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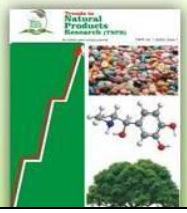

Anti-arthritic and Antioxidant Potentials of Leaf Extract of *Atrocarpus heterophyllus* Lam

Victoria Nonyelum Olli[1]* Nneoma Ngozi Okpalanma[2], Ernest C. Orji[3], Jude Nnaemeka Okoyeh[4]

[1]Department of Pharmacology and Toxicology, Chukwuemeka Odumegwu Ojukwu University Igbariam Campus, Nigeria,
[2]Department of Clinical and Pharmacy Management, Chukwuemeka Odumegwu Ojukwu University Igbariam Campus, Nigeria,
[3]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, P.M.B 5025 Awka,420110 Anambra state, Nigeria
[4]Department of Medical Laboratory Science and Biology, School of Nursing and Health Sciences, Neumann University, One Neumann Drive, Aston, PA, 19014. USA

Abstract

Oxidative stress predisposes human and animal bodies to diseases like cancer, diabetes, rheumatoid arthritis, atherosclerosis and chronic inflammatory disorders. This study is aimed to determine the antioxidant, and anti-arthritic activities of ethanol leaf extract of *Atrocarpus heterophyllus* which have been used traditionally to treat arthritis and inflammation. The shade-dried and pulverized leaves of *A. heterophyllus* were cold macerated in 80 % ethanol for 48 hours and filtered; the filtrate was dried over water bath at 40 ºC. Acute toxicity study and phyto chemical screening were carried out. The in-vivo anti-arthritic property of the extract was tested orally on formalin induced arthritic model at 250 and 500mg/kg doses for 8 days using a set of 20 albino rats of both sexes that were grouped into four (n=5). Groups I and II served as the negative (10ml/kg distilled water) and positive (diclofenac sodium 10mg/kg) controls, respectively. Groups III and IV received 250 and 500 mg/kg of the extract, respectively. *In-vitro* antioxidant activities of the extract were determined at 517 nm with spectrophotometer using 2,2-Diphenyl-1-picrylhydrazyl (DPPH) model. Histopathological examinations of the proximal interphalangeal joints from the induced arthritic rats were also carried out. The estimated oral median lethal dose (LD_{50}) of the extract was higher than 5000 mg/kg. Secondary metabolites such as tannins and saponins were present in the extract. The extract conferred a dose-related significant ($p<0.05$) reduction in paw diameter when compared to control. The in-vitro IC_{50} values for the extract (9.62ug/ml) were higher than that of standard drug vitamin C (6.12ug/ml). The result of the histopathology analysis revealed a dose-dependent anti-arthritic potential of the leaf extract from *Atrocarpus heterophyllus.*

Keywords
Artocarpus heterophyllus, leaf extract, anti-arthritis, anti-oxidant.

*Corresponding author:
vn.umeh@coou.edu.ng,
+2348064482047
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Introduction

Medicinal plants are rich in bioactive compounds with therapeutic effects and they are used for the treatment of various diseases (Patil *et al*., 2011). *Artocarpus heterophyllus* (Moraceae) (Figure 1), is an evergreen fruit tree belonging to the *Artocarpus* genus. It is known as Epa Oyibo (Yoruba), Jack'ya'yanitace (Hausa) and Ukwa Oyibo (Igbo) by some ethnic groups of Nigeria but its common name is Jackfruit tree. It is found in tropical and subtropical regions (Morton, 1987 and Saxena 2011). Jack fruit trees are perennials and can produce fruits for 30 to 60 years. The tree itself can live up to 100 years and a fruit can contain 100 to 500 seeds which can be consumed roasted, boiled, steamed, or eaten as snack (Morton, 1987 and Saxena 2011).

All parts of the Jackfruit tree are used in traditional medicine. They are recommended for the treatment of inflammation, malarial fever, kidney stones (Araújo and Lima, 2010), ulcers, infected wounds, diarrhea, asthma, anaemia, and dermatitis (Jagtap and Bapat, 2011). Its potential benefits in strengthening the bones have also been suggested (https://www.paybima.com>blog). The antioxidant constituents of medicinal plants may contribute to the protection of humans and animals from a variety of metabolic and infectious diseases (Fotina *et al.,* 2013, Saeed *et al.,* 2012). It is also known that reactive oxygen species act by oxidizing polyunsaturated fatty acids within cell membranes and lipoproteins via metal ion-dependent hydroxyl radical formation causing disruption of the cell membrane (Aust *et al.,* 1985). Proteins exposed to free radical attack may fragment or aggregate, adversely interfering with ion channels, cell receptors and oxidative phosphorylation (Aruoma *et al.,* 1989)

The intake of natural antioxidants has been inversely associated with morbidity and mortality from degenerative disorders and other infections (Gulcin, 2012). The determination of antioxidant capacity is reaction-mechanism dependent and closely linked to the complex nature of phytochemicals (Zau *et al.,* 2011). Arthritis is a common problem observed more in elderly people. Nearly one-fifth of the world's population suffers from this debilitating disease (Muruganenther *et al.,* 2013). Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder which is characterized by inflammation (painful swelling) disability and stiffness (Bullock *et al*.,2019). It affects the lining of the joints which eventually result in bone erosion and joint deformity. The cause is unknown, however free radicals are known to play role in inflammation and cartilage

destruction (Pinchuk *et al.;* 2012). The damaging effect on cells by free radicals can be prevented or reversed by antioxidants (Amraoui, *et al.,* 2019). Plants are excellent sources of antioxidants (Zubair *et al.,* 2012, Atwodi *et al.,* 2013). Natural products can control d i s e a s e through multiple pathways such as inhibition of effector molecules (Dudics *et al*., 2018) and regulation of the production of free radicals and cytokines (Patel *et al*.,2013). The management of arthritis and other inflammatory disorders involve the use of different classes of medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease modifying anti-rheumatic drugs (DMARD) (https://www.arthritis.org>treatment). Non-steroidal anti-inflammatory drugs have gastrointestinal side effects, which includes irritation of the gastric mucosa, belching, gastric ulceration and bleeding (https://www.arthritis.org>treatment). Long-term use of NSAIDs may impair renal and hepatic functions, predisposing the patient to cardiovascular diseases (Reddy *et al.,* 2014).

Hence, there is a need for the continuous search for alternative drugs that are efficacious, with reduced side effects, from plants and other natural sources for the management of rheumatoid arthritis.

Materials and Methods

Collection and identification of plant materials

The leaves of *A. heterophyllus Lam* were obtained from Ukwulu town, Dunukofia Local Government Area of Anambra state, Nigeria in June. It was identified and authenticated by a Taxonomist at the Department of Botany, Nnamdi Azikiwe University Awka, Nigeria and herbarium specimen: *Artocarpus heterophylla*- NAUH-224A, was kept in the herbarium of the University.

Animals

A total of twenty albino rats of both sexes (120-150 g) were obtained from the Animal house of the Department of Pharmacology and Toxicology, Chukwuemeka Odumegwu Ojukwu University (COOU), Anambra State, Nigeria. The rats were housed in clean plastic cages, supplied with clean drinking water and fed with commercial pelleted (Guinea Feed®, Nigeria). Ethical approval number *(PHACOOU/AREC/2023/008)* was assigned to attest the animals were cared for according to the

Faculty of Pharmacy (COOU) Animal Research Ethics Committee guidelines (PHACOOUAREC), which are in line with the National Institute of Health (NIH), USA, guidelines for the care and use of laboratory animals.

Figure 1. *Artocarpus heterophyllus* tree and fruits

Methods

Extraction of plant material

The fresh leaves of *A. heterophyllus* were thoroughly washed under running tap-water to remove dust and other debris and air dried for two weeks. Dried leaves of *A. heterophyllus* were pulverized with an electric blender. About 600 g of the powdered material was cold macerated in 80% ethanol with constant agitation for 48 hours. Thereafter, the macerated product was first filtered through a cotton plug and further filtered with filter paper (Whatman filter paper, No 1). The filtered extract was concentrated to dryness using a water bath at 40 ^{O}C, the percentage yield of the extract was determined, and the extract was stored in a refrigerator.

Acute toxicity study (LD_{50})

The acute toxicity test was conducted using the up and down procedure (UDP) adopted by *Lorgue et al* (1996) and revised by *Saganuwan* (2014). Using this method, the animals were dosed one at a time and the doses were dependent on the response of the first animal to the initial dose. The second animal receives a lower dose if the first animal dies (the initial dose is decreased by a factor of 3.2) or the *second animal receives a higher dose if the first animal survives (the initial dose is increased by a* factor of 3.2). Three rats weighing 150-200 g were used as starting points. Two rats served as negative control having received 10 ml/kg of distilled water orally while the test animal received a default oral dose of 5000 mg/kg of the extract. The animals were then observed continuously for 4 hours for changes in behavior and any other obvious signs of toxicity and subsequently daily for a total of 14 days for delayed toxicity.

Phytochemical Analysis

Phytochemical screenings of the extract for the presence of secondary metabolites such as terpenoids, saponins, alkaloids, flavonoids, tannins, and cardiac glycosides were investigated using standard qualitative methods as described by Trease and Evans (1989).

Assessment of the in-vivo anti-arthritic potential of the extract

The assessment of anti-arthritic potential of the extract was as described by Chinnasamy *et al* (2019). The rats were divided into four groups (n=5) and treated orally as follows:
Group 1: 10 ml/kg distilled water (negative control).
Group 2: Diclofenac sodium 10mg/kg (positive control, standard drug)
Group 3: 250 mg/kg extract.
Group 4: 500 mg/kg leaf extract.

Chronic phase of arthritis was induced in the rats using formaldehyde (2%v/v) (Chinnasamy *et al.,*2019). Thirty minutes after oral treatments, arthritis was induced by sub-plantar administration of 0.1ml formaldehyde (2 %v/v) into the left hind paw of the animal. This was noted as day 1; vehicle/drug, treatments continued for 7 more days. Paw volume and paw thickness were measured from day 2 to day 16th using Plethysmometer. The percentage inhibition of the paw volume was calculated from the mean difference between the paw volumes of the treated and control groups using the following formula:

$$\% \text{ Inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Where Vc is the paw volume of the control group and Vt is the paw volume of the treated group (Chinnasamy *et al.,*2019).

Assessment of the In-vitro antioxidant activity of the extract.

The ability of the plant extract to scavenge DPPH (1, 1diphenyl-2-picrylhydrazyl) free radical was assessed using the method described by Baba and Malik, (2015) with little modification. Seven different concentrations of the leaf extract (15.625, 31.25, 62.5, 125, 250, 500 and 1000 ug/ml) were prepared in 70 % methanol (analytical grade). The same concentrations were also prepared for Ascorbic acid using same solvent. Each extract concentration, (1ml) was transferred into clean test tubes which contain 0.5 ml of 0.3M DPPH in methanol. The mixture was shaken and left to stand in the dark at room temperature for 15 minutes. The absorbance of the mixtures was measured at 517nm using a UV/VI Spectrophotometer. The scavenging activity of the extract was compared with that of ascorbic acid. The percentage DPPH scavenging effect was calculated using the following equation (Baba and Malik, 2015);

% DPPH Scavenging activity=

$$\frac{\text{Abs blank} - \text{Abs sample}}{\text{Abs blank}} \times 100$$

Where Abs blank=Absorbance of control and Abs sample=Absorbance of extract solution. The IC_{50} value of the extract was calculated using log dose inhibition curve. The IC_{50} value is the concentration of the sample required to inhibit 50 % of the DPPH free radical.

Histopathology analysis

Histological examination of the pancreas was carried out using the method described by Drury and Wallington (1980). The proximal interphalangeal joints from the adjuvant induced arthritic rats were removed and fixed in 10 % formaldehyde solution, dehydrated using ascending grades of isopropyl alcohol, cleared using xylene and finally embedded in molten paraffin wax. The sections were dried completely before staining with haematoxylin and eosin and subsequently examined under the microscope (Motic Panthera E2 Binocular Microscope).

Statistical Analysis

The data were analyzed using statistical package for social sciences (SPSS-20). Results were presented as mean ± Standard error of mean (SEM) of sample replicates. Raw data was subjected to One-way Analyses of Variance (ANOVA) followed by post hoc turkey's test. Values of $p < 0.05$ were considered to be statistically significant.

Results

Yield of extract

The weight of the pulverized *A. heterophyllus* leaves was 600 g and the crude extract obtained after drying was 490 g. The yield of the extract was 490 g (81.7%)

Acute toxicity study (LD50)

After 24 hours of oral administration of *A. heterophyllus* leaf extract for up to 5000 mg/kg dose; no sign of acute toxicity or lethality was observed. Therefore, the LD50 of *A. heterophyllus* is greater than 5000 mg/kg.

Phytochemical analysis

The qualitative phytochemical screening of the extract revealed the presence of some bioactive substances. There was abundance of tannins, flavonoids, carbohydrates, saponins, alkaloids, phenols and cardiac glycosides with moderate occurrence of terpenoids, and glycosides while steroids were in traces (Table 1).

Table 1. Phytochemical analysis of A. *Heterophyllus* leaf extract

Tannin	Flavonoid	Steroid	Saponin	Card gly	Phenol	Gly	Carb	Alk	Terp
+++	+++	++	+++	+++	+++	+++	++	+++	+++

Key. (+) =faintly present, (++) = moderately present, (+++) = abundance Card=cardiac, Gly=glycoside, Carb= carbohydrate, Alk=alkaloids, Terp= terpenoids

Effects of the extract on arthritis

The extract (250 and 500 mg/kg) exerted dose related significant ($P < 0.05$) anti-arthritic effect when compared to control. On day 14th the 500 mg/kg dose produced 83.64% reduction in the paw edema which was comparable to that of Diclofenac (82.21%) (Table 2).

Table 2. Effect of extract on formalin induced arthritis

	Change in paw diameter (mm)						
	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14
Dist water 10ml/kg	1.65±1.44	2.07±0.43	3.80±0.42	3.90±0.34	3.95±0.32	4.56±0.64	4.89±0.23
Diclo 10mg/kg	1.44±0.21 (12.73%)	1.57± 0.11 (24.15%)	1.52± 0.16* (60.00%)	1.23±0.16* (68.46%)	1.05±0.21* (73.42%)	0.97±0.54* (78.73%)	0.87±1.34* (82.21%)
250mg/kg extract	1.61± 0.27 (2.42%)	1.52± 0.39 (26.57%)	1.47±0.16* (61.32%)	1.40±0.40* (64.10%)	1.35± 0.54* (67.09%)	1.30±0.268* (71.49%)	1.25±0.99* (74.44%)
500 mg/kg extract	1.40±0.65 (15.15%)	1.35± 0.60 (34.78%)	1.31±0.54* (65.53%)	1.28± 0.14* (67.18%)	0.98± 0.64* (75.19%)	0.90±0.55* (80.26%)	0.80±0.35* 83.64%

Values are represented as mean ± standard error of mean (n=5). P<0.05. Key: Diclo=diclofenac, Dist =distilled

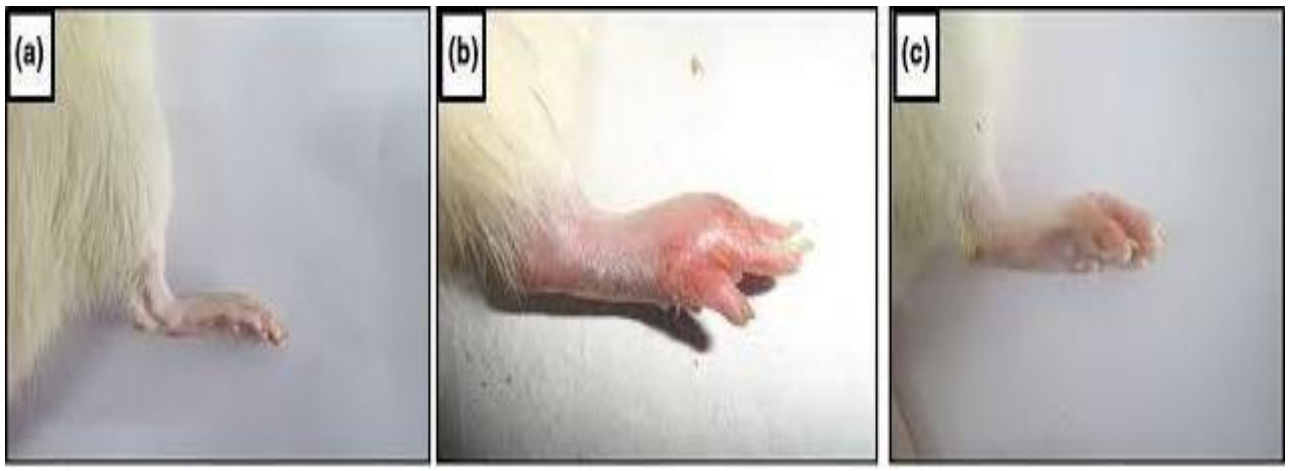

Figure2. The pictorial view of left hind limb of a study animal treated with 500 mg/kg.
A=Before induction, B= After induction, C=On 14th day of treatment using the extract

In-vitro antioxidant effect of the extract.

The extract demonstrated dose-related significant ($P < 0.05$) DPPH radical scavenging activities when compared to the control (Table 3). The IC_{50} value for the extract was 9.32 ug/ml, while that for the Ascorbic acid was 6.12 ug/ml. The smaller the IC_{50} value the higher the anti-oxidant effect.

Table 3. DPPH scavenging activity of the extract

Conc. ug/ml	15.625	31.25	62.5	125	250	500	1000	IC_{50}
Ascorbic acid	6.17±1.16	14.12±0.87	54.16±0.65*	85.33±1.76*	93.64±0.46*	94.76±1.11*	94.10±0.81*	6.12
A.H	8.39±0.44	10.36±0.56	45.67±0.32*	69.18±0.56*	84.07±0.38*	87.23±0.55*	89.30±0.34*	9.32

Values are represented as mean ± standard error of mean (n=5). $P<0.05$. AH=*Artocapus heterophyllus* leaf extract

Histopathological effects of the extract on proximal inter phalangeal joints

The result revealed that the histoarchitectural structure of the negative control group was strongly affected (Figure 3A), while that for positive control was slightly affected (Figure 3B). The low dose of the extract (250 mg/kg) caused a moderate change in the histoarchitectural structure (Figure 3C). The group treated with higher dose of the extract (500 mg/kg) showed a slightly affected histoarchitectural structure (Figure 3D). The leaf extract was able to confer a protective effect on the histoarchitectural structure of the proximal interphalangeal joints of the rats resulting in the observed lesser damage in the extract-treated group when compared to the negative control group.

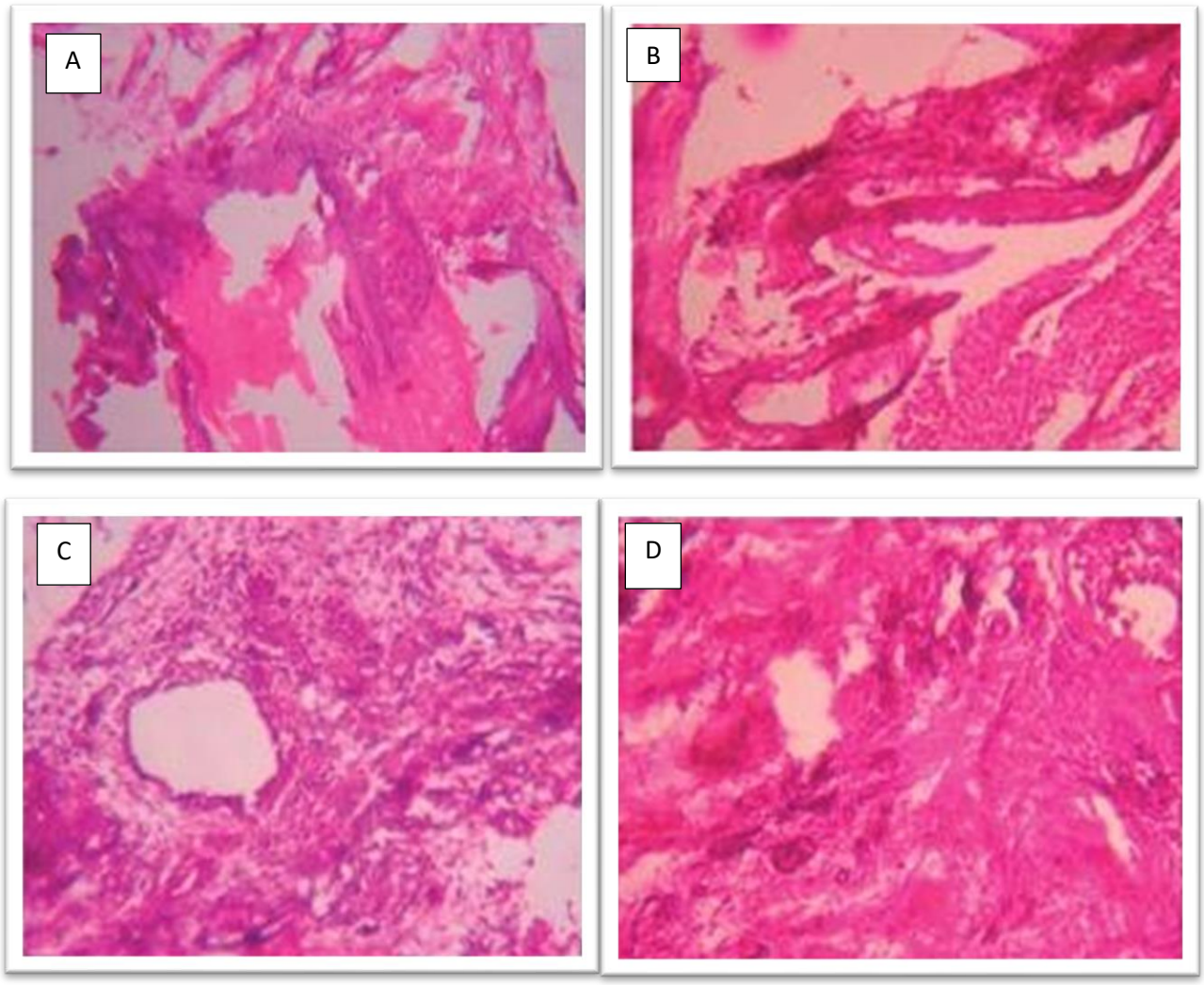

Figure 3. Histopathology of proximal interphalangeal joints on formalin induced arthritic rats. Figure 3A: Negative control histoarchitectural structure strongly affected; Figure 3B: Positive control; histoarchitectural structures lightly affected; Figure 3C: Extract 250mg/kg; histoarchitectural structure moderately affected; Figure 3D: Extract 500 mg/kg; histoarchitectural structures lightly affected

Discussion

Herbal medicines have played vital roles in the field of medicine (Taric *et al*., 2018). About 325 species and 95 families of medicinal plants were recognized as being used by most people in Nigeria for the treatment of various diseases (Monier, 2016). However, some herbal medicines have been implicated in organ damage and fatal events (Frenzel and Teschke 2016). Oral administration of the leaf extract up to 5000 mg/kg dose produced neither death nor any sign of toxicity in all the animals; attesting to the relative safety of the extract. Pharmacological properties of plant extracts are attributed to the presence of secondary metabolites such as phenols, flavonoids, tannins, flavonoids, proanthocyanidins, nitrogenous compounds, vitamins and terpenoids (Saeed *et al*.; 2012). The phytochemical screening of the leaf extract revealed the abundance of tannins, flavonoids, carbohydrates, saponins, alkaloids, phenols and cardiac glycosides with moderate presence of terpenoids, glycosides and traces of steroids. These secondary metabolites were also reported by Baliga *et al* (2011) to be present in *A. heterophyllus* fruit extract.

The radical-scavenging capacity of tannins has previously been reported (Serrano *et al*., 2009). The antioxidants inhibit the production of reactive oxygen species, which is a major factor in inflammation (Desai *et al*., 2009). Phenolics like flavonoids and tannins exert their antioxidant effects by decreasing oxygen concentration, intercepting singlet oxygen, preventing first chain initiation by scavenging initial radicals, such as hydroxyl radicals (Do *et al*., 2014). Flavonoids were also reported to interfere with the different stages of the arachidonate cascade via cyclooxygenase or lipoxygenase pathways to alleviate inflammatory responses (Mulaudzi *et al.,* 2013).

Formaldehyde induces an arthritic model that resembles human arthritis, thus allowing for the evaluation of the anti-arthritic activities of test substances. Formaldehyde injection causes localized inflammation, and it is one of the methods of evaluating the potentials of anti-arthritic agents. Formaldehyde induces arthritis by breaking down proteins at the site of injection, which produces an immune response against the degraded substances (Nair *et al*., 2012). Arthritic action of formaldehyde consists of two phases. In the initial phase, substance P is released, while in the late phase bradykinin, histamine, serotonin, and prostaglandins are released, which results in marked permeability and vasodilation of the tissues. These mediators are also responsible for hyperalgesia by stimulating nerve terminals and pain receptors (Pinchuk *et al.;* 2012). Hypersensitivity is evoked at the injection site (Desai *et al*., 2012). It has been revealed that central nervous system (CNS) acting drugs hinder both phases uniformly, but peripherally acting drugs hamper the late phase (Uttra and Hasan, 2017).

In this study, 0.1 ml formaldehyde solution induced a chronic phase of inflammation (Amraoui *et al*., 2019). On day 14 of treatment, the extract was able to confer a dose-dependent anti-arthritic effect which led to observed significant ($p < 0.05$) reduction in paw thickness which was comparable to Diclofenac sodium. This result attests to the anti-arthritic effect of the extract. The observed anti-arthritic effect could be due to a decrease in the release of inflammatory mediators since the ameliorative effects of saponins on inflammation had been linked to their ability to block inflammatory mediators including histamine, serotonin, and prostaglandin (Desai *et al*., 2009).

Furthermore, the dose related protective effects of the leaf extract on the histoarchitectural structures of proximal interphalangeal joints of the rats, as seen in the histology study, confirmed the anti-arthritic potentials of this leaf extract.

Conclusion

In conclusion the promising activities of the *A. heterophyllus* leaf extract support the traditional claims of its use as a remedy for arthritis.

Conflict Of Interest

There was no conflict of interest in the execution and reporting of this study.

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