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Phenolic acids in some under-utilized medicinal and leafy vegetables, their anti-inflammatory and wound healing activities

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ABSTRACT

The present study aimed to investigate anti-inflammatory and wound healing potentials of *Launea taraxacifolia, Solanecio biafrae, Basella alba, Gnetum africanum, Solanum macrocarpon*, and *Crassocephalum rubens*, which are traditionally used as food and ethnomedicinally for alleviating body pains, arthritis, wounds, and fever in Africa. Bioactivity assays were conducted using ethanol and water extracts, as well as partitioned fractions from crude ethanol extracts. *In vitro* anti-inflammatory activity was evaluated by inhibiting 15-lipoxygenase (LOX), xanthine oxidase (XO), and nitric oxide (NO) scavenging. *In vivo* assessments included the carrageenan-induced paw edema model, abdominal constriction test with p-benzoquinone, Freund's Complete Adjuvant (FCA) pyrexia induction, and excision and incision wound models in mice to evaluate anti-inflammatory, antinociceptive, antipyretic, and wound healing activities, respectively. Additionally, HPLC fingerprinting and phenolic compound quantification were performed. Among the plants studied, *Crassocephalum rubens* and *S. biafrae* exhibited the most significant 15-LOX and XO inhibition, NO scavenging, *in vivo* anti-inflammatory, antinociceptive, antipyretic, and wound healing effects. HPLC analysis identified chlorogenic, caffeic, and *p*-coumaric acids, resveratrol, and rutin, which showed significant NO scavenging and XO inhibitory activities, suggesting these compounds may contribute to the anti-inflammatory effects of these plants. These findings support the ethnomedicinal use of *C. rubens* and *S. biafrae* for treating arthritis and wounds.
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1. Introduction

Inflammation is an essential host defense mechanism of the body against external stimuli such as injuries or infections caused by pathogens. However, chronic inflammation adversely affects critical cells and organs, contributing to the development of various diseases, including diabetes, inflammatory bowel disease, neurological disorders, skeletal muscle conditions, cardiovascular diseases, and cancer, all of which can accelerate the aging process (Gandhi et al., 2022). Cyclooxygenases (COXs), lipoxygenases (LOXs), and nitric oxide synthases (NOS) are key enzymes involved in the inflammatory pathway. Cellular damage results in the release of arachidonic acid, leading to the production of leukotrienes and prostaglandins, which act as stimulators of inflammatory conditions such as arthritis, fever, chronic pain, asthma, and burn injuries (Shrivastava et al., 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for pain and inflammatory conditions, including rheumatoid arthritis and osteoporosis. However, these conventional treatments are associated with side effects, particularly gastrointestinal and central nervous system disorders (Abdel-Tawab et al., 2009). Recent research has therefore focused on identifying anti-inflammatory agents that can inhibit the release of prostaglandins and leukotrienes via both COX and LOX pathways, aiming to develop safer alternatives to NSAIDs (Shrivastava et al., 2017). Additionally, the exploration of medicinal herbs and dietary plants traditionally used to treat fever, pain, and arthritis has emerged as a logical strategy for discovering novel and safer anti-inflammatory drugs (Conforti et al., 2009).

In recent years, food science has increasingly integrated clinical research to better understand the health benefits of food, including the identification of bioactive phytochemicals responsible for these effects (Kumar et al., 2023). Pharmaceutical and nutritional sciences are likewise investigating food plants for their wide range of health benefits and potential clinical applications (Ramalingum and

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Mahomoodally, 2014). Several under-utilized vegetables with ethnopharmacological uses were evaluated in this study for their potential anti-inflammatory and wound healing activities. These include *Basella alba* L. (BA), *Gnetum africanum* Welw. (GA), and *Solanum macrocarpon* Linn. (SM) from the Basellaceae, Gnetaceae, and Solanaceae families, respectively. Additionally, *Crassocephalum rubens* (Juss. Ex Jacq.) S. Moore (CR), *Launea taraxacifolia* (Willd.) Amin ex C.Jeffrey (LT), and *Solanecio biafrae* (Oliv. & Hiern) C.Jeffrey (SB) from the Asteraceae family were also assessed.

Traditionally, *B. alba* is used to treat fever, ulcers, as a laxative, and to relieve labor pain (Kumar et al., 2022). *Crassocephalum rubens* is employed in some African regions for the treatment of wounds, burns, diabetes, breast cancer, epilepsy, and leprosy (Adjatin et al., 2012). *Gnetum africanum* is utilized for conditions like sore throat, boils, nausea, and childbirth pain (Coker et al., 2021). *Launea taraxacifolia* is traditionally used for rheumatism, fever, malaria, diabetes, ulcers, skin diseases, and hypertension (Adinortey et al., 2018). *Solanecio biafrae* is applied to treat rheumatism, diabetes, wounds, piles, and hypertension (Ayoola et al., 2019), while *S. macrocarpon* is used for skin diseases, constipation, ulcers, toothache, asthma, rheumatism, and sores (Oluwagunwa et al., 2019). Despite their ethnopharmacological significance, these medicinal herbs and leafy vegetables are considered under-utilized by many African researchers due to challenges related to their propagation and availability (Dansi et al., 2012; Oseni and Olawoye, 2015; Bello et al., 2018; Osafo, 2021).

There is a significant gap in research regarding the anti-inflammatory potential of these leafy vegetables and medicinal herbs. Consequently, this study aimed to evaluate the anti-inflammatory and wound healing activities of these plants using both *in vivo* and *in vitro* experimental models.

Inhibition of 15-LOX is considered a therapeutic approach for inflammatory diseases, as it can reduce leukotriene production, which mediates inflammatory and allergic reactions (Gandhi et al., 2022). Additionally, XO inhibitors are recognized as vital in treating gout arthritis, which is characterized by inflammation. NO production inhibitors also play a crucial role in mitigating inflammation due to the pro-inflammatory effects of NO. In this study, the 15-LOX and xanthine oxidase (XO) inhibitory activities, as well as NO scavenging activities of the selected plant extracts, were first assessed *in vitro* to establish their anti-inflammatory potential. Subsequently, the *in vivo* anti-inflammatory, analgesic, antipyretic, and wound healing activities of these extracts were evaluated using various animal models, including the carrageenan-induced paw edema model, the abdominal constriction test (p-benzoquinone), pyrexia induction by Freund's Complete Adjuvant (FCA), and excision and incision wound models in mice.

2. Materials and methods

2.1. Plant materials

Leaves of *Launea taraxacifolia* (herbarium number FHI 113627), *Crassocephalum rubens* (herbarium number FHI 113720), *Solanecio biafrae* (herbarium number FHI 113776) and *Basella alba* (herbarium number FHI 113741) were collected from the forest center of the International Institute of Tropical Agriculture (Ibadan, Nigeria), while samples of *Solanum macrocarpon* (herbarium number FHI 113641) and *Gnetum africanum* (herbarium number FHI 113862) were purchased from the local markets in July, 2021, in Oyo and Calabar, Nigeria, respectively. The plants were identified by Prof. Omokafe Ugbogu and authenticated at Forest Herbarium Ibadan (FHI). The samples were dried with a lyophilizer, ground to powder, and then stored in airtight containers until their use.

2.2. Extraction and fractionation

The powdered samples of each plant were macerated separately in 96% ethanol or distilled water for 72 h, filtered, and concentrated *in vacuo*. The ethanol extracts were later dissolved in methanol: water (9:1), then partitioned with aliquots of *n*-hexane to give *n*-hexane fraction (NHF). The aqueous fraction was partitioned with aliquots of dichloromethane, ethyl acetate, and *n*-butanol, resulting into dichloromethane fraction (DCMF), ethyl acetate fraction (EAF), *n*-butanol fraction (NBF), and aqueous methanol fraction (AQF).

2.3. In vitro *biological assays*

2.3.1. 15-LOX inhibition assay

In a 96-well microplate, 10 μL of each sample (plant extract, reference inhibitor or negative control) was added and 60 μL buffer (50 mM Tris HCl buffer, pH 7.4) followed by the addition of 20 μL LOX from *Glycine max* (500 U/mL stock concentration) prepared in buffer, and incubated at 25 °C for 5 min, following the method of Chung et al. (2009) with slight modifications. The reaction was initiated by the addition of linoleic acid (10 μL, 12.5 mM stock concentration) dissolved in Tween 20 and buffer, afterwards the reaction was incubated in the dark at 25 °C for 20 min. Ferrous oxidation−xylenol orange (FOX) reagent (100 μL) prepared just before use, which comprises of sulfuric acid (3 M), xylenol orange (10 mM), ammonium iron (II) sulfate (10 mM), water: methanol (9:1) was used to terminate the assay. The reaction was incubated in the dark for 30 min at 25 °C, before measuring at 560 nm using a microplate reader (SpectraMax® ABS Plus, Molecular Devices, USA). For the negative control wells, 10 μL of DMSO was used in place of samples, while baicalein was used as the positive control. Blanks were prepared for both negative control and all samples. LOX was present in blank wells during incubation, but the substrate (linoleic acid) was added after FOX reagent, before measurement. 15-LOX inhibition (%) was calculated from inhibition of hydroperoxide production from the changes in absorbance values at 560 nm using the following formula:

$$\text{Inhibition } \% = \frac{(Acontrol - Ablank) - (Asample - Ablank)}{(Acontrol - Ablank)} \times 100$$

Where $A_{control}$ is the absorbance of control well, A_{blank} is the absorbance of blank well and A_{sample} is the absorbance of sample well.

2.3.2. Xanthine oxidase (XO) inhibition assay

The assay was performed following the method described by Kekilli et al. (2021). In a 96-well plate, 10 μL samples or allopurinol (reference drug) or DMSO (negative control) were mixed with 150 μL phosphate buffer (0.1 M, pH 7.5), and 20 μL XO enzyme from bovine milk (0.003 units/well) was added and incubated for 10 min. The substrate, xanthine (20 μL, 0.1 mM), was added and the change in absorbance was measured at 295 nm for 10 min using a microplate reader (SpectraMax® ABS Plus, Molecular Devices, USA). XO inhibition (%) of the samples from three parallel experiments was calculated using following formula;

$$Inhibition\ \% = \frac{Acontrol - Asample}{Acontrol} \times 100$$

Where $A_{control}$ is the absorbance of the control solution, and A_{sample} is the absorbance of the sample solution.

2.3.3. NO scavenging activity

The method described by Deniz et al. (2021) was used to determine the NO scavenging activity of the extracts. Briefly, in a 96 well plate, 10 mM sodium nitroprusside was added to the sample and reference (ascorbic acid) prepared at different concentrations and incubated for 2 h 30 min at room temperature under light. After incubation, 120 μL Griess reagent (1% sulfanilamide in 5% H_3PO_4, and

0.1% naphthyl ethylenediamine dihydrochloride) was added to the well and the absorbance was measured at 577 nm using a microplate reader (SpectraMax® ABS Plus, Molecular Devices, USA). Percentage inhibition was calculated for triplicate parallel experiments according to the same formula for XO inhibition percentage given above.

2.4. In vivo *assays*

2.4.1. *Animals*

Male Swiss albino mice (20 - 25 g) were bought from the animal breeding laboratory of NESA (Ankara, Türkiye). The animals were acclimatized for 2 days to animal room conditions and fed with standard pellet diet and water *ad libitum*. The animals were starved for 24 h before the experiment, but were allowed to drink water. For the anti-inflammatory and antinociceptive activity experiments, a minimum of seven animals were utilised per group, whereas for the wound healing experiments, fifteen groups of mice were employed, with each group comprising six mice. The NESA Experimental Animals Ethical Council Project Number: 007 permitted the study and was performed according to the established European ethical standards for the care of laboratory animals.

2.4.2. *Test samples preparation*

For anti-inflammatory and antinociceptive assays, extracts were suspended with 0.5% sodium carboxymethylcellulose (CMC) in distilled water and were given at 250 and 500 mg/kg doses. Both the animals in the control and test groups were kept in same conditions, but dosing vehicle was used in place of the drug treatment in the control group. Reference drugs used were indomethacin (10 mg/kg) and acetylsalicylic acid (200 mg/kg) in 0.5% CMC. For wound healing experiments, extracts were mixed with glycol stearate:1,2-propylene glycol:liquid paraffin (3:6:1) in 1% concentration. The animals in the reference drug group were topically treated with nitrofurazone (0.2%) ointment. The test material groups received 5% w/w extract ointments, while the animals in the vehicle group were treated with simple ointment. The animals in the negative control group were left untreated.

2.4.3. *Anti-inflammatory assay*

2.4.3.1. Carrageenan-induced edema anti-inflammatory assay. Firstly, the plant extracts or dosing vehicle were administered. To induce inflammation, carrageenan suspension (0.5 mg/25 μL) was prepared in physiological saline (154 nM NaCl) and injected into the subplantar tissue of the right hind paw of each mouse, after 1 h. Saline solutions (25 μL) were injected into that of the left hind paw as control, while indomethacin (10 mg/kg) was used as the reference drug. Paw edema was measured at an interval of 90 min for 6 h. Gauge caliper (Ozaki Co., Tokyo, Japan) was used to measure the difference in footpad thickness. For the determination of acute toxicity, morbidity or mortality was recorded for all animal groups during 48 h observation period (Yeşilada & Küpeli, 2002).

2.4.4. *Antinociceptive assay*

2.4.4.1. p-benzoquinone-induced abdominal constriction test. The method described by Küpeli et al. (2003) was used to perform the assay. Briefly, test samples were administered orally and after 1 h, the mice were intraperitoneally injected with 0.1 mL/10 g body weight (b.w.) of 2.5 % (w/v) *p*-benzoquinone (PBQ) solution in distilled H_2O. Control animals were given an appropriate volume of dosing vehicles and reference drug used was acetylsalicylic acid (200 mg/kg). The mice were observed separately for the total number of abdominal contractions or writhing movements, which was counted for the next 15 min, starting from 5th min after the PBQ injection. The data were presented as the average of total number of the writhes observed. The antinociceptive activity was expressed as a percentage change from the writhing controls. At the end of the experiment, mice were slaughtered under deep ether anesthesia and the stomach of each mouse was removed, opened and examined for lesions or bleeding to determine the gastric-ulcerogenic effect.

2.4.5. *Antipyretic assay*

2.4.5.1. Freund's complete adjuvant (FCA)-induced antipyretic assay. Antipyretic activity was determined following the method of Yeşilada and Küpeli (2002). Freund's Complete Adjuvant (FCA) 2.5 μL/25 g b.w. was injected into the dorsal part of each mouse, after 1 h the rectal temperature of each mouse was measured with a digital thermometer (Prima long) and recorded. Plant extracts, reference drug (acetylsalicylic acid), or 0.5% CMC solution was administered orally after 24 h of FCA injection, and 1 h later rectal temperatures were measured. This procedure was repeated for the following 7 days, *i.e.,* 1 h after the daily administration of plant extracts, reference drug or CMC solution and rectal temperatures were measured.

2.4.6. *Wound healing assay*

2.4.6.1. Circular excision wound model. The mice were anaesthetized with intraperitoneal 0.05 mL Xylazine (2% Alfazine®) and 0.15 mL ketamine (10% Ketasol®) (Küpeli Akkol et al., 2022). The dorsal fur of the animals was shaved with a shaving machine before wound area preparation. A circular excision wound of 314 mm^2 was created on the dorsothoracic area. According to the groups, extracts, reference drug and vehicle ointments were applied daily to the wound area until the wound in the test groups completely healed. The wound area was measured every 2 days using a transparent sheet and a permanent marker. The wound healing activities of the extracts were assessed by measuring the period of epithelialization and the percentage of wound contraction.

2.4.6.2. Linear incision wound model. Experiment was performed following the method of (Rawat and Gupta, 2011). Briefly, a 3 cm linear-par vertebral incision was made through the full thickness of the skin on both sides of the vertebral column, one centimeter away from the midline. The skin was stitched together using black braided silk and a curved needle at 1 cm intervals. The ointments were applied according to the grouping and dosing instructions. The treatments were applied topically once a day for nine consecutive days. On the 8th day, the suture was removed, and on the 10th day, the tensile strength of the skin was measured to determine the extent of healing. The skin's breaking point was measured using the continuous water flow technique, which calculates the amount of water in grams required to break it. Tensile strength was then calculated.

2.5. *Quantification of phenolics and flavonoids using HPLC-DAD*

2.5.1. *Sample preparation for HPLC analysis*

For quantitative determination of the phenolic compounds, 5 mg/mL of each plant extract was dissolved in 50% acetonitrile (ACN) and filtered through a 0.20 μm cellulose acetate membrane filter prior to the analysis. A total of 17 samples consisting of ethanol extracts and ethyl acetate fractions of all six plants in addition to *n*-butanol fraction of SM as well as water extracts of CR, LT, SB, and SM, were analyzed in duplicate using HPLC. Selected phenolic acid standards were dissolved in 25% ACN, while standards of chosen flavonoids were dissolved in 50% ACN, in total, 23 standards were analyzed. For the calibration curve, peak areas were plotted against five concentrations of the standards (1, 10, 25, 100, and 200 ppm).

2.5.2. HPLC method

Phenolic and flavonoid compounds were determined and quantified by reverse phase HPLC on ACE 5 (150 × 4.6 mm, 5 μm, 25 °C) C18 column following the method described by Ekin et al. (2019). The mobile phase system contained 0.1% formic acid (FA) in acetonitrile 80% (solvent A) and 0.1% FA in H_2O (solvent B). Gradient system was set as follows: from 5% A to 15% A with 0.8 mL/min flow rate for 10 min, 15% A with flow rate from 0.8 to 0.6 mL/min for 5 min; 15% A with 0.6 mL/min flow for 2 min; from 15% to 20% A with 0.8 mL/min flow for 5 min, from 20% to 30% A with 0.8 mL/min flow for 4 min, from 30% to 100% A with 0.8 mL/min flow for 8 min, 100% A at 1 mL/min flow for 3 min, and returned to initial conditions within 5 min. 20 μL samples was injected. The detection wavelengths used were 260, 280, 320, and 350 nm.

2.6. Statistical analysis

Results are expressed as the mean ± standard deviation (SD). IC_{50} values were calculated from linear regression analysis using GraphPad prism 5.0. Statistical differences were evaluated by ANOVA and Students-Newman-Keuls *post-hoc* tests. $p<0.05$ was considered to be significant [* $p<0.05$; ** $p<0.01$; *** $p<0.001$].

3. Results

3.1. In vitro studies

3.1.1. 15-LOX inhibitory activity

Percentage inhibition of 15-LOX varied widely across the plant extracts ranging from 5.97% to 90.97% (Table 1). The highest inhibitory activity was caused by ethanol extract of *C. rubens* (CREE, 90.97.0%, IC_{50}: 41.66 ± 6.59 μg/mL), water extract of *C. rubens* (CRWE, 72.67%, IC_{50}: 53.81 ± 1.25 μg/mL) and *B. alba* ethanol extract (BAEE, 66.35%, IC_{50}: 54.55 ± 6.22 μg/mL), whose activities as depicted by their IC_{50} values were not significantly different from each other. Other fractions with good and significant activity are *n*-hexane fraction of *G. africanum* (GANHF, 87.13%, IC_{50}: 74.58 ± 9.69 μg/mL) and that of *C. rubens* (CRNHF, 70.92%, IC_{50}**:** 83.20 ± 8.39 μg/mL), ethanol extract of *S. biafrae* (SBEE, 67.68%, IC_{50}: 96.61 ± 10.70 μg/mL) and ethyl acetate fraction of *S. biafrae* (SBEAF, 64.08%, IC_{50}: 88.55 ± 5.54 μg/mL). The reference, *i.e.,* baicalein, displayed 85.49% inhibition and IC_{50} value of 12.80 ± 0.42 μg/mL.

3.1.2. XO inhibition

In this study, XO inhibition varied significantly across all the plant extracts tested and ranged from 4.46 – 65.27% at 100 μg/mL. Ethyl acetate fractions (EAF) and ethanol extracts (EE) of most of the plants as well as *n*-butanol fraction (NBF) of *C. rubens* displayed significant XO inhibitory activity (Table 1). *C. rubens* ethanol extract gave the highest activity (65.27%, IC_{50}: 22.41 ± 4.34 μg/mL), followed by EAF (52.88%, IC_{50}: 95.05 ± 6.80 μg/mL) and *n*-NBF (55.19%, IC_{50}: 84.47 ± 8.33 μg/mL) of *C. rubens*, whose activity are not significantly different from each other. Other fractions with significant XO inhibitory activity are ethyl acetate fractions of *Launea taraxacifolia* (46.29%, IC_{50}: 118.55 ± 8.98 μg/mL) and *S. biafrae* (42.81%, IC_{50}: 132.00 ± 7.46 μg/mL) at 100 μg/mL, while the reference drug, *i.e.,* allopurinol (50 μg/mL), resulted in 95.23% inhibition (IC_{50}: 2.67 ± 0.08 μg/mL).

3.1.3. NO scavenging activity

NO inhibition was measured by using Griess reagent and ethyl acetate fractions of *G. africanum* (82.93 ± 0.35%) and *S. biafrae* (79.08 ± 0.21%) were found to have highest activity comparable to the reference (Table 1), not statistically different from the activity, *i.e.,* ascorbic acid (82.57 ± 1.30%) at the same final concentration (500 μg/mL). Other fractions with significant NO scavenging activity are as follows; ethyl acetate (75.41 ± 1.54%) and *n*-butanol (77.69 ± 0.96%) fractions of *C. rubens*, dichloromethane fraction (77.08 ± 1.20%) and ethanol extract (76.45 ± 0.51%), of *G. africanum* and *S. biafrae* dichloromethane fraction (77.00 ± 1.44%).

3.2. In vivo studies

3.2.1. In vivo anti-inflammatory activity

The plant extracts were investigated for anti-inflammatory activity using the carrageenan-induced hind paw edema model in mice at doses of 250 and 500 mg/kg (b.w.). Among them, ethanol extracts of *B. alba, C. rubens, S. biafrae*, and water extracts of *S. biafrae*, and *S. macrocarpon* exhibited significant anti-inflammatory activity ranging between 10.8 - 28.4%, 19.4 - 29.3%, 22.0 - 31.4%, 18.7 -28.9%, and 12.2 - 28.0%, respectively, at a dose of 500 mg/kg (Table 2). *S. biafrae* ethanol extract gave the highest percentage inhibition (31.4%) followed by *C. rubens* ethanol extract (29.3%), while indomethacin, the reference, gave 41.6% inhibition at the dose of 10 mg/kg after 360 min. However, none of the other extracts displayed anti-inflammatory activity in this model at the tested doses. In addition, all the extracts were safe in the preliminary acute toxicity test.

3.2.2. Antinociceptive activity

In this study, nociception was induced by *p*-benzoquinone and abdominal contractions were measured in the mice to reveal the antinociceptive activity. As presented in Table 3, ethanol extracts of *C. rubens* (34.9%), *G. africanum* (28.8%), *S. biafrae* (26.5%), and water extracts of *C. rubens* (31.1%) and *G. africanum* (26.3%) displayed a significant antinociceptive activity at the dose of 500 mg/kg, without inducing any apparent gastric lesion and comparable to the reference drug, acetylsalicylic acid (ASA, 48.9%). However, ASA induced apparent gastric lesion. The rest of the extracts were not significantly effective at treated doses. In addition, *Launea taraxacifolia* extracts groups induced apparent gastric lesions.

3.2.3. Antipyretic activity

In the present study, the inhibitory effect of the extracts on fever, was determined using the killed mycobacterial toxin (FCA) as an adjuvant in mice. As shown in Table 4, ethanol and water extracts of *B. alba* and *S. biafrae* as well as ethanol extract of *C. rubens* showed potent antipyretic activity, although less potent than the reference, *i.e.* ASA.

3.2.4. Wound healing activity

Excision wound model was used to evaluate the effect of the test samples on wound contraction and time of epithelialization, while the tensile strength of the wound area was determined from the linear incision model. In the excision wound model, ethanol extracts of *Basella alba, Crassocephalum rubens, Solanecio biafrae*, and *Solanum macrocarpon* showed significant wound healing activity, when compared with the reference, nitrofurazone. Among them, *C. rubens* and *S. biafrae* showed the highest wound healing activity and comparable to the reference. For *C. rubens*, significant wound healing activity (44.2%) was observed after the 10^{th} day of treatment and there was complete wound contraction (100%) on day 14 as seen in Table 5, while for *S. biafrae*, significant wound healing activity (38.5%) was observed after the 8^{th} day of treatment and there was complete wound contraction (100%) on day 14. Similar result was obtained from the linear incision wound model, where ethanol extracts of *B. alba* (44.7%), *C. rubens* (51.5%), *S. biafrae* (49.4%), and *S. macrocarpon* (37.2%) showed significant wound healing activity determined from the increase in tensile strength of the wound after day 10 of treatment, while nitrofurazone increased the tensile strength of the wound by 63.7% (Table 6).

Table 1
15-LOX, XO and NO inhibitory activities of basella alba (BA), crassocephalum, rubens (CR), gnetum africanum (GA), launea taraxacifolia (LT), solanecio biafrae (SB), and solanum macrocarpon (SM).

Plant Extract/Fractions Inhibition % ± S.D.[a]		**15-LOX** (at 200 μg/mL final concentration)	**XO** (at 100 μg/mL final concentration)	**NO** (at 500 μg/mL final concentration)
BA	Ethanol	**66.35 ± 6.70** (**IC_{50}: 54.55 ± 6.22 μg/mL*****)	11.54 ± 4.17	52.67 ± 1.74
	n-Hexane	68.17 ± 5.84 (**IC_{50}: 127.75 ± 0.49 μg/mL***)	30.82 ± 0.37	57.24 ± 1.82
	Dichloromethane	43.76 ± 3.05	15.09 ± 2.43	63.65 ± 2.47
	Ethyl acetate	29.50 ± 0.61	11.40 ± 1.07	68.04 ± 3.07*
	n-Butanol	26.15 ± 2.73	5.96 ± 3.82	69.80 ± 0.41*
	Aqueous methanol	5.97 ± 1.60	NA	39.05 ± 1.44
	Water extract	27.75 ± 2.99	9.69 ± 1.95	41.55 ± 1.87
CR	Ethanol	**90.97 ± 1.68** (**IC_{50}: 41.66 ± 6.59 μg/mL*****)	**65.27 ± 1.19***** (**IC_{50}: 22.41 ± 4.34 μg/mL**)	66.15 ± 1.29
	n-Hexane	**70.92 ± 1.13** (**IC_{50}: 83.20 ± 8.39 μg/mL****)	25.90 ± 0.74	58.15 ± 0.85
	Dichloromethane	59.21 ± 0.71 (IC_{50}: 146.85 ± 3.60 μg/mL)	37.30 ± 3.30	64.14 ± 1.77
	Ethyl acetate	**58.33 ± 3.59** (**IC_{50}: 93.95 ± 9.55 μg/mL****)	**52.88 ± 2.50**** (**IC_{50}: 95.05 ± 6.80 μg/mL**)	**75.41 ± 1.54****
	n-Butanol	49.79 ± 1.83	**55.19 ± 2.59**** (**IC_{50}: 84.47 ± 8.33 μg/mL**)	**77.69 ± 0.96****
	Aqueous methanol	44.43 ± 6.96	14.23 ± 4.22	51.02 ± 0.88
	Water extract	**72.67 ± 3.44** (**IC_{50}: 53.81 ± 1.25 μg/mL*****)	16.34 ± 1.15	54.42 ± 0.48
GA	Ethanol	62.74 ± 1.55 (**IC_{50}: 125.17 ± 4.14 μg/mL***)	13.26 ± 3.08	**76.45 ± 0.51****
	n-Hexane	**87.13 ± 0.61** (**IC_{50}: 74.58 ± 9.69 μg/mL****)	27.07 ± 3.58	56.50 ± 1.63
	Dichloromethane	57.56 ± 0.33 (**IC_{50}: 141.75 ± 1.48 μg/mL**)	28.97 ± 3.75	**77.08 ± 1.20****
	Ethyl acetate	33.85 ± 1.21	32.07 ± 0.77	**82.93 ± 0.35*****
	n-Butanol	9.01 ± 1.31	4.02 ± 1.53	72.80 ± 0.03*
	Aqueous methanol	12.90 ± 2.71	NA	57.57 ± 1.24
	Water extract	17.73 ± 2.10	5.79 ± 2.64	65.07 ± 0.94
LT	Ethanol	43.78 ± 2.11	4.46 ± 0.57	59.23 ± 1.25
	n-Hexane	29.61 ± 2.40	11.54 ± 1.60	55.79 ± 0.39
	Dichloromethane	48.59 ± 3.32	20.75 ± 9.43	48.38 ± 0.66
	Ethyl acetate	62.91 ± 3.95 (IC_{50}: 131.40 ± 5.52 μg/mL*)	**46.29 ± 4.21*** (**IC_{50}: 118.55 ± 8.98 μg/mL**)	52.95 ± 0.73
	n-Butanol	46.95 ± 0.64	17.55 ± 3.21	38.40 ± 0.60
	Aqueous methanol	36.32 ± 4.98	5.45 ± 2.77	27.96 ± 2.77
	Water extract	**68.51 ± 3.39** (**IC_{50}: 100.29 ± 17.83 μg/mL****)	14.60 ± 2.86	43.76 ± 0.88
SB	Ethanol	**67.68 ± 4.51** (**IC_{50}: 96.61 ± 10.70 μg/mL****)	26.78 ± 0.17	63.93 ± 0.70
	n-Hexane	41.32 ± 1.94	23.42 ± 6.46	57.40 ± 0.32
	Dichloromethane	56.89 ± 1.04 (**IC_{50}: 229.30 ± 28.43 μg/mL**)	22.45 ± 2.12	**77.00 ± 1.44****
	Ethyl acetate	**64.08 ± 2.39** (**IC_{50}: 88.55 ± 5.54 μg/mL****)	**42.81 ± 2.97*** (**IC_{50}: 132.00 ± 7.46 μg/mL**)	**79.08 ± 0.21*****
	n-Butanol	11.99 ± 3.72	17.77 ± 0.71	60.71 ± 1.68
	Aqueous methanol	12.66 ± 0.71	8.70 ± 1.85	39.40 ± 3.45
	Water extract	82.24 ± 1.16 (**IC_{50}: 114.70 ± 5.94 μg/mL***)	10.55 ± 2.30	1.10 ± 0.40
SM	Ethanol	59.16 ± 1.77 (**IC_{50}: 217.35 ± 7.57 μg/mL**)	23.31 ± 2.76	70.36 ± 1.85*
	n-Hexane	66.05 ± 2.73 (**IC_{50}: 125.90 ± 6.22 μg/mL***)	20.51 ± 3.60	59.36 ± 0.36
	Dichloromethane	56.07 ± 3.39 (**IC_{50}: 154.30 ± 14.28 μg/mL**)	13.80 ± 2.40	48.42 ± 0.61
	Ethyl acetate	30.90 ± 2.75	15.16 ± 4.71	57.02 ± 0.80
	n-Butanol	27.83 ± 2.24	20.99 ± 1.74	71.56 ± 0.81*
	Aqueous methanol	24.26 ± 2.89	11.29 ± 2.11	37.02 ± 0.83
	Water extract	33.12 ± 3.07	12.18 ± 3.91	45.90 ± 0.99
References	**Baicalein**[b] (100 μg/mL)	**93.91 ± 1.65** (**IC_{50}: 12.80 ± 0.42 μg/mL******)		
	Allopurinol[b] (50 μg/mL)		**95.23 ± 0.73****** (**IC_{50}: 2.67 ± 0.08 μg/mL**)	
	Ascorbic acid[b] (500 μg/mL)			**82.57 ± 1.30*****

[a] Standard deviation of the mean (n: 3)
[b] Reference drug
* $p<0.05$
** $p<0.01$
*** $p<0.001$
**** $p<0.0001$, significant from the control. NA means no activity

Table 2
Effect of ethanol (EE) and water extracts (WE) of *basella alba* (BA), *crassocephalum, rubens* (CR), *gnetum africanum* (GA), *launea taraxacifolia* (LT), *solanecio biafrae* (SB), and *solanum macrocarpon* (SM) on carrageenan-induced paw edema model in mice.

Extracts	Dose(mg/kg)	Swelling thickness (x 10^{-2} mm) ± SEM[a] (Inhibition%)			
		90 min	**180 min**	**270 min**	**360 min**
Control		41.7 ± 3.6	45.4 ± 3.2	51.8 ± 3.0	56.7 ± 3.9
BAEE	250	42.1 ± 3.0	47.2 ± 3.4	49.2 ± 3.6 (5.0)	54.1 ± 4.6 (4.6)
	500	37.2 ± 2.6 (10.8)	38.4 ± 2.3 (15.4)	38.6 ± 2.0 (**25.5**)*	40.6 ± 2.2 (**28.4**)*
BAWE	250	45.4 ± 3.9	47.3 ± 3.4	53.6 ± 3.9	59.1 ± 3.2
	500	35.1 ± 2.1 (15.8)	36.7 ± 2.2 (19.2)	41.3 ± 2.7 (20.3)	45.9 ± 2.9 (19.0)
CREE	250	36.4 ± 2.6 (12.8)	39.1 ± 2.5 (13.9)	43.7 ± 2.4 (15.6)	47.5 ± 2.1 (16.2)
	500	33.6 ± 2.5 (19.4)	33.1 ± 2.6 (**27.1**)*	38.7 ± 2.8 (**25.3**)*	40.1 ± 2.4 (**29.3**)**
CRWE	250	44.3 ± 3.8	49.5 ± 3.1	55.7 ± 3.4	57.3 ± 4.6
	500	38.1 ± 3.0 (8.6)	41.2 ± 2.8 (9.3)	42.5 ± 2.3 (17.9)	42.6 ± 2.1 (24.9)
GAEE	250	42.9 ± 3.1	46.2 ± 3.3	52.9 ± 3.1	58.4 ± 3.7
	500	45.0 ± 4.2	49.3 ± 3.9	52.3 ± 3.5	58.6 ± 3.5
GAWE	250	47.1 ± 4.1	50.7 ± 4.3	54.4 ± 3.9	59.8 ± 3.7
	500	44.9 ± 3.9	47.5 ± 3.8	55.1 ± 4.1	59.3 ± 3.4
LTEE	250	49.5 ± 3.8	51.2 ± 3.9	56.9 ± 4.3	57.4 ± 4.2
	500	37.5 ± 3.2 (10.1)	40.1 ± 2.4 (11.7)	41.5 ± 2.6 (19.9)	43.9 ± 2.3 (22.6)
LTWE	250	48.2 ± 3.7	53.1 ± 3.9	53.7 ± 3.8	57.2 ± 4.1
	500	43.5 ± 3.3	46.7 ± 3.9	54.1 ± 3.2	58.2 ± 4.3
SBEE	250	37.1 ± 3.4 (11.0)	38.2 ± 3.0 (15.9)	40.4 ± 2.9 (22.0)	42.6 ± 2.8 (24.9)
	500	32.5 ± 2.3 (22.0)	33.7 ± 2.2 (**25.8**)*	36.4 ± 2.5 (**29.7**)**	38.9 ± 2.1 (**31.4**)**
SBWE	250	38.4 ± 2.9 (7.9)	40.6 ± 3.1 (10.6)	41.2 ± 2.7 (20.5)	45.8 ± 2.4 (19.2)
	500	33.9 ± 2.4 (18.7)	35.0 ± 2.5 (22.9)	37.6 ± 2.4 (**27.4**)*	40.3 ± 2.2 (**28.9**)**
SMEE	250	35.8 ± 2.7 (14.1)	36.8 ± 2.9 (18.9)	39.9 ± 2.4 (22.9)	41.5 ± 2.7 (**26.8**)*
	500	36.6 ± 2.8 (12.2)	34.2 ± 2.9 (24.7)	38.7 ± 2.5 (**25.3**)*	40.8 ± 2.1 (**28.0**)*
SMWE	250	39.5 ± 3.1 (5.3)	40.2 ± 3.3 (11.5)	45.7 ± 2.6 (11.8)	46.0 ± 2.8 (18.9)
	500	36.1 ± 3.0 (13.4)	37.9 ± 3.1 (16.5)	40.2 ± 2.9 (22.4)	42.8 ± 2.6 (24.5)
Indomethacin[b]	10	30.1 ± 2.1 (**27.8**)**	32.4 ± 2.0 (**28.6**)**	33.6 ± 2.2 (**35.1**)**	33.1 ± 1.9 (**41.6**)***

[a] Standard error of the mean
[b] Reference drug
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$ significant from the control
BAEE: *B. alba* ethanol extract, BAWE: *B. alba* water extract, CREE: *C. rubens* ethanol extract, CRWE: *C. rubens* water extract, GAEE: *G. africanum* ethanol extract, GAWE: *G. africanum* water extract, LTEE: *L. taraxacifolia* ethanol extract, LTWE: *L. taraxacifolia* water extract, SBEE: *S. biafrae* ethanol extract, SBWE: *S. biafrae* water extract, SMEE: *S. macrocarpon* ethanol extract, SMWE: *S. macrocarpon* water extract

3.3. Identification, HPLC quantification and anti-inflammatory activity of phenolic compounds

Phenolic quantification by HPLC analyses revealed the presence of chlorogenic, caffeic, and *p*-coumaric acids along with resveratrol and rutin in the tested samples (Table 7; Fig. 1). Other phenolic acids and flavonoids tested (catechin hydrate, hesperetin, myricetin, morin, apigenin, quercetin, kaempferol, amentoflavone, rosmarinic acid, gallic acid, vanillic acid, syringic acid, ferulic acid, tyrosol, oleuropein, ellagic acid, naringin, and epigallocatechin gallate) were not detected in the samples at 5 mg/mL. Chlorogenic acid was found in almost all samples tested in varying amounts, and was in very high amount in *S. macrocarpon n*-butanol fraction (SMB, 162.39 ± 0.27 mg/g) and *S. biafrae* ethanol extract (SBEE, 29.86 ± 0.38 mg/g). Caffeic acid was highest in *S. biafrae* (SBEAF, 4.29 ± 0.00 mg/g) and *C. rubens* (CREAF, 1.09 ± 0.00 mg/g) ethyl acetate fractions. Also, *p*-coumaric acid was also highest in SBEAF (6.99 ± 0.00 mg/g), resveratrol was most abundant in *G. africanum* ethyl acetate fraction (GAEAF, 2.70 ± 0.06 mg/g), while rutin was highest in *S. macrocarpon* ethyl acetate fraction (SMEAF, 26.14 ± 0.03 mg/g). None of the compounds tested was found in all *Launea taraxacifolia* extracts and all water extracts analyzed. The five compounds (chlorogenic, *p*-coumaric, caffeic acids, resveratrol, and rutin) identified in the samples were further tested for their NO scavenging, XO and 15-LOX inhibitory activities and the result is presented in Table 8. The mentioned phenolic compounds exhibited significant NO scavenging activity, but low level of 15-LOX inhibition. For XO inhibition, resveratrol (96.79%, IC_{50}: 0.09 μM) possessed the highest inhibition followed by *p*-coumaric (82.56%, IC_{50}: 0.22 μM) and caffeic (72.38%, IC_{50}: 0.21 μM) acids. Chlorogenic acid and rutin caused 33.88% and 14.02% inhibition, respectively.

4. Discussion

In this study, six under-utilized leafy vegetables and medicinal plants used traditionally in especially in Africa and some Asian countries were investigated their anti-inflammatory activity. The plants are generally eaten as vegetables and traditionally used for the treatment of inflammatory related diseases such as arthritis, wound, body pain, fever, ache, ulcer, asthma, and sore throat, among others. Inhibition of 15-LOX is considered as one of the treatments of inflammatory diseases because it is able to prevent the production of leukotrienes, which are mediators of inflammatory and allergic reactions (Gandhi et al., 2022). Among all plant samples, the crude extract and fractions of *C. rubens* exhibited the highest 15-LOX inhibition, which is reported here for the first time and validates its ethnomedicinal use for the treatment of arthritis. *Basella alba* ethanol extract and *n*-hexane fraction of *Gnetum africanum* are the other extracts with marked 15-LOX inhibition in this study. Accordingly, Kumar et al. (2011) reported the anti-inflammatory activity of aqueous and ethanol extracts of *B. alba* measured by human red blood cell membrane stabilization method. Leaf ethanol extract of *G. africanum* was investigated for its COX-2 inhibitory capacity by Pompermaier et al. (2018), which was reported to have 78% inhibition at 100 μg/mL.

Researchers have continued to explore medicinal plants for safer alternatives to conventional drugs for the treatment of gout by XO inhibition as against treatment with allopurinol, febuxostat,

Table 3
Effects of ethanol (EE) and water extracts (WE) of *basella alba* (BA), *crassocephalum, rubens* (CR), *gnetum africanum* (GA), *launea taraxacifolia* (LT), *solanecio biafrae* (SB), and *solanum macrocarpon* (SM)against *p*-benzoquinone-induced writhing in mice.

Extracts	Dose (mg/kg)	Number of writhings SEM[a]	Inhibition (%)	Ratio of ulceration
Control		47.9 ± 4.5	-	
BAEE	250	48.5 ± 4.7	-	0/6
	500	41.4 ± 3.1	13.6	0/6
BAWE	250	51.7 ± 4.1	-	0/6
	500	49.3 ± 4.3	-	0/6
CREE	250	42.0 ± 2.4	12.3	0/6
	500	31.2 ± 2.0	**34.9****	0/6
CRWE	250	45.5 ± 4.1	5.0	0/6
	500	33.0 ± 4.2	**31.1****	0/6
GAEE	250	43.5 ± 2.1	9.2	0/6
	500	34.1 ± 3.7	**28.8***	0/6
GAWE	250	41.1 ± 3.9	14.2	0/6
	500	35.3 ± 1.7	**26.3****	0/6
LTEE	250	49.4 ± 4.5	-	0/6
	500	39.4 ± 2.6	17.7	3/6
LTWE	250	48.8 ± 2.9	-	0/6
	500	44.2 ± 2.5	7.7	2/6
SBEE	250	37.7 ± 3.5	21.3	0/6
	500	35.2 ± 2.3	**26.5***	0/6
SBWE	250	50.4 ± 3.9	-	0/6
	500	49.4 ± 1.4	-	0/6
SMEE	250	48.3 ± 1.8	-	0/6
	500	38.8 ± 3.3	18.9	0/6
SMWE	250	39.5 ± 2.8	17.5	0/6
	500	40.3 ± 2.6	15.9	0/6
Acetyl salicylic acid	200	24.5 ± 0.7	**48.9*****	5/6

[a] Standard error of the mean
* $< p$: 0.05
** $< p$: 0.01
*** $< p$: 0.001 significant from the control
BAEE: *B. alba* ethanol extract, BAWE: *B. alba* water extract, CREE: *C. rubens* ethanol extract, CRWE: *C. rubens* water extract, GAEE: *G. africanum* ethanol extract, GAWE: *G. africanum* water extract, LTEE: *L. taraxacifolia* ethanol extract, LTWE: *L. taraxacifolia* water extract, SBEE: *S. biafrae* ethanol extract, SBWE: *S. biafrae* water extract, SMEE: *S. macrocarpon* ethanol extract, SMWE: *S. macrocarpon* water extract

Table 4
Antipyretic effects of ethanol (EE) and water extracts (WE) of *basella alba* (BA), *crassocephalum, rubens* (CR), *gnetum africanum* (GA), *launea taraxacifolia* (LT), *solanecio biafrae* (SB), and *solanum macrocarpon* (SM) on Freund's complete adjuvant (FCA)-induced pyrexia model.

Extracts	Dose (mg/kg)	Mean rectal temperature (°C) ± SEM[a] (Day)						
		1	2	3	4	5	6	7
Control		37.8 ± 0.09	38.4 ± 0.11	38.9 ± 0.10	39.3 ± 0.09	39.7 ± 0.06	39.5 ± 0.04	38.3 ± 0.07
BAEE	250	37.3 ± 0.07	38.5 ± 0.10	38.7 ± 0.12	38.5 ± 0.08	38.0 ± 0.07	**37.8 ± 0.05***	**37.7 ± 0.07***
	500	37.6 ± 0.06	38.1 ± 0.09	38.8 ± 0.11	38.1 ± 0.10	**37.8 ± 0.07****	**37.7 ± 0.07***	**37.4 ± 0.04****
BAWE	250	37.9 ± 0.05	38.7 ± 0.07	38.9 ± 0.13	38.2 ± 0.07	**37.9 ± 0.09**	**37.5 ± 0.09***	**37.4 ± 0.07***
	500	37.8 ± 0.08	38.4 ± 0.09	38.1 ± 0.12	**37.9 ± 0.12***	**37.9 ± 0.05****	**37.4 ± 0.06***	**37.5 ± 0.05****
CREE	250	37.7 ± 0.07	38.8 ± 0.11	38.5 ± 0.14	38.0 ± 0.10	38.8 ± 0.07	38.5 ± 0.06	38.5 ± 0.06
	500	37.9 ± 0.09	38.9 ± 0.12	38.8 ± 0.11	38.3 ± 0.08	**37.9 ± 0.04***	**37.6 ± 0.02***	**37.4 ± 0.08***
CRWE	250	37.8 ± 0.04	38.7 ± 0.08	38.6 ± 0.13	38.1 ± 0.11	38.9 ± 0.06	38.8 ± 0.04	38.4 ± 0.04
	500	37.6 ± 0.09	38.5 ± 0.07	38.7 ± 0.10	38.2 ± 0.08	38.0 ± 0.08	38.1 ± 0.05	38.0 ± 0.08
GAEE	250	37.9 ± 0.08	38.4 ± 0.13	39.5 ± 0.17	39.9 ± 0.13	39.8 ± 0.11	39.6 ± 0.09	38.7 ± 0.05
	500	37.8 ± 0.07	38.5 ± 0.09	39.3 ± 0.15	39.5 ± 0.14	39.9 ± 0.12	39.5 ± 0.10	38.8 ± 0.07
GAWE	250	37.7 ± 0.06	38.6 ± 0.09	39.1 ± 0.13	39.9 ± 0.13	39.8 ± 0.09	39.5 ± 0.10	38.6 ± 0.09
	500	37.9 ± 0.11	38.7 ± 0.12	39.2 ± 0.10	39.8 ± 0.11	39.8 ± 0.10	39.8 ± 0.09	38.5 ± 0.07
LTEE	250	38.1 ± 0.09	38.0 ± 0.12	38.9 ± 0.11	38.9 ± 0.06	39.6 ± 0.07	39.5 ± 0.04	38.8 ± 0.10
	500	37.9 ± 0.07	38.2 ± 0.09	39.2 ± 0.12	39.3 ± 0.11	39.7 ± 0.09	39.6 ± 0.02	38.5 ± 0.08
LTWE	250	37.8 ± 0.05	38.1 ± 0.08	39.1 ± 0.11	39.4 ± 0.13	39.8 ± 0.08	39.4 ± 0.05	38.4 ± 0.09
	500	37.6 ± 0.06	38.3 ± 0.07	39.3 ± 0.13	39.5 ± 0.12	39.9 ± 0.09	39.5 ± 0.09	38.9 ± 0.11
SBEE	250	37.9 ± 0.10	38.6 ± 0.09	38.1 ± 0.11	37.9 ± 0.09*	37.8 ± 0.04	37.8 ± 0.09	**37.5 ± 0.09***
	500	37.9 ± 0.09	38.3 ± 0.12	38.6 ± 0.11	38.4 ± 0.07	38.1 ± 0.05	**37.6 ± 0.07***	**37.6 ± 0.05***
SBWE	250	37.9 ± 0.05	38.8 ± 0.13	38.8 ± 0.13	38.1 ± 0.08	38.2 ± 0.08	38.3 ± 0.06	38.1 ± 0.07
	500	37.8 ± 0.08	38.7 ± 0.11	38.5 ± 0.12	38.0 ± 0.09	**37.8 ± 0.06***	**37.7 ± 0.05***	**37.6 ± 0.06***
SMEE	250	37.5 ± 0.08	38.7 ± 0.09	39.1 ± 0.10	39.3 ± 0.11	39.6 ± 0.07	39.8 ± 0.08	38.5 ± 0.12
	500	37.7 ± 0.09	38.0 ± 0.12	39.4 ± 0.11	39.4 ± 0.10	39.7 ± 0.09	39.6 ± 0.09	38.6 ± 0.10
SMWE	250	37.8 ± 0.04	38.2 ± 0.07	39.2 ± 0.14	39.5 ± 0.14	39.9 ± 0.10	39.4 ± 0.09	38.5 ± 0.09
	500	37.9 ± 0.08	38.3 ± 0.10	39.0 ± 0.12	39.3 ± 0.12	39.8 ± 0.11	39.7 ± 0.07	38.9 ± 0.08
Acetyl salicylic acid	100	37.5 ± 0.05	**37.6 ± 0.05****	**37.6 ± 0.06*****	**37.6 ± 0.07*****	**37.7 ± 0.05*****	**37.5 ± 0.03*****	**37.4 ± 0.02*****

Table 5
Effect of ethanol (EE) and water extracts (WE) of *basella alba* (BA), *crassocephalum, rubens* (CR), *gnetum africanum* (GA), *launea taraxacifolia* (LT), *solanecio biafrae* (SB), and *solanum macrocarpon* (SM) on circular excision wound model in mice.

Material	0	2	4	6	8	10	12	14
Vehicle	309.14 ± 4.68	305.27 ± 4.12	275.42 ± 3.87 (2.4)	251.34 ± 3.93 (1.6)	192.13 ± 3.01 (2.1)	88.05 ± 2.58 (9.2)	64.22 ± 1.85 (6.7)	26.34 ± 1.22 (12.5)
Negative Control	308.32 ± 3.23	307.11 ± 3.07	282.11 ± 3.23	255.65 ± 3.06	196.34 ± 2.51	98.91 ± 2.02	68.84 ± 2.14	30.11 ± 1.20
BAEE	308.07 ± 4.91	293.52 ± 4.12 (3.8)	241.17 ± 3.75 (12.4)	219.62 ± 3.15 (12.6)	125.01 ± 1.54 (**34.9**)*	52.34 ± 2.14 (**40.6**)*	32.14 ± 1.55 (**49.9**)*	10.53 ± 1.02 (**60.0**)**
BAWE	311.92 ± 2.18	302.71 ± 1.99	278.09 ± 1.86	262.32 ± 2.52	195.12 ± 2.70	90.49 ± 2.03	65.15 ± 1.64	30.08 ± 1.17
CREE	310.56 ± 3.75	290.34 ± 3.09 (4.9)	254.28 ± 3.12 (7.7)	208.14 ± 3.06 (17.2)	134.07 ± 1.49 (30.2)	49.61 ± 2.03 (**44.2**)**	21.73 ± 1.41 (**66.2**)**	0.00 ± 0.00 (**100.0**)***
CRWE	310.52 ± 2.72	307.71 ± 2.51	285.67 ± 2.73	204.25 ± 3.02 (18.7)	158.43 ± 2.40 (17.5)	71.84 ± 1.90 (18.9)	57.31 ± 1.51 (10.8)	23.26 ± 1.03 (11.7)
GAEE	309.78 ± 3.32	292.16 ± 2.01 (4.3)	258.51 ± 3.07 (6.1)	217.45 ± 3.13 (13.5)	190.28 ± 3.08	90.76 ± 1.21	70.42 ± 1.92	34.81 ± 1.57
GAWE	311.32 ± 3.16	298.43 ± 3.01 (2.2)	272.36 ± 2.95	233.27 ± 1.94 (7.2)	193.09 ± 2.51	84.53 ± 2.19 (3.9)	60.17 ± 1.52 (6.3)	30.15 ± 1.93
LTEE	309.28 ± 2.37	303.65 ± 3.14	280.11 ± 2.18	236.37 ± 3.02 (5.9)	204.26 ± 2.73	78.22 ± 2.01 (11.2)	66.34 ± 1.73	32.29 ± 1.54
LTWE	312.45 ± 2.52	304.48 ± 2.19	276.16 ± 2.54	254.32 ± 2.31	199.05 ± 1.03	90.09 ± 1.17	67.58 ± 1.92	30.41 ± 1.24
SBEE	305.41 ± 4.51	303.53 ± 4.02	238.61 ± 3.86 (13.4)	202.19 ± 3.71 (19.6)	118.20 ± 2.43 (**38.5**)*	59.31 ± 2.12 (**32.6**)*	31.40 ± 1.76 (**51.1**)**	0.00 ± 0.00 (**100.0**)***
SBWE	309.78 ± 4.31	285.51 ± 4.03 (6.5)	246.27 ± 3.88 (10.6)	204.52 ± 2.57 (18.6)	152.71 ± 2.46 (20.5)	51.13 ± 1.53 (20.4)	20.06 ± 1.18 (23.8)	22.18 ± 1.06 (15.8)
SMEE	308.23 ± 4.63	301.14 ± 4.02 (1.4)	263.29 ± 3.95 (4.4)	213.46 ± 2.54 (15.1)	146.13 ± 2.72 (23.9)	55.09 ± 2.26 (**37.4**)*	41.25 ± 1.74 (**35.8**)*	14.91 ± 1.05 (**43.4**)*
SMWE	307.26 ± 3.23	302.42 ± 3.05	283.18 ± 3.11	263.10 ± 2.84	168.26 ± 2.31 (12.4)	65.17 ± 2.07 (25.9)	52.53 ± 1.72 (18.2)	21.72 ± 1.13 (17.4)
Nitrofurazone	308.31 ± 2.75	287.23 ± 2.06 (5.9)	203.22 ± 2.11 (26.2)	171.47 ± 2.03 (**31.8**)*	115.08 ± 2.12 (**39.7**)*	34.15 ± 1.49 (**61.2**)***	0.00 ± 0.00 (**100.0**)***	0.00 ± 0.00 (**100.0**)***

Table 6
Effect of ethanol (EE) and water extracts (WE) of *basella alba* (BA), *crassocephalum, rubens* (CR), *gnetum africanum* (GA), *launea taraxacifolia* (LT), *solanecio biafrae* (SB), and *solanum macrocarpon* (SM) on linear incision wound model in mice.

Material	Statistical mean ± SEM (gmean SEM) (Tensile strength %)
Vehicle	231.02 ± 3.29 (1.5)
Negative Control	227.41 ± 3.52
BAEE	334.29 ± 3.17 (**44.7**)**
BAWE	225.14 ± 4.23
CREE	350.08 ± 3.45 (**51.5**)***
CRWE	246.09 ± 5.24 (6.5)
GAEE	211.63 ± 4.47
GAWE	209.71 ± 4.15
LTEE	243.66 ± 4.82 (5.5)
LTWE	218.92 ± 3.09
SBEE	345.13 ± 3.68 (**49.4**)**
SBWE	270.62 ± 5.91 (17.1)
SMEE	317.06 ± 3.92 (**37.2**)*
SMWE	223.84 ± 5.46
Nitrofurazone	378.32 ± 3.05 (**63.7**)***

* < p: 0.05
** <p: 0.01
*** <p: 0.001 significant from the control
BAEE: *B. alba* ethanol extract, BAWE: *B. alba* water extract, CREE: *C. rubens* ethanol extract, CRWE: *C. rubens* water extract, GAEE: *G. africanum* ethanol extract, GAWE: *G. africanum* water extract, LTEE: *L. taraxacifolia* ethanol extract, LTWE: *L. taraxacifolia* water extract, SBEE: *S. biafrae* ethanol extract, SBWE: *S. biafrae* water extract, SMEE: *S. macrocarpon* ethanol extract, SMWE: *S. macrocarpon* water extract

topiroxostat or uricosurics (*e.g.* benzbromarone, probenecid, losartan, etc), due to their associated side effects (Sattui & Gaffo, 2016; Jordan & Gresser, 2018). In this study, ethyl acetate and *n*-butanol fractions of *C. rubens* exhibited very potent activity against XO as well as the ethyl acetate fraction of *Launea taraxacifolia*. Our data constitutes the first report on XO inhibitory activity of these plant species having traditional uses in the treatment of rheumatism and osteoarthritis (Adinortey et al., 2018).

The increase in nitric oxide (NO) is implicated in inflammatory diseases (Ersoy, 2002), therefore, the presence of NO inhibitors can help to alleviate inflammatory problems (Adebayo et al., 2019). In this study, NO inhibition was measured by using Griess reagent and ethyl acetate fractions of both *S. biafrae* (79%) and *L. taraxacifolia* (83%) gave the highest inhibition, which was comparable and not statistically different ($p < 0.001$) from ascorbic acid (83%) at the same dose. *n*-Butanol fraction of *C. rubens* also exhibited marked NO scavenging activity among others. Other studies have reported the antioxidant activity of these plants by the scavenging of free radicals such as 2,2-diphenyl,1-picrylhydrazyl (DPPH) and hydroxyl radical scavenging activity (Ayoola et al., 2019; Yusuff et al., 2020). Similarly, Borokini and Labunmi (2017) reported NO scavenging activity of *C. rubens* and *L. taraxacifolia* aqueous and alcoholic extracts with high activity comparable to that of the reference, *i.e.* ascorbic acid.

Carrageenan-induced paw edema method, a widely used method, was used to evaluate the *in vivo* anti-inflammatory activity of the plant extracts and the result revealed the potential of the studied plant species in the treatment of arthritis. Among all the extracts from the six plants, the ability of ethanol extracts of *S. biafrae, C. rubens, B. alba* and water extract of *S. biafrae* to reduce edema induced by carrageenan were the most prominent at the highest dose (500 mg/kg). This result is in tandem with *in vitro* 15-LOX anti-inflammatory activity, while correlation analysis and Pearson's correlation coefficient revealed a good positive correlation (r^2 = 0.78) between the results from both assay methods. The results of this study indicated that anti-inflammatory property of the active plants might be due to inhibition of both prostaglandins and leukotrienes as

Table 7
Retention times, amount of compounds in plant samples, linear relationships between peak areas and concentrations.

Compound	Retention time (min)	Maximum absorbance (nm)	Plant sample	Amount (mg/g, mean ± SD)	Standard curve	R^2
Chlorogenic acid	15.595	320	CREE	9.07 ± 0.02	y = 28.919x + 54.92	0.9974
			CREAF	4.54 ± 0.02		
			SBEE	**29.86 ± 0.38**		
			SBEAF	14.95 ± 0.03		
			SMEE	**25.46 ± 0.10**		
			SMEAF	16.46 ± 1.78		
			SMB	**162.39 ± 0.27**		
			BAEE	0.56 ± 0.00		
			BAEAF	1.08 ± 0.00		
			GAEAF	0.18 ± 0.01		
Caffeic acid	18.407	320	CREE	0.31 ± 0.00	y = 72.799x - 56.706	0.9994
			CREAF	1.09 ± 0.00		
			SBEE	0.54 ± 0.01		
			SBEAF	**4.29 ± 0.01**		
p-Coumaric acid	25.293	320	CREE	0.81 ± 0.00	y = 206.16x - 729.76	0.9883
			CREAF	1.40 ± 0.00		
			SBEE	1.49 ± 0.01		
			SBEAF	**6.99 ± 0.00**		
Resveratrol	37.198	320	GAEE	1.02 ± 0.01	y = 234.4x - 166.53	0.9955
			GAEAF	**2.07 ± 0.06**		
			SBEE	0.19 ± 0.00		
			SBEAF	0.37 ± 0.01		
Rutin	29.999	260	SMEE	7.55 ± 0.10	y = 36.127x + 150.42	0.9993
			SMEAF	**26.14 ± 0.03**		
			SMB	24.61 ± 0.56		
			SBEE	0.20 ± 0.02		
			SBEAF	1.27 ± 0.00		
			BAEE	1.03 ± 0.01		
			BAEAF	5.38 ± 0.01		

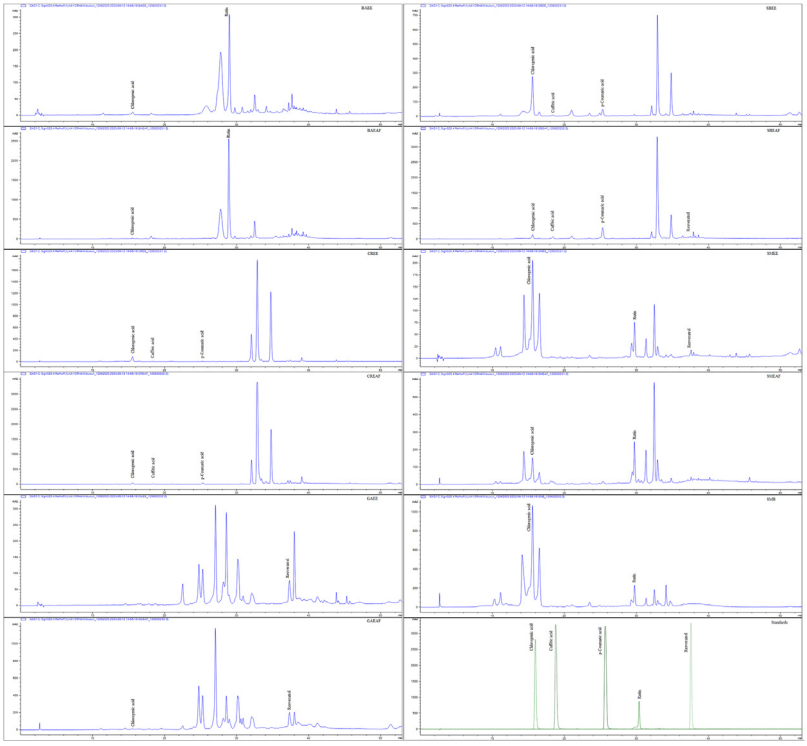


Fig. 1. HPLC chromatograms of plant fractions (BAEE, BAEAF, CREE, CREAF, GAEE, GAEAF, SBEE, SBEAF, SMEE, SMEAF, and SMB) and a standard mixture containing chlorogenic acid, caffeic acid, p-coumaric acid, rutin, and resveratrol, recorded at 320 nm.

Table 8
NO scavenging, 15-LOX and XO inhibitory activities of identified phenolic acids and flavonoids.

Standards	**NO** (Inhibition % ± S.D.[a] at 500 μg/mL final concentration)	**LOX** (Inhibition % ± S.D.[a] at 200 μg/mL final concentration)	**XOD** (Inhibition % ± S.D.[a] at 100 μg/mL final concentration)
Chlorogenic acid	68.38 ± 0.51	1.44 ± 0.12	33.88 ± 3.75 (IC_{50}: 0.36 μM)
Caffeic acid	89.20 ± 1.20	15.34 ± 6.56	72.38 ± 2.78 (IC_{50}: 0.21 μM)
p-Coumaric acid	90.04 ± 2.89	1.82 ± 0.94	82.56 ± 4.30 (IC_{50}: 0.22 μM)
Rutin	82.69 ± 0.31	20.77 ± 3.97	14.02 ± 3.98
Resveratrol	77.46 ± 0.16	NA	96.79 ± 3.50 (IC_{50}: 0.09 μM)
Ascorbic acid	82.57 ± 1.30		
Biacalein		93.91 ± 1.65	
Allopurinol			95.23 ± 0.73 (IC_{50}: 0.02 μM)

[a] Standard deviation of the mean (n = 3),

LOX-mediated products, since the plants were active in the *in vitro* 15-LOX inhibition and the *in vivo* assays. This is the first report on *in vivo* anti-inflammatory study on *C. rubens* and *S. biafrae* extracts to the best of our knowledge. However, Rodda et al. (2012) investigated anti-inflammatory activity of *B. alba* ethanol extract using similar model as the one used in this study, *e.g.* carrageenan-induced paw edema. The extract had a significant activity at a dose of 500 mg/kg, which is similar to the result of our study.

From the antinociceptive assay results, number of the writhing movements was significantly reduced by ethanol and water extracts of *C. rubens* and *G. africanum* as well as ethanol extract of *S. biafrae* at comparable level to that of ASA, the reference. Interestingly, there was no accompanying ulceration by these extracts, whereas ASA induced gastric ulceration. There is paucity of studies on the antinociceptive activity of the studied plants. Taïwe et al. (2012) reported the antinociceptive effects of *Crassocephalum bauchiense* Hutch leaf aqueous extract, a close species to *C. rubens*, which exhibited significant antinociceptive activity in both chemical (formalin-, acetic acid-, glutamate-induced nociception) and thermal models of nociception.

Pyrexia is a secondary effect of infection, injury and other inflammatory diseases and anti-inflammatory and antinociceptive drugs that act through the inhibition of prostaglandin biosynthesis may have a fever-suppressing capacity (Akkol et al., 2009). The extracts of *C. rubens, S. biafrae*, and *B. alba* that had significant anti-inflammatory activity also displayed significant antipyretic activity, indicating that they have inhibitory effect on prostaglandin synthesis.

The excision and incision wound models were used in order to assess wound healing activity and ethanol extracts of *C. rubens* and *S. biafrae* displayed the best wound healing activity in terms of the progression in wound contraction and tensile strength. These results contribute to the information about the wound healing activity of these two plants since there is paucity of studies on their wound healing activity. Can and Thao (2020) reported the wound healing activity of *C. crepidoides*, a close species to *C. rubens*.

Phenolic quantification by HPLC analyses revealed the presence of chlorogenic, caffeic, and *p*-coumaric acids along with resveratrol and rutin in the samples. The most active extracts, *C. rubens* and *S. biafrae* contained three mentioned phenolic acids, while *S. biafrae* additionally had resveratrol. *Basella alba* contained only chlorogenic acid and rutin. Only a few reports on the phytochemical constituents of *C. rubens* and *S. biafrae* exist in the literature. Borokini and Labunmi (2017) reported the presence of caffeic, chlorogenic, gallic, and coumaric acids, rutin, quercetin, and kaempferol in *C. rubens* and *L. taraxacifolia*. Adefegha et al. (2016) also confirmed by HPLC the presence of gallic, chlorogenic, and caffeic acids, rutin, quercetin, and kaempferol in *C. rubens*. Our results revealed high NO scavenging activity of all tested phenolic and flavonoids, but low 15-LOX inhibition. For XO inhibition, resveratrol, caffeic, and *p*-coumaric acids exhibited high inhibitory activity. *C. rubens* and *S. biafrae* have high content of chlorogenic acid, whose anti-inflammatory potential has been reported (Kim et al., 2017; Bao et al., 2018; Tan et al., 2020). Hwang et al. (2014) investigated the anti-inflammatory potential of chlorogenic acid in lipopolysaccharide (LPS)-stimulated murine RAW 264.7 macrophages and BV2 microglial cells. The results pointed out the significant inhibition of expression of inflammatory and pro-inflammatory markers (COX-2, IL-1b, IL-6, NF-κB, and TNF) by this compound without any cytotoxicity. Caffeic and *p*-coumaric acids have also been reported to exert anti-inflammatory activity *via* different mechanisms (Zhu et al., 2018; Paciello et al., 2020) . Invariably, the presence of chlorogenic, caffeic, and *p*-coumaric acids in *C. rubens* and *S. biafrae* would have contributed largely to their anti-inflammatory activity.

5. Conclusion

In this study, we discussed the anti-inflammatory, analgesic, antipyretic and wound healing activities of some under-utilized vegetables for the first time and hereby verified their traditional uses for treating arthritis and other inflammatory related diseases. All extracts were found safe from the acute toxicity tests as expected because they are consumed. Additionally, this study also contributed to identification of some phenolic compounds present in these plants. The presence of chlorogenic, caffeic, and *p*-coumaric acids in *C. rubens* and *S. biafrae* would have contributed largely to their anti-inflammatory activity. This study has highlighted the health benefits of these vegetables and they can be considered for the formulation of nutraceuticals.

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Declaration of generative AI

During the preparation of this work the authors used ChatGPT (OpenAI o3 and 4o) solely to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics approval and consent to participate

Ethical approval for the *in vivo* study was given by The NESA Experimental Animals Ethical Council Project Number: 007 and the study was carried out in accordance with the established European ethical standards for the care of laboratory animals

Data availability statement

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Ibukun Oluwabukola Oresanya: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hasya Nazlı Gök:** Writing – review & editing, Formal analysis. **Esra Küpeli Akkol:** Writing – review & editing, Supervision, Formal analysis. **Mubo Adeola Sonibare:** Writing – review & editing, Supervision. **Ilkay Erdoğan Orhan:** Writing – review & editing, Supervision, Project administration, Methodology.

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