrometer was operated in electron impact ionization mode at 70Ev with ion source temperature of 230^oc

3. Results

Table 1 The quantitative characterization of phenolic compounds in aqueous leaf extract of *M. barteri*

| Compound | Retention Time (min) | Concentration (ppm) |
|--------------------------|----------------------|---------------------|
| Phenol | 3.842 | Below calculation |
| 2-Chloro-phenol | 3.877 | Below calculation |
| O-cresol | 4.477 | Below calculation |
| 2-Nitro phenol | 5.278 | 3.29 ppm |
| 2,4-Dimethyl phenol | 5.467 | Below calculation |
| 2,4-Dichlorophenol | 0.000 | Not detected |
| 4-Chloro-3-methyl-phenol | 7.848 | 5.09 ppm |
| 2,4,6-Trichloro-phenol | 0.000 | Not detected |
| 4-Nitro-phenol | 0.000 | Not detected |
| Pentachloro-phenol | 0.000 | Not detected |

Table 1 shows that in phenolic compounds, 2-nitro phenol and 4-chloro-3-methyl-phenol were present in the concentration of 3.29 ppm and 5.09 ppm respectively, while some of the compounds were below calculation and some were not detected.

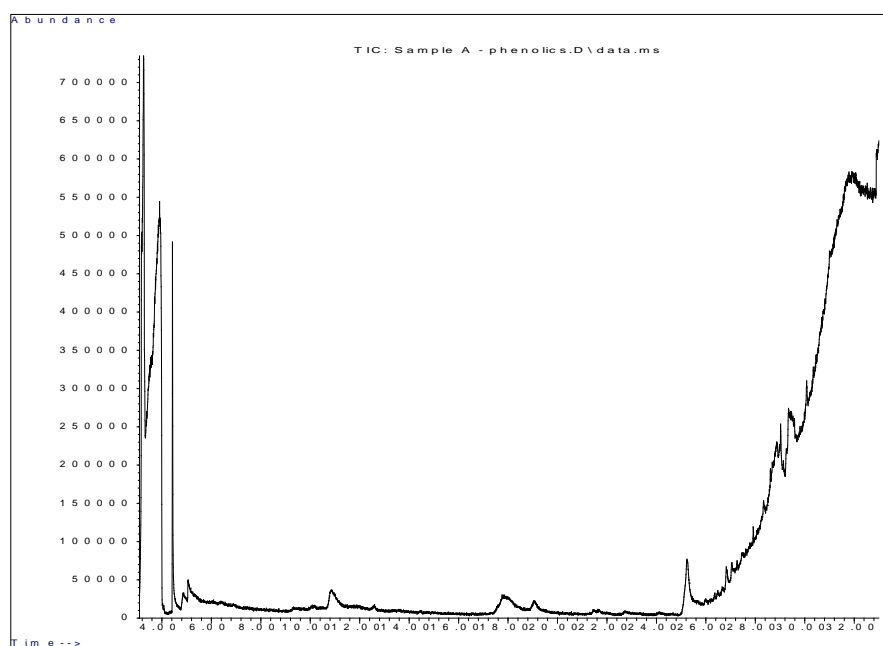


Figure 1 GCMS chromatogram of the characterization of phenolic compounds in aqueous extract of *Macaranga barteri*. Six peaks were detected with retention times of 5.278, and 7.848min appeared as 2-nitro phenol (3.29ppm) and 4-chloro-3-methyl-phenol (5.09ppm) respectively

Table 2 The effect of *Macaranga barteri* and Diclofenac on carrageenan induced paw edema over a period of 3 hours

| Groups | Treatment | Paw size after 1 hour (mm) | Paw size after 2 hours (mm) | Paw size after 3 hours (mm) | % inhibition of paw edema (%) |
|--------|---|----------------------------|-----------------------------|-----------------------------|-------------------------------|
| 1 | normal control | 4.37±0.11 ^d | 4.37 ± 0.11 ^d | 4.37 ± 0.11 ^d | - |
| 2 | Negative control (induced with + 1% carrageenan) | 8.00±0.14 ^a | 7.40 ± 0.30 ^a | 7.92 ± 0.13 ^a | - |
| 3 | 250mg/kg bw <i>Macaranga barteri</i> + 1% carrageenan | 7.36±0.44 ^a | 7.85 ± 0.20 ^a | 7.57± 0.17 ^a | 26.78 |
| 4 | 500mg/kg bw <i>Macaranga barteri</i> + 1% carrageenan | 7.32 ± 0.10 ^a | 7.30 ± 0.27 ^a | 6.69 ± 0.31 ^b | 46.92 |
| 5 | 50mg/kg bw Diclofenac + 1% carrageenan | 7.45 ± 0.28 ^a | 7.80 ± 0.21 ^a | 7.38 ± 0.30 ^a | 31.12 |

Values are reported as mean ± standard error of mean (M±SEM) (n =4). Values with different superscript letters indicate statistically significant differences ($p \leq 0.05$) down the column while those with similar superscripts letters show non-significant differences ($p \geq 0.05$) down the column when compared with the control and between groups. (a significant to control the rest significant to other groups).

3.1 Anti-inflammatory activity

Results shows a time dependent anti-inflammatory activity of leaf extract at varying dosage. A significant decrease in paw size of rats were observed in all treated groups after three hours (250 and 500mg/kg bw and diclofenac) when compared with the negative control. Also, result showed a dose dependent anti-inflammatory activity as a significant decrease in paw size was observed when comparing 500mg/kg with 250mg/kg bw treated groups after three hours. At dosage of 500mg/kg bw, a higher degree of effectiveness comparable to diclofenac was observed also after three hours.

Table 3 Effect of aqueous leaf extract of *Macaranga barteri* on selected hematological indices of carrageenan induced paw edema in wistar albino rats

| Group | Treatment | WBC (X10 ⁹ /L) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) | ESR (mm/hour) |
|-------|--|---------------------------|-----------------|-----------------|------------------------|-------------------------|---------------|------------------------|
| 1 | Normal control (water) | 12.98±4.27 | 37.00±1.22 | 51.25±1.22 | 6.00±1.08 | 5.00±0.00 ^b | 0.75±0.25 | 0.75±0.25 ^a |
| 2 | Control (-ve) 1% carrageenan | 10.88±2.71 | 40.75±6.64 | 55.00±6.94 | 2.75±1.11 ^a | 1.50±0.65 ^a | 0.00±0.00 | 3.00±1.91 ^b |
| 3 | 250mg/kg b.w <i>Macaranga barteri</i> + 1% carrageenan | 18.23±3.60 | 36.75±6.93 | 59.25±5.75 | 8.50±2.72 ^b | 2.25±0.95 ^a | 0.00±0.00 | 1.50±1.19 ^c |
| 4 | 500mg/kg b.w <i>Macaranga barteri</i> + 1% carrageenan | 15.11±5.83 | 29.00±4.14 | 61.75±3.28 | 3.75±1.49 ^c | 5.50±0.87 ^{bc} | 0.00±0.00 | 0.50±0.50 ^a |
| 5 | Diclofenac 50mg/kg b.w + 1% carrageenan | 11.88±1.47 | 32.50±8.77 | 58.25±7.60 | 4.75±0.48 | 2.50±0.65 ^c | 0.00±0.00 | 2.50±0.29 ^d |

Values are reported as mean ± standard error of mean (M±SEM) (n=4). The values with different superscript letters indicate statistical significant differences ($p \leq 0.05$) down the column, while those with similar superscripts show non-significant differences ($p \geq 0.05$) down the column when compared negative control and between groups.

Table 4 Effect of aqueous leaf extract of *Macaranga barteri* on selected biochemical parameters of carrageenan induced paw-edema in wistar rats

| Group | Treatment | C-Reactive Protein (Mg/L) | Interleukin-6 (Pg/MI) | Prostaglandin (Ng/MI) |
|-------|---|---------------------------|--------------------------|------------------------|
| 1 | Normal Control (Water Only) | 0.18±0.03 ^a | 3.11±0.44 ^a | 0.22±0.03 ^a |
| 2 | Control (1% Carrageenan) | 1.24±0.25 ^b | 8.73±2.35 ^b | 0.98±0.56 ^a |
| 3 | 250mg/Kg Bw <i>Macaranga barteri</i> + 1% Carrageenan | 2.13±1.14 ^b | 8.76±2.39 ^b | 1.15±0.23 ^b |
| 4 | 500mg/Kg Bw <i>Macaranga barteri</i> + 1% Carrageenan | 0.85±0.07 ^a | 11.26±4.55 ^c | 0.91±0.07 ^b |
| 5 | 50mg/Kg Bw Diclofenac + 1% Carrageenan | 1.01±0.83 ^b | 27.60±16.01 ^d | 1.46±0.10 ^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 when compared with the control and between groups.

4. Discussion

Inflammatory diseases, are a major healthcare problem worldwide and majority of human population is affected by inflammation-related disorders. Though there are several agents are accessible to treat multiple inflammatory diseases, their prolonged use leads to serious adverse effects [13]. Toxicity and recurrence of symptoms that occurs on discontinuation of the use of currently available synthetic drugs is a major problem [14]. The development of safer plant based anti-inflammatory agent's remains to be a subject of great interest [15].

Phenolic compounds detected were 2-nitro phenol (3.29 ppm) and 4-chloro-3-methyl-phenol (5.09 ppm) in Table 1. Some phenolic compounds have exhibited anti-inflammatory properties and there is a correlation between the high intake of food rich in phenolic compounds and a down regulation of the inflammatory response [16]. Anti-inflammatory activity of phenolic compounds include inhibition of the synthesis of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activated immune cells, or inhibition of nitric oxide synthase and xyclooxygenase-2 via its inhibitory effects on nuclear factor NF- κ B [16, 17, 18].

Result from Table 2 showed significant increase in carrageenan-induced oedema in rat paws when group 2 was compared with group 1 in all the hours of investigation signifying induction of oedema in rat paws. Significant reduction in carrageenan-induced oedema in rat paws was observed when rats in group 4 was compared with group 2 three hours after carrageenan administration with percentage carrageenan-induced oedema inhibition of 46.91. The extract at 500mg/kgbw exhibited higher percentage carrageenan-induced oedema inhibition than group five- diclophenac treated group. The edema developed by carrageenan is represented as biphasic curve [19]. The first phase of carrageenan-induced inflammation is partly assigned to the injection trauma and released of acute phase mediators especially the serotonin and histamine [20]. Prostaglandins are the main players for the occurrence of second phase of carrageenan-induced inflammation, which occurs around 3 hr after carrageenan injection [21]. This result suggest that aqueous leaf extract of *Macaranga barteri* act in the second phase of edema development indicating that *Macaranga barteri* possessed inhibitory effects against acute inflammation.

Assessment of hematological parameters is needed for the determination of the degree of harmful effects of xenobiotics on the blood. It is used to explain the hematological functions of secondary metabolites obtained from plant extracts in experimental animal mode.

Mean ESR values of rats in groups 2, 3 and 5 significantly increased and that of group 4 none significantly reduced when compared to control indicating restoration of ESR value at 500mg/kg.b.wt. Treatment (group 4) in Table 3.

Inflammatory markers include C reactive protein (CRP), erythrocyte sedimentation rate(ESR), plasma viscosity, fibrinogen, ferritin, and several other acute phase proteins, though only the first three are commonly referred to as inflammatory markers [22].

Non-significant differences were observed in mean WBC, neutrophil and lymphocyte counts when compared to control while significant reduction of mean eosinophil counts in groups 2 and 3 and non-significant increase in group 4 were observed when compared to control signifying restoration of eosinophil count at 500mg/kgb.wt. Treatment. Eosinophils play two roles which include destroying foreign substances and regulating inflammation [23]. A lower-than normal eosinophil count may be due to: Alcohol intoxication; Overproduction of certain steroids in the body (such as cortisol) [24].

Table 4 revealed significant increase in mean CRP concentration in rats was observed when group 2 was compared to control group and a significant reduction in group 4 treated with 500mg/kgb.wt. When compared to group 2 though the reduction didn't revert to normal control value probably due to the dosage of the extract.

C-reactive protein (CRP) is a nonspecific inflammatory marker which has been studied extensively in cardiovascular diseases and CRP itself mediate the athero-thrombosis [25, 26, 27].

Mean concentration of IL-6 significantly increased in all the groups when compared to control. Stimulation of hepatocytes by IL-6 leads to initiation of the acute phase response and release of acute phase proteins, including C-reactive protein (CRP), serum amyloid A, haptoglobin, ferritin, and fibrinogen [28]. Elevated levels of acute phase proteins are the hallmark of inflammation and are routinely measured when monitoring inflammation in clinical practice [29]. IL 6 is the principal driver of the acute phase response in the pathogenesis of rheumatoid arthritis (RA), as evidenced by neutralization of IL-6 by the anti-IL-6R antibody tocilizumab, which led to the normalization of CRP [30].

Significant increase in mean prostaglandin level in rat in all the groups when compared to control was observed. Several studies conducted to evaluate the role of PGE2 in acute inflammation model revealed that elevated levels of PGE2 is responsible for increase in paw volume [31, 32, 33] indicating that COX-2 and COX-2 mediated PGE2 production plays significant role in inflammation.

However a non-significant reduction in group 4 treated with 500mg/kgb.wt of the extract was observed when compared to group 2 indicating mild reduction of prostaglandin concentration probably due to dosage level.

Bioactive phytochemicals exhibit potential anti-inflammatory activities by interaction with certain components of the inflammatory pathways like the proinflammatory mediator production, complement cascade activation, and leukocyte migration, matrix-degrading enzymes, proinflammatory cytokines, and the components of signaling pathways as well as regulation of pro-inflammatory substance gene expression [34, 35, 36, 37].

Many scientific studies on plant species which has been used as folk medicine against inflammation have established the recognition of natural products as potential anti-inflammatory drugs [38]. The anti-inflammatory effects of phytoconstituents are exerted through their action on key regulatory molecules, including cyclooxygenase (COX), inducible nitric oxide synthase (iNOS), and cytokines) [39, 40].

5. Conclusion

Aqueous leaf extract of *Macaranga barteri* act in the second phase of edema development indicating that 500mg/kgb.wt *Macaranga barteri* possess inhibitory effects against acute inflammation.

Compliance with ethical standards

Acknowledgments

This research was carried out by the authors, with equal contribution.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Disclosure of conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/publication of this article.

Statement of ethical approval

The Department of Biochemistry Research Ethics Committee approved the ethical application of the research proposal titled “Anti-inflammatory, anti-pyretic and analgesic effect of aqueous leave extract of *Macaranga barteri* on biochemical and haematological parameters of Wistar rats” on the 11th of March 2022, with ref no. UPH/BCHREC/2022/007.

References

- [1] Sosa, S., Balick, J., Arvigo, R. Screening of the topical anti-inflammatory activity of some Central American plants. *Journal of Ethnopharmacology*. 2002; 81(2): 211-215.
- [2] Mahat, A., Patil, M. Evaluation of anti-inflammatory activity of methanol extract of *Phyllanthus amarus* in experimental animal models. *Indian Journal of Pharmaceutical Sciences*. 2007; 69(1): 33-36.
- [3] Rousin, A., Le Cabec, V., Lonchampt, M., De Nadai, J., Canet, E., Maridonneau Parini, I. Neutrophil associated inflammatory responses in rats are inhibited by phenylarsine oxide. *Eur. J. Pharmacol.* 1997; 322: 91-96.
- [4] Ferrero-millan, L., Nielsen, O., Andersen, P., Girardin, S. Chronic inflammation: Importance of NOD2 and NALP3 in interleukin-1 beta generation. *Clin. Exp. Immunol.* 2007; 147(2): 227-235.
- [5] Arfan, M., Amin, H., Khan, N., Khan, I., Saeed, M., Khan, A., Fazal-ur-Rehman, G. Analgesic and anti-inflammatory activities of 11-O-galloyl-bergenin. *J. Ethnopharmacol.* 2010; 131: 502-4.
- [6] Ong, K., Lirk, P., Tan, H., Seymour, A. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res.* 2007; 5: 19-34.
- [7] Sun, X., Lee, Y., Bertram, T., Goldstein, L. Withdrawal of COX-2 selective inhibitors rofecoxib and valdecoxib: impact on NSAID and gastroprotective drug prescribing and utilization. *Curr Med Res Opin.* (2007); 23: 1859-66.
- [8] Operations Management Suite (OMS) (2002). Promotion du rôle de la médecine traditionnelle dans le système de santé: stratégie de la région africaine. *AFR/RC50/9*, pp. 12-15.
- [9] Shrestha, M and Dhillion, S. Medicinal plant diversity and use in the highlands of Dolakha district, Nepal. *J. Ethnopharmacol.* 2003; 86(1): 81-96.
- [10] Decker, A., Welch B. Role of ferritin as a lipid oxidation catalyst in muscle food. *J. Agric. Food Chem.* 2010; 38: 674-677.
- [11] Sarika, Amdeka., Purabi, Roy., Vinod, Singh., Avnish, Kumar., Rambir, Singh., Poonam, Sharma. Anti-inflammatory activity of lactobacillus on carrageenan induced paw edema in male wistar rats. *International Journal of Inflammation*. 2012; volume 2012.
- [12] Herve, E., Bernard, G., Landre, K., Paul, Y., Ettienne, E. Acute toxicity and gastric anti-ulcer activity of an aqueous extract of the leaves of *Macaranga barteri* Mull. Arg. (Euphorbiaceae) on rat models. *J Med Plants Res.* 2018; 12(9): 96-105.
- [13] Divya, T., Latha, P., Usha, K., Anuja, G., Suja, S., Shyamal, S., Shine, V., Sini, S., Shikha, P., Rajasekharan, S. Anti-inflammatory, analgesic and anti-lipid peroxidative properties of *Wattakaka volubilis* (Linn. f.) Stapf. *Indian J. Nat. Prod. Resour.* 2009; 8: 137-141.
- [14] Jo, W.S., Yang, K.M., Choi, Y.J., Jeong, C.H., Ahn, K.J., Nam, B.H., Lee, S.W., Seo, S.Y., Jeong, M.H. In-vitro and in-vivo anti-inflammatory effects of pegmatite. *Mol. Cell. Toxicol.* 2010; 6: 195-202. [CrossRef]
- [15] Gorzalczy, S., López, P., Acevedo, C., Ferraro, G. Anti-inflammatory effect of *Lithrea molleoides* extracts and isolated active compounds. *J. Ethnopharmacol.* 2011; 133: 994-998. [CrossRef]
- [16] Alarcón de la Lastra, C., & Villegas, I. Resveratrol as an anti-inflammatory and anti-aging agent: Mechanisms and clinical implications. *Molecular Nutrition & Food Research*. 2005; 49: 405-430.
- [17] Chuang, C. C., & McIntosh, M. K. Potential mechanisms by which polyphenol-rich grapes prevent obesity mediated inflammation and metabolic diseases. *Annual Review of Nutrition*. 2011; 31: 155-176.
- [18] Emerit, J., Edeas, M., & Bricaire, F. Neurodegenerative diseases and oxidative stress. *Biomedicine & Pharmacotherapy*. 2004; 58: 39-46.
- [19] Winter, C.A., Risley, E.A., Nuss, G.W. Carrageenin-Induced Edema in Hind Paw of the Rat as an Assay for Anti-inflammatory Drugs. *Exp. Boil. Med.* 1962; 111: 544-547. [CrossRef]

- [20] Perianayagam, J.B., Sharma, S., Pillai, K. Anti-inflammatory activity of *Trichodesma indicum* root extract in experimental animals. *J. Ethnopharmacol.* 2006; 104: 410-414. [CrossRef]
- [21] Patil, K.R., Patil, C.R. Anti-inflammatory activity of bartogenic acid containing fraction of fruits of *Barringtonia racemosa* Roxb. in acute and chronic animal models of inflammation. *J. Tradit. Complementary Med.* 2017; 7: 86-93. [CrossRef]
- [22] Jessica, Watson., Alison, Round., William, Hamilton. Raised inflammatory markers. *BMJ.* 2012; 344: 454.
- [23] Arika, W.M., Nyamai, D.W., Musila, M.N., Ngugi, M.P., Njagi, E.N. Hematological Markers of In Vivo Toxicity. *J Hematol Thrombo Dis.* 2016; 4: 236. doi:10.4172/2329-8790.1000236
- [24] Wintrobe, M.M., Greer, J.P. (2009) *Wintrobes Clinical Hematology.* Lippincott Williams & Wilkins, Philadelphia.
- [25] Wang, J., Tan, G.J., Han, L.N., Bai, Y.Y., He, M., Liu, H.B. Novel biomarkers for cardiovascular risk prediction. *J. Geriatr. Cardiol. JGC.* 2017; 14: 135. [CrossRef]
- [26] Bassuk, S.S., Rifai, N., Ridker, P.M. High-sensitivity C-reactive protein: Clinical importance. *Curr. Probl. Cardiol.* 2004; 29: 439-493.
- [27] Devaraj, S., Xu, D.Y., Jialal, I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: Implications for the metabolic syndrome and atherothrombosis. *Circulation.* 2003; 107: 398-404. [CrossRef]
- [28] Gabay, C., Kushner, I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med.* 1999; 340(6): 448-454.
- [29] Pincus, T., Sokka, T. Laboratory tests to assess patients with rheumatoid arthritis: advantages and limitations. *Rheum Dis Clin North Am.* 2009; 35(4): 731-734, vi-vii.
- [30] Genovese, M.C., McKay, J.D., Nasonov, E.L. Interleukin-6 receptorinhibition with tocilizumab reduces disease activity inrheumatoid arthritis with inadequate response to diseasemodifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 2008; 58(10): 2968-2980.
- [31] Mancini, J. A., Blood, K., Guay, J., Gordon, R., Claveau, D., Chan, C.C. Cloning, expression, and up-regulation of inducible rat prostaglandin E synthase during lipopolysaccharide-induced pyresis and adjuvant-induced arthritis. *J. Biol. Chem.* 2001; 276: 4469-4475. doi: 10.1074/jbc.M006865200
- [32] Nakatani, Y., Hokonohara, Y., Kakuta, S., Sudo, K., Iwakura, Y., Kudo, I. Knockout mice lacking cPGES/p23, a constitutively expressed PGE 2 synthetic enzyme, are peri-natally lethal. *Biochem. Biophys. Res. Commun.* 2007; 362: 387-392. doi: 10.1016/j.bbrc.2007.07.180
- [33] Guruprasad, B., Chaudhary, P., Choedon, T., and Kumar, V. L. Artesunate ameliorates functional limitations in Freund's complete adjuvant-induced monoarthritis in rat by maintaining oxidative homeostasis and inhibiting COX-2 expression. *Inflammation.* 2015; 38: 1028-1035. doi: 10.1007/s10753-014-0067-z
- [34] Kulkarni, R.G., Achaiah, G., Sastry, G.N. Novel targets for anti-inflammatory and antiarthritic agents. *Curr. Pharm. Des.* 2006; 12: 2437-2454. [CrossRef]
- [35] Calixto, J.B., Otuki, M.F., Santos, A.S. Anti-Inflammatory Compounds of Plant Origin. Part I. Action on Arachidonic Acid Pathway, Nitric Oxide and Nuclear Factor κ B (NF- κ B). *Planta Med.* 2003; 69: 973-983.
- [36] Safayhi, H., Sailer, E.R. Anti-Inflammatory Actions of Pentacyclic Triterpenes. *Planta Med.* 1997; 63: 487-493. [CrossRef]
- [37] Okoli, C.O., Akah, P.A. Mechanisms of the anti-inflammatory activity of the leaf extracts of *Culcasia scandens* P. Beauv (Araceae). *Pharmacol. Biochem. Behav.* 2004; 79: 473-481. [CrossRef]
- [38] Nagori, K., Singh, M.K., Dewangan, D., Verma, V., Tripathi, D. Anti-inflammatory activity and chemo profile of plants used in traditional medicine: A review. *J. Chem. Pharm. Res.* 2010; 2: 122-130.
- [39] De Oliveira, R.G., Mahon, C.N., Ascêncio, P.G.M., Ascêncio, S.D., Balogun, S.O., Martins, D.O. Evaluation of anti-inflammatory activity of hydroethanolic extract of *Dilodendron bipinnatum* Radlk. *J. Ethnopharmacol.* 2014; 155: 387-395. [CrossRef]
- [40] Bellik, Y., Boukraa, L., Alzahrani, H.A., Bakhotmah, B.A., Abdellah, F., Hammoudi, S.M., Iguer-Ouada, M. Molecular Mechanism Underlying Anti-Inflammatory and Anti-Allergic Activities of Phytochemicals: An Update. *Molecules.* 2012; 18: 322-353. [CrossRef]