ORIGINAL PAPER

Nig. J. Pharm. Res. 2017, 13 (2) pp 157-166
ISSN 0189-8434 **Available online at http://www.nigjpharmres.com**

Anti – inflammatory and Antioxidant Effects of *Tetrapleura tetraptera* (Schumach & Thonn.) Taub. Fruit Extract in Carrageenan/Kaolin-induced Acute Monoarthritis in Rats

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: *Tetrapleura tetraptera* has been reported traditionally for the treatments of various ailments, which include convulsion, leprosy, inflammation and rheumatic pains, schistosomiasis, asthma and hypertension. The anti-inflammatory activity of the aqueous extract of *T. tetraptera* fruit in egg albumin-induced paw oedema as well as *in vitro* anti-inflammatory and antioxidant activity had been documented. However, there had been no studies on the antiarthritic properties of the plant.

Objectives: The present study was designed to investigate *in vivo* anti-inflammatory and anti-oxidant activities of the methanol extract *Tetrapleura tetraptera* in carrageenan/kaolin-induced acute monoarthritis in rat.

Materials and methods: The acute toxicity of the methanol plant extract was determined using Lorke's method. *In vivo* carrageenan/kaolin induced arthritis assay was performed on *Tetrapleura tetraptera* (*Tt*ME) extract (100, 200 and 400 mg/kg) using albino rats. Indomethacin (10 mg/kg) and normal saline were employed as positive and negative controls, respectively. Histological study was performed on the knee joint of the animals after collection of blood for antioxidants analysis.

Results: Acute toxicity study showed that *Tt*ME is safe by oral administration up to 5000 mg/kg body weight. Oral administration of *T*tME and indomethacin (10 mg/kg) produced a significant ($p < 0.05$) time and dose-dependent decrease in joint diameter. There was a decrease in malondialdehyde and increase in glutathione and superoxide dismutase. The histological assessment revealed no major adverse effects on the animals.

Conclusion: *Tetrapleura tetraptera* fruit extract possesses anti-arthritic activity, which may be attributed to its anti-inflammatory and antioxidant activity.

Keywords: *Tetrapleura tetraptera,* Antioxidant, Anti-inflammatory, Anti-arthritic activity, Histopathology

INTRODUCTION

Osteoarthritis (OA) is a progressive rheumatic disease characterized by the degeneration of articular cartilage. It is the most common of all rheumatic disorders and is destined to become one of the most prevalent and costly diseases in our society (Brooks and March, 1995). OA affects the entire joint complex including subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles. Clinically the disease presents as joint pain, tenderness, limited movement, crepitus (grating sound on movement), and occasional joint swelling (Brandt *et al*., 2003). Thus, therapeutic management of OA traditionally involved the use of steroidal and non-steroidal anti-inflammatory drugs to mitigate the inflammatory progression and provides relief from pain. In addition, therapeutic intervention may employ the use of physiotherapy, antidepressant therapies and more importantly, patient education (Long *et al.,* 2001). Recently, the introduction of biologics (e.g IL-1 receptor antagonist, soluble TNF

receptor-2 antagonists) among others has brightened the prospects of improved therapeutic outcome for the patients. However, challenges arising from serious adverse effects of NSAIDs to the cost of biologics are driving the search for better cost effective and well tolerated agents. Hence, there appears to be a need for drugs with good efficacy and low toxicity in the treatment of OA (Crofford, 2013; Ungar *et al.,* 2013). Specifically, there is a need for safe and effective drugs for patients who do not respond well to conventional medical therapy. Such patients are turning increasingly to complementary/alternative medicine.

Medicinal plants and their extracts have long been used as therapeutic agents for arthritis treatment in the traditional systems of medicine in many parts of the world (Jung *et al*., 2012; Kim *et al.,* 2012). Most of the commonly used herbal remedies by traditional medical practitioners have not been scientifically validated. In addition, there is a rapid disappearance of traditional herbal knowledge in the society and increased biodiversity degradation, all leading to loss of the economically valuable cultural heritage. All these call for conscious and concerted efforts to collect, document and scientifically validate medicinal plants use in our communities (Lee, 2000).

Tetrapleura tetraptera (Schumach & Thonn.) Taub. (Fabaceae) locally known as Aridan, is a large tree growing throughout the rain forest belt of West Africa. It is generally found in the lowland forest of tropical Africa. The fruit consists of a fleshly pulp with small, brownish – black seeds. The dry fruit has a pleasant aroma and it is used as a popular seasoning spice, a medicine and a dietary supplement rich in vitamins in Southern and Eastern Nigeria (Essien *et al*, 1994, Okwu, 2003). The fruit is used to prepare soup for mothers from the first day of birth to prevent postpartum contraction (Nwawu and Akali, 1986). The plant has many traditional uses mainly in the management of convulsion, leprosy, inflammation and rheumatic pains, schistosomiasis, asthma and hypertension (Aladesanmi, 2007). The root extract has been proven to be useful for the treatment of gastrointestinal related clinical problem (Noamesi *et al*., 1994). The alleopathic potential of *T. tetraptera* has led to its integration into an agro forestry system (Amoo *et al*., 2008).

Toxicological reports have shown that *T. tetraptera* has no cytotoxic and genotoxic effects in chinese hamster ovary cells (Adewunmi *et al*., 1991). *Tetrapleura tetraptera* has been shown to cause elevation in serum AST and alteration of various metabolic parameters and did not induce any marked pathological lesion in the liver (Lawal *et al*., 2009). Ethnopharmacological survey of *T. tetraptera* has shown the traditionally uses of the fruit infusion and decoction in inflammation and pain (Ojewole and Adesina, 1983; Sofodiya *et al.,* 2007; Olowokudejo *et al.,* 2008; Fasola and Iyamah, 2015). It has been reported that the fruit of *T. tetraptera* contains phenolic compounds such as caffeic acid, catechin, gallic acid, coumaric acid, apigenin, quercetin, rutin and syringic acid (Moukette *et al.,* 2015).

The ethanolic extract of *T. tetraptera* fruit exhibited antiplasmodial activity in mice (Okonkon *et al*., 2007). The extract has been reported to possess analgesic and anticonvulsant properties (Ojewole, 2005; Aderibigbe *et al.,* 2007). Ojewole and Adewunmi (2004) had earlier reported the anti-inflammatory activity of the aqueous extract of *T. tetraptera* fruit in egg albumin-induced paw oedema, but no other studies on the anti-arthritic properties. We recently reported the *in vitro* antioxidant and membrane stabilizing properties of the fruit extract and fractions of *T. tetraptera* (Sonibare *et al.,* 2015). It is in this interest that this study was designed to investigate the *in vivo* anti-inflammatory and anti-oxidant activities of the methanol extract *Tetrapleura tetraptera* in carrageenan/kaolin-induced acute monoarthritis in rat.

MATERIALS AND METHODS

Chemicals

Indomethacin, carrageenan (type 1), dithios nitrobenzoic (DTNB), thiobarbituric acid (TBA) were obtained from Sigma Aldrich (Steinhem, Germany). Sodium carbonate, epinephrine (BDH, England). Trichloroacetic acid, DTNB, potassium chloride, methanol and formaldehyde were of analytical grade.

Collection and identification of plant material and Extraction

The dry fruits of *Tetrapleura tetraptera* were collected during the month of March 2014, from Wasinmi village, Ogun State, Nigeria. The botanical identity of the plant was confirmed in Forest Herbarium (FHI), Ibadan, Nigeria where voucher specimen **FHI 110141** was deposited. The fruits were air dried under shade and pulverized into fine powder first using a grinding machine and thereafter an electronic blender. Powdered plant material (1.5 kg) was macerated at room temperature with 12 L of distilled methanol with frequent stirring for 72 h. The extract was filtered with Whatman filter paper No. 1. The extraction was repeated three times until complete extraction and the extract concentrated *in vacuo*. The final combined extract was 12.8% of the initial starting material (Sonibare *et al*., 2015).

Experimental animals

Wistar female rats weighing 150 to 200 g were obtained from the College of Medicine Central Animal House, University of Ibadan. The animals were housed in cages maintained under standard conditions and fed with standard pellets (Vital Feeds Ltd, Ibadan, Nigeria) and received water *ad libitum.* All experiments were carried out with strict compliance to the "Principle of Laboratory Animal Care" (NIH Publication No. 85-23) and ethical guidelines for investigation of experimental pain in conscious animals (Zimmerman, 1985).

Acute toxicity study

The acute toxicity study was conducted in two phases using Lorke's method (Lorke, 1983). In phase 1, twelve female rats, which were fasted for 12 hours were randomly divided into four groups of three rats per group. Three groups were administered *Tt*ME (10, 100, 1000 mg/kg) and the fourth group received vehicle (10 mL/kg per body weight). The rats were observed in the first 2 h for behavioral alterations or death in a Perspex chamber, and once daily for 14 days. In Phase 2, three rats each received 1600, 2900 and 5000 mg/kg body weight. The rats were observed for signs of adverse effects and death for 24 h and daily for 14 days. The geometric mean of the least dose that killed rat and the highest dose that did not kill rat was taken as the median lethal dose.

Carrageenan/Kaolin-induced acute monoarthritis in rats

The anti-inflammatory activity of *Tt*ME and indomethacin on carrageenan / kaolin-induced acute monoarthritis in rats was investigated according to the method of Sluka and Westlund (1993). The animals were divided into six groups, each consisting of five rats. Briefly, three doses of *Tt*ME (100, 200 and 400 mg/kg) were administered orally to rats for seven consecutive days. Indomethacin (10 mg/kg) was administered once on the last day 1 hour before induction. One hour after the last treatment, rats were lightly anaesthetized with ether, then 0.1 mL of a mix of 3% carrageenan and 3% kaolin were injected into the knee joint cavity and the leg was flexed and extended for about 2 min. The following parameters were then assessed.

Measurement of Knee swelling: The swelling caused by intra-articular CK injection was assessed by measuring the knee circumference with the aid of electronic digital vernier caliper (Mytutoyo, Japan), the measurements were taken immediately before the injection of CK and at different time points (1, 3 and 5 h). The values obtained were expressed as an index of increases in knee circumference by subtracting the value from the knee circumference obtained before and after CK injection.

Assessment of Pain behavior (Locomotory activity):

Reduction in locomotory activity as an index of pain was determined in CK injected rats (Larsen and Arnt, 1985). Rats induced with monoarthritis following injection of 3% carrageenan/kaolin mixture were placed individually in the Ugo Basile activity meter cage. The activity meter cage measures ambulatory activity (horizontal beam breaks) and rearing (vertical beam breaks). The beam interruptions were counted and recorded by the electronic unit. The locomotory activity was quantified for 5 min after 24 hours carrageenan/kaolin injection.

Biochemical assessment: Twenty four hours after the injection of Carrageenan/kaolin into the knee joint cavity, all animals were subjected to deep ether anaesthesia. Blood was collected by cardiac puncture into heparinized bottles. The plasma was separated by centrifugation at 3000 rpm below 30^{o}C for 15 min and used for the assay of total protein, nitrite, reduced gluthathione (Sin *et al.,* 1997), malondialdehyde (Nagababu, 2010), and superoxide dismutase (Misra and Fridovich, 1972).

Histological analysis: Ankle joints were separated from the hind paw, weighed and immersed in 10% buffered formalin for 24 h. Histological tissue were processed for haematoxylin – eosin staining. Photographs of the prepared slides haematoxylin – eosin stained tissue sections were taken with a camera attached to a compound light microscope.

Statistical analysis:

All data were presented as mean ± standard error of mean (SEM) and statistical significance was taken for $p< 0.05$. Data were analysed using one-way analysis of variance (ANOVA), significant main effects were further analysed by Bonferroni's *post hoc* test for multiple comparison of treatment groups with GraphPad Prism® software version 5.01 (GraphPad Software, Inc. La Jolla, CA 92037 USA).

RESULTS

Anti-inflammatory effect of *T. tetraptera* fruit extract on carrageenan/kaolin-induced knee swelling in rats

Injection of carrageenan/kaolin into the paw produced an increase in joint diameter peaked at the fifth hour (Table 1). Injection of normal saline in the control animals produced no increase in the joint diameter. The inhibitory effect of *Tt*ME was monitored at the 1, 3 and 5th hour. Oral administration of *Tt*ME (100, 200 and 400 mg/kg) and indomethacin (10 mg/kg) produced a significant ($p < 0.05$) time and dose-dependent decrease in joint diameter. *Tt*ME at 100, 200 and 400 mg/kg produced maximal effect at 5th hour in reducing knee swelling by 1.54 ± 0.27, 0.67 ± 0.14 and 0.35 ± 0.13 (inhibition by 46.0, 76.5, and 87.7%) respectively, when compared to arthritic control (2.85 ± 0.09). Indomethacin was more effective in reducing joint diameter to 0.15 ± 0.05 (inhibition by 94.7%).

Table 1: Effect of *T. Tetraptera* on carrageenan/kaolin-induced knee swelling

Treatment	Dose (mg/kg)	Increase in Knee circumference (mm)[a,b]		
		1h	3h	5h
Vehicle control	10 mL/kg	0.046 ± 0.02	0.076 ± 0.01	0.036 ± 0.02
Arthritic control	10 mL/kg	1.22 ± 022	2.74 ± 0.15	2.85 ± 0.09
***Tt*ME**	100	1.11 ± 0.25	1.56 ± 0.27*	1.54 ± 0.27*
		(9.01)	(43.1)	(46.0)
***Tt*ME**	200	0.54 ± 0.07*	0.74 ± 0.07*	0.67 ± 0.14*
		(55.7)	(73.0)	(76.5)
***Tt*ME**	400	0.26 ± 0.06*	0..50 ± 0.12*	0..35 ± 0.13*
		(78.7)	(81.8)	(87.7)
Indomethacin	10	0.47 ± 0.11*	0.58 ± 0.13*	0.15 ± 0.05*
		(61.5)	(78.8)	(94.7)

[a] Values are expressed as Mean ± SEM (n=5). [b] Values in parenthesis are Percentage of inhibition of knee swelling.
*p<0.05 when compared with control using two way ANOVA followed by Bonferroni post hoc test for multiple comparisons.

Effect of *T. tetraptera* fruit extract on carrageenan/kaolin-induced impairment of locomotory activity in rats

The effect of *Tt*ME on locomotory activity determined 24 hours after intra-articular injection of CK in rats is shown in Table 2. The exploratory activity (total horizontal beam breaks/5 min) and rearing (vertical beam breaks/5 min) was significantly reduced by 24.6 and 40.5% respectively, in CK injected rats (arthritic control) when compared to rats injected with normal saline (vehicle control). Oral administration of *Tt*ME (100, 200 and 400 mg/kg) and indomethacin (10 mg/kg) alleviated CK-induced locomotory activity impairment. Only *Tt*ME (400 mg/kg) and Indomethacin (10 mg/kg) significantly ($p < 0.05$) alleviated CK-induced reduction in rearing activity in rats.

Table 2: Effect of *Tt*ME on the locomotory activity in carrageenan/kaolin induced monoarthritic rats

Treatment	Dose	Parameters[a]			
		exploratory activity	% reduction	rearing	% reduction
Vehicle control	10 mL/kg	379.8 ± 14.7	-	117.4 ± 5.1	-
Arthritic control	10 mL/kg	286.2 ± 21.8#	24.6	69.8 ± 3.5#	40.5
***Tt*ME**	100	318.4 ± 31.3	16.1	75.2 ± 4.2	35.9
***Tt*ME**	200	316.2 ± 23.9	16.7	78.0 ± 5.0	33.5
***Tt*ME**	400	367.2 ± 37.5	3.2	125.4 ± 5.1*	-0.06
Indomethacin	10	328.8 ± 51.7	13.4	115.6 ± 5.0*	0.02

[a] Values are expressed as Mean ± SEM (n=5). # $p < 0.05$ vs VC or * $p < 0.05$ vs AR; 1-way ANOVA followed by Bonferroni's post hoc test. VC- Vehicle control; AR – Arthritic control rats.

Effect of *T. Tetraptera* fruit extract on serum anti-oxidant status in carrageenan/kaolin-induced monoarthritic rats

The serum malondialdehyde (MDA) levels significantly ($p < 0.05$) increased by 45% in arthritic control rats compared to normal saline injected rats (Figure. 1A). Pretreatment of arthritic rats with *Tt*ME (100, 200 and 400 mg/kg) significantly reduced MDA by 23.8, 29.1 and 22.9% respectively. The antioxidant level of reduced glutathione (GSH) was significantly ($p < 0.05$) depleted in arthritic control rats by 50% when compared to normal saline injected rats (Figure. 1B). GSH depletion was however reversed significantly ($p < 0.05$) by *Tt*ME (100 and 400 mg/kg). In a similar manner, the activity of SOD was significantly ($p < 0.05$) elevated in rats pretreated with *Tt*ME (100, 200 and 400 mg/kg) by 25.7, 16.7 and 19.1%, respectively (Figure. 1C). Indomethacin (5 mg/kg) significantly ($p<0.01$) reduced serum MDA (30.4%), but increased the levels of GSH (47.1%) and SOD (20.2%).

Histological changes in arthritic rats

No visible lesions on the joint capsule of normal saline injected rats. There is acute inflammation of the joint capsule, congested blood vessels (arrow) as well as numerous cellular aggregates in the arthritic control rats (Figure 2B). There is marked widespread aggregates of inflammatory cells mostly neutrophils and macrophages suggestive of acute inflammation of the joint capsule in Figure 2C. There is moderate proliferation of fibroblasts as well as slight increase in number of mononuclear cells in the joint capsule of TtME (200 mg/kg). Histology of animals that received TtME (400 mg/kg) showed no visible lesions and there is mild localized fibroblastic proliferation in the connective tissue of the joint capsule. Indomethacin treated animals showed a few foci of mild accumulation of mononuclear cells (macrophages) in the joint capsule (Figure 2F).

DISCUSSION

Tetrapleura tetraptera fruit has been reported to contain many chemical compounds, including: triterpenoid glycoside (aridanin), coumarins, flavonoids and other phenolic compounds (Adesina *et al*., 1980). However, there is absolutely no previous scientific information on the anti – arthritic properties of the plant, though the anti – inflammatory activity of the plant has been reported by Ojewole and Adewunmi (2004). Also the exact chemical constituent/s of the fruit that is/are responsible for the observed anti-arthritic effect of the plant extract still remains speculative. Several investigators have shown that phenolic compounds (e.g., tannins, coumarins and flavonoids), triterpenoids and a host of other secondary plant metabolites possess anti-inflammatory effect in various experimental animal models (Dongmo *et al*., 2003; Taesotiku *et al*., 2003; Adzu *et al*., 2003). Since the fruit of *T. tetraptera* contains triterpenoid (aridanin), coumarin (scopoletin) and flavonoids, it is not unlikely that these compounds might have contributed largely to the observed anti- arthritic and effect of the plant's fruit methanol extract.

Acute toxicity study of *T. tetraptera* methanolic extract showed that the extract possesses high safety profile as no death was observed at oral doses of 10 – 5000 mg/kg and there were no behavioural changes in rats.

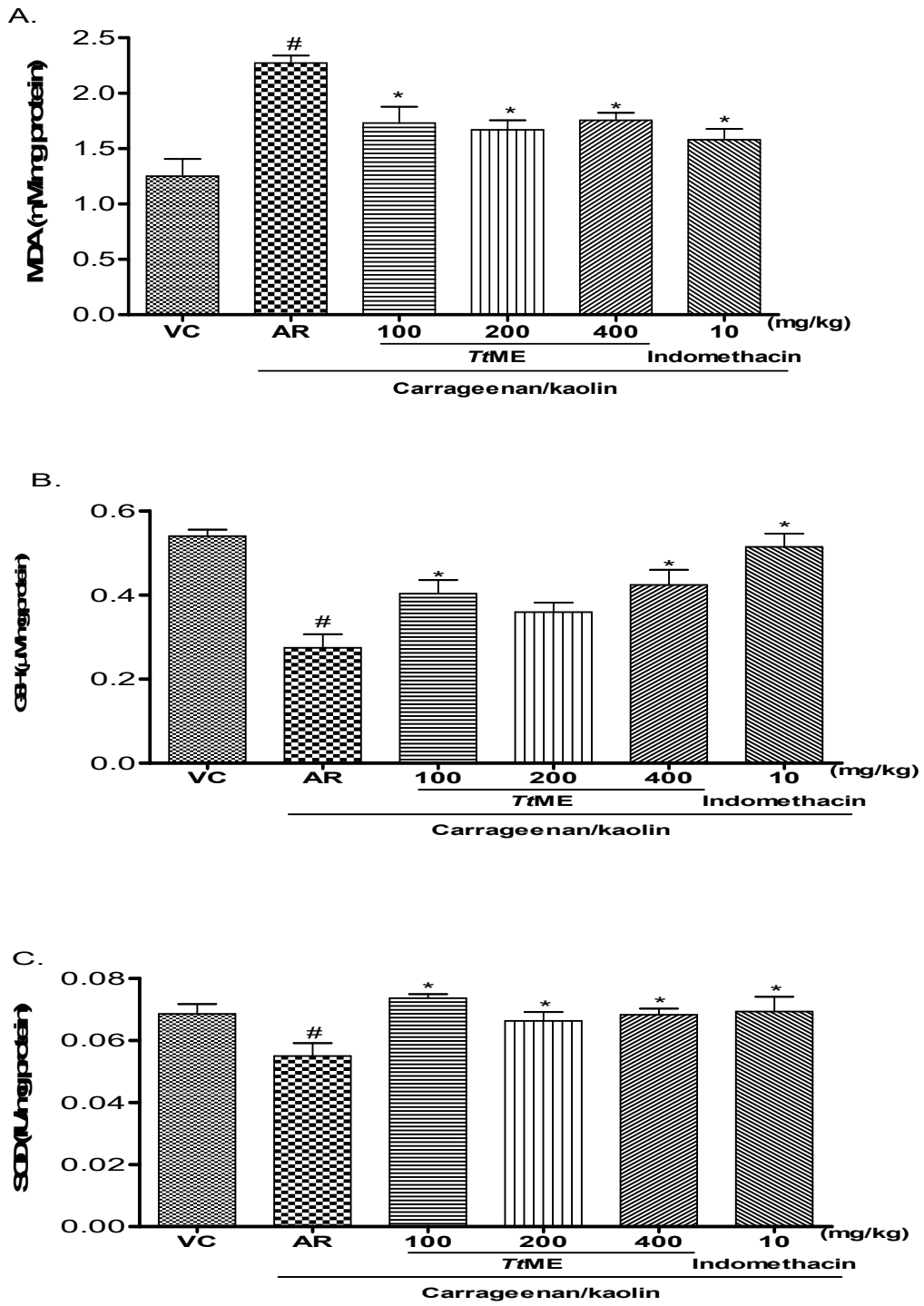

Figure 1: Antioxidant effects of *Tetrapleura tetrapera* extract A. MDA, B. GSH C. SOD. Data represent Mean ± SEM of five rats. # $p < 0.05$ vs VC or * $p < 0.05$ vs AR; 1-way ANOVA followed by Bonferroni's post hoc test. VC- Vehicle control; AR – Arthritic control rats

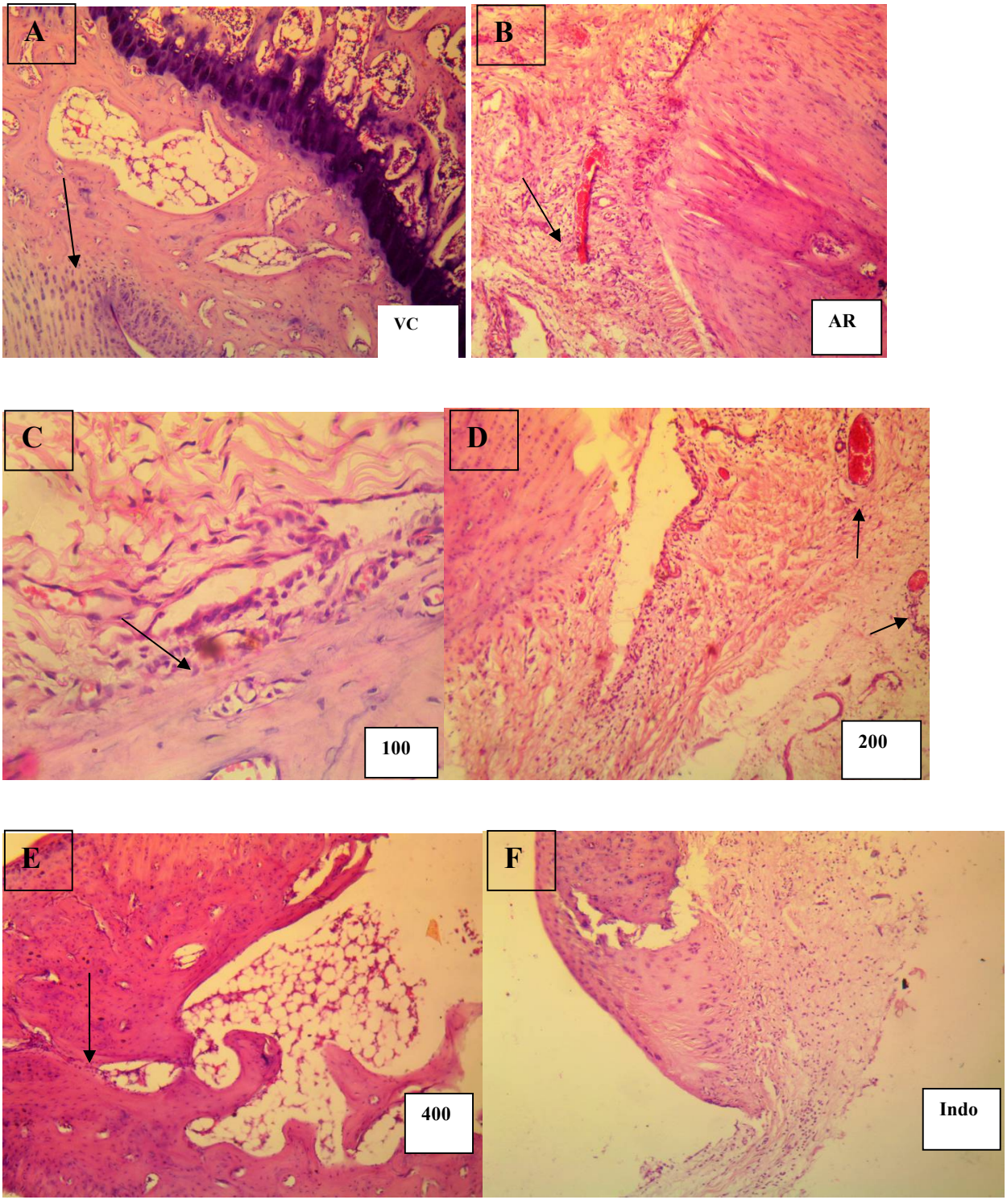

Figure 2 A-F: Effect of *Tetrapleura tetraptera* Methanol extract on histology of inflamed joint in Rats

The *in vivo* anti – arthritic activity of *T. tetraptera* extract which is made up of dry fruits of *T. tetraptera* was further evaluated in the kaolin/carrageenan induced arthritis model in rats. Kaolin/Carrageenan induced arthritis is biphasic in nature with the first phase mediated by histamine and serotonin, the second mediated by prostaglandins particularly the E series and cyclo-oxygenase products which includes prostacyclins and thromboxanes. The continuity between the two phases is ensured through the action of kinins (Silva *et al.*, 2005; Perianayagam *et al.,* 2006). Inhibition of these mediators in effecting their pharmacologic activity is a sure way of curbing the incidence of inflammation at the site of injury. This study has shown that the methanolic fruits extract of *T. tetraptera* has important anti-arthritic effect in rats induced by kaolin/carrageenan. Since kaolin/carrageenan-induced inflammation model is a significant predictive test for anti-inflammatory agents acting by the mediators of acute inflammation, the result of this study is an indication that methanolic fruits extract of *T. tetraptera* can be effective in acute inflammatory disorders. The kaolin/carrageenan induced arthritis model is considered as an acute and proliferative arthritis similar to clinical arthritis. In kaolin/carrageenan arthritis model, rats develop an acute swelling in the left knee joint with influence of inflammatory cells, erosion of joint cartilage and bone destruction. These inflammatory changes ultimately result in the complete destruction of joint integrity and function in affected animals. This is a most frequently used model for screening the anti–arthritic agents, especially NSAIDs, as the inflammation associated with kaolin/carrageenan dependent on macrophages generated by neutrophils.

In this study, reduction of joint swelling in the drug treated rats from 1 h onwards may be due to joint protection rendered by the plant extract. Kaolin/carrageenan inoculation triggers the production of activated macrophages and lymphocytes or their products like monokines, cytokines and chemokines. These in turn produce lipid peroxides due to abnormal lipid peroxidation leading to increased inflammation (Kim *et al.,* 2011). A significant reduction in the joint diameter was shown in animals treated with TtME when compared to the arthritic control rats, indicating the antiperoxidative nature of the plant extracts. It was reported that the expression of inflammatory cytokines such as TNF–α and IL–1 β and the tissue enzymes such as metalloproteinases were observed to be increased in the sub – chondral bone region of the knee joint samples from human osteoarthritis or rheumatoid arthritis patients. Biological agents that specifically inhibit the effects of TNF–α or IL–1 or leukocyte migration and accumulation in arthritis may have beneficial effects for joint preservation.

Carrageenan injection is linked to the production of neutrophil-derived reactive oxygen species (ROS) and nitrogen species (RNS), such as the hydrogen peroxide, superoxide and hydroxyl radicals and to the release of other neutrophil-derived mediators in approximately 1- 5 hours (Salvimenin *et al,* 1996). Oxidative stress plays a pivoted role in modulating the disease state in arthritis. Kaolin/Carrageenan induced arthritic model demonstrates a severe rise in the various cytotoxic free radicals in plasma joint (Cerha *et al*., 2003). In kaolin/carrageenan arthritis, the tissue damage is mediated by lipid peroxidation and is associated with the aggravation of arthritis (Halliwell *et al*., 1998). Lipid peroxidation causes lysosomal destruction which plays a role in arthritis development. The level of these enzymes represents the oxidative stress in the entire body of the animal. Hence MDA, GSH and SOD were measured in the blood serum of the rats in the various treatment groups. Glutathione is synthesized in the liver and acts as a first line of defense against oxidative stress and peroxidation (Rasool and Varalakshmi, 2007). MDA is an index of lipid peroxidation. The infiltrating cells also generate reactive oxygen species and free radicals that destruct the inflamed joint. As a result, the scavenging enzyme SOD is utilized and reduced in arthritic rats. The hydrogen peroxide generated by this process is decomposed by catalase and glutathione peroxidase. This may also contribute to decreased activity in arthritic condition. The level of glutathione, a non-enzymatic reducing agent, is also decreased in arthritis (Lawrence, 1976). In this present study, the level of oxidative stress markers in the serum was determined at the end of the study. *Tetrapleura tetraptera* fruit extract was able to inhibit the oxidative changes brought about by kaolin/carrageenan induced arthritis. The elevated Malondialdehyde levels in the arthritic control group were reduced whereas the reduced Superoxide Dismutase and Gluthatione levels were elevated to restore normal level of oxidative markers in the blood serum. It could be postulated that the amelioration of arthritis was due to the suppression of oxidative stress in the blood serum of the animals and attributed to the synergistic contribution of a plethora of phytoconstituents such flavanoids, terpenoids and polyphenols.

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Conflict of Interest: None declared

Received: 13 September 2017

Accepted: 06 November, 2017