Journal of Applied Pharmaceutical Science Vol. 4 (06), pp. 068-073, June, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40610
ISSN 2231-3354

Anti-Inflammatory Activities of Methanol Leaf Extract of *Bridelia micrantha* (Hochst) Baill. (Euphorbiaceae) In Wistar Rats

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ARTICLE INFO

Article history:
Received on: 24/04/2014
Revised on: 09/05/2014
Accepted on: 19/05/2014
Available online: 28/06/2014

Key words:
Edema, Inflammation, *Bridelia Micrantha*, Acetylsalicylic Acid, Phenylbutazone

ABSTRACT

Aerial parts of *Bridelia micrantha*, a semi-deciduous tree are widely used in African traditional medical practice in the treatment of painful inflammatory conditions of the joints. This study evaluated the anti-inflammatory activities of the methanol leaf extract of *Bridelia micrantha* using acute, sub-acute and chronic models of inflammation in Wistar rats. In the carrageenan-induced acute inflammation model, 400 mg/kg of extract produced 71.79 % edema inhibition while 200 mg/kg of the extract produced 55.13 % inhibition relative to 56.41 % inhibition of the rat paw edema with 200 mg/kg of Acetylsalicylic Acid (ASA) within 5 h. In the histamine-induced rat paw edema model, the extract exhibited 72.97 % protection at 400 mg/kg compared to 83.33 % edema inhibition with phenylbutazone (100 mg/kg) after 6 h. In the sub-acute model using formaldehyde-induced paw edema, 400 mg/kg of extract showed 59.77 % (0.35±0.03) inhibition after 24 h, while 54.02 % inhibition was produced by 200 mg/kg of extract and 200 mg/kg of ASA produced 56.32 % (0.38±0.04) inhibition when compared with the negative control group (0.87±0.05). In the cotton pellet-induced granuloma test, 400 mg/kg of extract gave 52.55 % (40.57±1.3) protection, while 200 mg/kg extract gave 47.25 % protection and 200 mg/kg ASA gave 49.38 % (43.25±1.8) when compared with normal saline treated group (85.5±3.2) after 7 days. The results obtained in this study showed that *Bridelia micrantha* leaf extract exhibited potent anti-inflammatory activities thus authenticating its acclaimed anti-inflammatory efficacy. It was concluded that the extract of *Bridelia micrantha* may be a potential anti-inflammatory agent in alleviating edema associated with arthritis and musculo-skeletal pains in humans.

INTRODUCTION

Edema is the medical term for swelling or accumulation of excess fluid in body tissues either within cells or in the interstitial spaces (Aukland and Reed, 1993; Dongaonkar *et al.*, 2008; Reed *et al.*, 2010; Svendsen *et al.*, 2011). Edema formation limits diffusional removal of toxins and byproducts of cellular metabolism, limits diffusion of oxygen and nutrients to tissues and may compromise cellular metabolism (Scallan *et al.*, 2010). Edema symptoms depend on the amount of fluid in the affected body part. In congestive heart failure, nephrotic syndrome and cirrhosis, fluid accumulates in extremities and abdominal cavity (Runyon, 1993; Khan, 2005). Local allergic reaction and tissue injury may cause swelling and pain in the affected area (Peartman, 1999; Khan, 2005). Also, tense skin, pain and limited movement can be symptoms of edema (Yuen *et al.*, 2008; Edge *et al.*, 2001; Suryakumar and Shukla, 2011). Most edema is associated with inflammation and treatment of the underlying cause of the inflammation cures the edema (Edge *et al.*, 2001). Thus depending on the underlying cause, edematous conditions can be treated using anti-histamines, corticosteroids, diuretics and non-steroidal anti-inflammatory drugs (Khan, 2005; Deschenis *et al.*, 2004). These synthetic drugs reported to be used for the treatments of inflammatory disorders are of least interest nowadays due to their potential side effects and serious adverse effects in humans and animals (Freidman and Kaiser, 2007; Rocca *et al.*, 2005; Green *et al.*, 2004; Abatan *et al.*, 2006). In the last few decades, alternative anti-inflammatory and analgesic agents have regained their popularity in the treatment against several human ailments such as inflammation (Bawa and Khanum, 2009; Tripathy *et al.*, 2010).

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These anti-inflammatory agents contain various classes of phyto-constituents including flavonoids, alkaloids, glycosides, terpenoids, steroids and polyphenolic compounds which act singly or synergistically in relieving inflammation (Gupta *et al.*,2006; Mohammad *et al.*, 2012). Due to the efficacy and safety of plant derived drugs, there is immense interest on medicinal plants used in traditional medicine in the treatment of inflammatory disorders. Plant materials have been reported to be present in or have provided the models for about 50 % of Western drugs, with herbal remedies demonstrating encouraging results in the cure of many diseases (Ndip *et al.*, 2007). These plants include *Acanthopanax senticosus, Albizia chinensis, Croton zambesicus, Cussonia paniculata, Kalopanax pictus, Khaya grandifoliola, Kigelia africana, Securidaca longipedunculata, Uncaria tomentosa, Zizyplus rugosa, Mallotus oppositifolius, Sterculia tragacantha,* (Yuen *et al*., 2008; Suryakumar and Shukla, 2011; Bawa and Khanum, 2009; Schriner *et al*., 2009; Udegbunam *et al*., 2011; Nwaehujor *et al.*, 2012). *Bridelia micrantha* (Hochst.) Baill. (Euphorbiaceae), also known as Coast gold leaf in English (Munzere in Venda) is a semi-deciduous to deciduous tree of up to 20 m tall, with a dense rounded crown and tall, bare stem which is widespread in Africa. The stem bark has been traditionally employed in South Africa to treat several pathological conditions, including helminthosis, gastro-enteritis, acquired immune deficiency syndrome, infertility, neurosis, psychosis and painful joints (Bessong *et al*., 2006; Iwalewa *et al*., 2007; Lin *et al*., 2002). The leaf sap of *Bridelia micrantha* is used by the Haya (Northwestern Tanzania) as an application to sore eyes; the Shambala (Tanzania) use the roots as a remedy for severe epigastric pain while the Zigula (Southern Tanzania) rub a preparation of the powdered root, made with oil or butter, into the scalp for the relief of headache (Samie *et al*., 2005). In both East and West Africa the root is used as a purgative (Watt and Breyer-Brandwijk, 1992). Steenkamp reported the use of the bark as an abortifacient with a potentially toxic effect probably due to the presence of delphinidin and methyl salicylate (Steenkamp, 2003). In five districts of Lagos state of Nigeria, *Bridelia micrantha* stem bark is used in traditional medicine for treating diabetes (Gbolade, 2009); in South Western Nigeria a leaf decoction is used traditionally as part of recipe for the management of diabetes mellitus and inflammation of joints (Abo *et al.*, 2008). In the Sango bay ecosystem in Rakai district, central Uganda, a decoction of bark and leaves is indicated for treating syphilis and the bark for pre-hepatic jaundice (Ssegawa and Kasenene, 2007). To the best of our knowledge no empirical study has evaluated its anti-inflammatory effect. Therefore, bearing in mind its use in South Africa and South western Nigeria in the management of joint inflammation, we considered it worthwhile to investigate the anti-inflammatory effect of *Bridelia micrantha*.

MATERIALS AND METHODS

Plant Material

Fresh leaves of *Bridelia micrantha* were collected in September, 2011 from Orba in Nsukka area, Enugu State, Nigeria. They were authenticated by Mr. A.O. Ozioko, a taxonomist with the International Centre for Ethno medicine and Drug Development, Nsukka, Enugu State, Nigeria.

Preparation of Extract

The fresh leaves were air dried and pulverized. The plant materials (1.0 kg) were cold macerated in 80 % v/v of methanol for 72 h with intermittent shaking. Thereafter, filtration was done using Whatman #1 filter papers. The solvent was evaporated in a rotary evaporator at 40 °C to obtain the extract (yield: 11.15 % w/w). The extract was stored at 4 °C.

Animals

Adult Wistar rats weighing 130-140 g and albino mice weighing 22 -32 g were used for the experiments. They were housed at 25 ± 5 °C under a 12-h light/12-h night conditions with free access to standard pelleted feed and clean drinking water. All experiments carried out in this study were approved by the Animal Ethics Committee, University of Calabar, Nigeria.

Acute Toxicity

Acute toxicity of the extract was investigated as described by Lorke (1983). Five groups of mice of both sexes were treated orally with the extract (200, 400, 800 and 1600 and 2500 mg/kg). The control group received distilled water (0.03 ml/10 g). They were observed for 48 h for mortality and adverse reactions.

Anti-Inflammatory Studies

Carrageenan-Induced Rat Paw Edema

Paw edema was induced by the modified method of Winter *et al.* (1962). Thirty (30) rats of mixed sexes were divided into 5 groups of 6 rats each. Group 1 (negative control) rats received 10 ml/kg normal saline, group 2 (positive control) rats were given 100 mg/kg Acetylsalicylate Acid (ASA) while groups 3, 4 and 5 rats received 100, 200 and 400 mg/kg of *Bridelia micrantha* extract respectively all by gastric gavage. Extracts and drug were given 1 h before paw edema induction. Induction in the rats was by injecting 0.1 ml of 1 % carrageenan in physiological solution into the subplantar aponeurosis of the left hind paw of each of the rats.

The right hind paw served as control. The paw volume of the rats was measured at 1, 2, 3, 4 and 5 h after carrageenan injection by the mercury displacement method using a plethysmograph. Percent inhibition of edema volume between treated and control groups were calculated as follows:

$$\text{Percent inhibition} = \frac{Bc - Bt}{Bc} \times 100$$

where, Bc and Bt represent the mean increase in paw volume in control and treated groups, respectively.

Histamine-Induced Rat Paw Edema

The experiment was conducted according to the methodology used by Singh and Pandey (1996). Thirty (30)

mature albino rats were randomly divided into 5 groups of 6 rats each for this study.

Histamine (1 mg/ml) was used as the phlogistic agent. The effect of *Bridelia micrantha* extract at 100, 200 and 400 mg/kg, *per os*, was tested. Right hind paw edema was induced by the sub plantar injection of 0.1 ml of histamine. Extract was administered 1 h prior to the inflammatory challenge. The pedal volume was measured just before 1, 3 and 6 h after the phlogistic challenge. Phenylbutazone (100 mg/kg, *per os*) was used in this study as reference standard and normal saline was used as negative control.

Formaldehyde-Induced Hind Paw Edema

Mature albino rats (n=30) were randomly divided into 5 groups of 6 rats each. Initially, the left hind paw thickness of the rats was measured using plethysmometer. Inflammation was induced by injection of 0.02 ml of 2.5 % freshly prepared formaldehyde solution into the sub plantar area of the hind paw of the rats (Sen and Nag-Chaudhari, 1991).

The rats were pre-treated *per os* using gastric gavage prior to formaldehyde injection as follows: Groups 1, 2 and 3 received 100, 200 and 400 mg/kg of *Bridelia micrantha* extract respectively. Group 4 (positive control) rats received 200 mg/kg Acetylsalicylic Acid (ASA). Group 5 (negative control) rats were given 0.03 ml/10 g normal saline. The left hind paw thickness of each of the rats was measured daily before each treatment from day 2.

Cotton Pellet-Induced Granuloma test

Wistar Albino rats of both sexes were divided into 5 groups of 6 rats per group. Two sterilized and autoclaved cotton pellets weighing 10 mg each were implanted subcutaneously into both sides of the dorsal area of each rat (D'Arcy *et al.*, 1960). Group 1, 2 and 3 received 100, 200 and 400 mg/kg of *Bridelia micrantha* extract respectively. Group 4 (positive control) rats received 200 mg/kg ASA. Group 5 (negative control) rats were given 0.03 ml/10 g normal saline. All treatment was orally by gastric gavage for 7 days. On the 8th day the animals were sacrificed and the pellets together with the granuloma tissues were carefully removed, dried in the oven at 60 °C, weighed and compared with the control.

Data Analysis

All data was presented as mean ± SEM and n = 6. The paw edema and granuloma weights of the groups were compared using one-way ANOVA followed by Duncan multiple range tests. $p<0.05$ was accepted as statistically significant.

RESULTS

Effects of *B. micrantha* methanol leaf extract on carrageenan-induced paw edema in rats

Table 1 shows the dose-dependent reduction of the size of carrageenan-induced rat paw edema with time in Wistar rats. A dose of 400 mg/kg b.w of the extract gave results which compared favorably with the results showed by Acetylsalicylic Acid (ASA) at between 1 to 4 h of drug administration. At 5 h after drug administration the extract at 400 mg/kg b.w reduced the rat paw edema by 71.79 % which was significantly ($p<0.05$) higher than the reduction (56.41 %) by ASA at 200 mg/kg b.w dose.

Table. 1: Effects of *B. micrantha* methanol leaf extract on carrageenan-induced paw edema in rats.

Dose (mg/kg)	Edema rate as mean ± S.E.M. (% inhibition)				
	1h	2h	3h	4h	5h
100	0.78±0.07 (12.36%)	0.75±0.04 (10.71%)	0.62±0.07 (26.57%)	0.52±0.02 (28.00%)	0.45±0.02* (42.31%)
200	0.77±0.06 (13.48%)	0.69±0.01 (17.86%)	0.60±0.02 (28.57%)	0.44±0.04* (45.00%)	0.35±0.05*** (55.13%)
400	0.73±0.05 (17.98%)	0.61±0.03 (25.84%)	0.54±0.08* (35.71%)	0.41±0.02** (48.75%)	0.22±0.02*** (71.79%)
ASA(200)	0.74±0.08 (16.85%)	0.61±0.06 (25.84%)	0.51±0.04* (39.29%)	0.40±0.05** (50.00%)	0.34±0.03*** (56.41%)
Normal saline (0.03ml/10 g	0.89±0.12	0.84±0.10	0.84±0.08	0.80±0.07	0.78±0.03

Values are mean ± S.E.M. n = 6. *p<0.05, **p<0.01, ***p<0.001 compared to respective negative control group

Effects of *B. micrantha* methanol leaf extract on histamine-induced paw edema in rats

As shown in Table 2, the performance of the extract at 400 mg/kg b.w against histamine-induced rat paw edema showed a similar comparison with Phenylbutazone at 100 mg/kg b.w. dose. In the histamine-induced rat paw edema model, Phenylbutazone gave significant ($p<0.05$) reduction (83.33 %) in edema size compared to the extract which gave 72.92 % after 6 h.

Table. 2: Effects of *B. micrantha* methanol leaf extract on histamine-induced paw edema in rats.

	Edema rate as mean ± S.E.M. (% inhibition)		
Dose (mg/kg)	1h	3h	3h
100	0.48±0.03 (12.73 %)	0.42±0.02 (12.50 %)	0.22±0.06** (54.17 %)
200	0.40±0.02 (27.27 %)	0.36±0.01* (25.00 %)	0.18±0.05*** (62.50 %)
400	0.35±0.03* (36.36 %)	0.22±0.03*** (54.17 %)	0.13±0.03*** (72.92 %)
Phenylbutazone (100 mg/kg)	0.31±0.01* (43.64 %)	0.18±0.01*** (62.50 %)	0.08±0.02*** (83.33 %)
Normal saline (0.03 ml/10 g)	0.55±0.01	0.48±0.02	0.48±0.03

Values are mean ± S.E.M. n = 6. *p<0.05, **p<0.01, ***p<0.001 compared to respective negative control group

Table. 3: Effects of *B. micrantha* methanol leaf extract on formaldehyde-induced paw edema in rats.

Dose (mg/kg)	Edema rate as mean ± S.E.M. (% inhibition)		
	3h	6h	24h
100	0.88±0.09 (7.37 %)	0.56±0.09* (42.86 %)	0.50±0.03 (42.53 %)
200	0.77±0.05 (18.95%)	0.53±0.06** (45.92%)	0.40±0.03** (54.02%)
400	0.74±0.03 (22.11%)	0.50±0.05** (48.98%)	0.35±0.03*** (59.77%)
ASA (200 mg/kg)	0.84±0.03 (11.58%)	0.54±0.07* (44.90%)	0.38±0.04** (56.32%)
Normal saline (0.03 ml/10 g)	0.95±0.06	0.98±0.07	0.87±0.05

Values are mean ± S.E.M. n = 6. *p<0.05, **p<0.01, ***p<0.001 compared to respective negative control group

Effects of *B. micrantha* methanol leaf extract on formaldehyde-induced paw edema in rats

In the formaldehyde-induced rat paw edema model (Table 3), the extract (400 mg/kg b.w) reduced the edema (59.77 %), better than the reduction (56.32 %) observed in ASA (200 mg/kg b.w) at 24 h after drug administration.

Effects of *B. micrantha* methanol leaf extract on cotton pellet-induced granuloma in rats

Table 4 shows the results obtained in the cotton pellet-induced granuloma model in which the extract (400 mg/kg b.w) produced 52.55 % protection against the edema inflammation when compared to the protection (49.38 %) by ASA at 200 mg/kg b.w dose after 7 days drug treatment.

Table. 4: Effects of *B. micrantha* methanol leaf extract on cotton pellet-induced granuloma in rats.

Dose (mg/kg)	Weight of cotton pellet granuloma (mg)	% protection (after 7 days)
100	52.76±2.1	38.36
200	45.18±1.8***	47.25
400	40.57±1.3***	52.55
ASA (200 mg/kg)	43.25±1.8***	49.38
Normal saline (0.03 ml/10 g)	85.50±3.2	0.00

*****p<0.05, *** p<0.001 compared to respective negative control. Values are mean ± S.E.M. n = 6 in each group

DISCUSSION

It is evident that carrageenan-induced edema is biphasic. In order words, the first phase is attributed to the release of histamine, serotonin and kinin and the second phase is related to the release of prostaglandins and bradykinins (Vane and Booting, 1987; Gupta *et al.*, 2006). Therefore the effect of the *Bridelia micrantha* extract against inflammation produced by histamine was studied. The extract effectively suppressed the inflammation produced by histamine (Table 2).

In carrageenan-induced inflammation, upon challenge by phlogistic stimuli, *Bridelia micrantha* extract produced significant inhibitory activity against carrageenan-induced hind paw edema in rats. The edema and inflammation induced by carrageenan is mediated by histamine and 5-HT during first 1 h, after which increased vascular permeability is maintained by the release of kinins up to two and half hours and from two and half hours to six hours, the mediators may be prostaglandins, the release of which is closely associated with migration of leucocytes into the inflamed site (Di-Rosa *et al.*, 1971). The carrageenan-induced paw edema model in rats is known to be sensitive to Cyclooxygenase (COX) inhibitors (Seibert *et al.*, 1994; Wallace *et al.*, 1998). It has been used to evaluate the effect of non-steroidal anti-inflammatory agents (Rao *et al.*, 2005). In histamine-induced inflammation, *Bridelia micrantha* extract exhibited a significant inhibitory action against histamine-induced hind paw edema, which indicates that the extract may be exhibiting its anti-inflammatory action by inhibiting the synthesis, release or action of inflammatory mediators like histamine, 5-HT and prostaglandins (Rao *et al.*, 2005).

In the formaldehyde-induced inflammation, the *Bridelia micrantha* extract showed significant anti-inflammatory activity that lasted up to 24 h which was comparable to ASA, suggesting its long duration of action even in crude form. Acute inflammation induced by formaldehyde results from cell damage, which provokes the production of endogenous mediators, such as, histamine, serotonin, prostaglandins and bradykinin (Yuh-Fung *et al.*, 1995). This acute inflammatory response is usually biphasic comprising of an early neurogenic phase mediated by substance P and bradykinin followed by a tissue mediated response where histamine, 5-HT, prostaglandins and bradykinin are known to be involved (Wheeler-Aceto and Cowan, 1991). It is well known that inhibition of edema induced by formaldehyde in rats is one of the best suitable test procedures for sub-acute anti-inflammatory agents as it closely resembles human inflammation (Greenwald, 1991). Inflammation induced by formaldehyde is also a model used for the evaluation of an agent with probable anti-proliferative activities (Kyei *et al.*, 2012). The popularly used cotton pellet-induced granuloma test was also performed to further investigate the efficacy of the extract on proliferative phase of inflammation in which tissue degeneration and fibrosis occur.

When tissue repair is going on in inflammation, there is proliferation of macrophages, neutrophils, fibroblasts and multiplication of small blood vessels, which are the basic sources of forming a highly vascularized reddish mass, termed granulation tissue (Bhattacharya *et al*., 1992; Kyei, 2012)). *Bridelia micrantha* extract (400 mg/kg, *per os*) significantly reduced the granuloma formation better when compared with ASA (200 mg/kg, *per os*) having the maximum percentage inhibition of 52.55 versus 49.38 respectively. The mechanism of anti-inflammatory activity of the extract on proliferative phase of inflammation in a rat model of cotton pellet granuloma is not exactly known and requires further study.

During inflammatory responses, the activation of phospholipase A2 induces the mobilization of fatty acids, in particular arachidonic acid from the membrane lipid pool (Fiorucci *et al.*, 2002). Arachidonic acid is then oxidized by constitutive Cyclooxygenase-1 (COX-1) or inducible cyclooxygenase-2 (COX-2) enzymes, leading to the production of prostaglandins (Modi *et al.*, 2012). Prostaglandins are a group of inflammatory mediators, implicated in many pain-related ailments (Rang *et al.*, 2001). COX-1 was constitutionally present in low abundance in most human tissues, acting as a housekeeping enzyme by regulating normal physiological processes such as the maintenance of gastric mucosal integrity, kidney function and platelet aggregation (Crofford, 1997). Conversely, COX-2 is selectively up regulated after exposure to inflammatory mediators or trauma, causing subsequent inflammatory responses and mediation of pain (Claria and Romano, 2005). There are number of non-steroidal anti-inflammatory drugs (COX-1 and COX-2 inhibitors) available in the market; and they are having good potential as anti-inflammatory and antipyretic drugs (e.g., diclofenac, aspirin, indomethacin,), but they cause undesired, unpleasant and serious adverse side effects on liver and gastrointestinal tract due to

inhibition of prostaglandin synthesis (Green *et al.*, 2004; Abatan *et al.*, 2006). Therefore, development of new and more powerful anti-inflammatory and hepatoprotective drugs is needed to substitute the chemical therapeutics. The extract of *Bridelia micrantha* may serve as a safer anti-inflammatory agent compared to acetylsalicylic acid and Phenylbutazone in the alleviating edema associated with arthritis and musculoskeletal pains in humans and animals.

CONCLUSION

This study showed that although well-established anti-inflammatory drugs are known to alleviate edema and pain conditions, the extract of *Bridelia micrantha* showed more potent anti-inflammatory effect in laboratory animal as shown by carrageenan, histamine, formaldehyde and cotton-pellet induced edema models. The significant reduction in rat paw edema size observed with the extract in the carrageenan-induced, histamine-induced and formaldehyde-induced paw edema models in rats is a definite proof of the anti-inflammatory effects of the plant which compared favorably with ASA and Phenylbutazone. It was concluded that this effect is caused by active secondary principles in the plant extract. Further studies are on-going to isolate the active compound(s), identify and characterize them.

REFERENCES

Abatan M.O., Lateef I. and Taiwo V.O. Toxic Effects of Non-Steroidal Anti-Inflammatory Agents in Rats. African Journal of Biomedical Research, 2006;9; 219-223

Abo K.A., A.A. Fred-Jaiyesimi and A.E.A. Jaiyesimi. Ethnobotanical studies of medicinal plants used in the management of diabetes mellitus in South Western Nigeria. J. Ethnopharmacol., 2008;115: 67-71. DOI: 10.1016/j.jep.2007.09.005

Adika O.A., Madubunyi I.I., Asuzu I.U. Antidiabetic and antioxidant effects of the methanol extract of *Bridelia micrantha* (Hochst) Bail. Euphorbiaceae leaves on Alloxan-induced diabetic albino rats. Comparative clinical pathology, 2012;21(5):945-951.

Aukland K. and Reed R.K. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol. Rev. 1993;73: 1–78.

Bawa P.A.S. and F. Khanum. Anti-inflammatory activity of *Rhodiola rosea*-'a second-generation adaptogen. Phytotherapy Res., 2009; 23: 1099-1102. DOI: 10.1002/ptr.2749

Bessong P.O., L.B. Rojas, L.C. Obi, P.M. Tshisikawe and E.O. Ignore. Further screening of Venda medicinal plants for activity against HIV type 1 reverse transcriptase and integrase. Afr. J. Biotechnol., 2006; 5: 526-528.

Bhattacharya S., S. Pal and A.K. Nag-Chaudhuri. Pharmacological studies of the anti-inflammatory profile of *Mikania cordata* (Burm) B.L. Robinson root extract in rodents. Phytotherapy Res.,1992; 6: 255-260. DOI: 10.1002/ptr.2650060507

Castro J., H. Sasame, H. Sussaman and P. Buttette. Diverse effect of SKF 52 and antioxidants on CCl_4 induced changes in liver microbial P-450 content and ethyl-morphine metabolism. Life Sci.,1968; 7: 129-136. DOI: 10.1016/0024-3205(68)90326-3.

Claria J. and N. Romano. Pharmacological intervention of cyclo-oxygenase-2 and 5-lipoxygenase pathways. Impact on inflammation and cancer. Curr Pharm Des., 2005; 11:3431-3447.

Crofford L. COX-1 and COX-2 tissue expression: implications and predictions. J. Rheumatology, 1997; 49(suppl):15-19.

D'Arcy P.F., E.M. Haward, P.W. Muggleton and S.B. Townseed. The anti-inflammatory action of griseofulvin in experimental animals. J. Pharm. Pharmacol., 1960; 12: 659-665. DOI: 10.1111/j.2042-7158.1960.tb12727.x

Deschenes G., V. Guigonis, A. Doucet. Molecular mechanism of oedema formation in nephrotic syndrome. Arch. Paediatr. 2004;11(19): 1084-1094.

Di-Rosa M., J.P. Giroud and D.A. Willoughby. Studies on the mediators of acute inflammatory response induced in rats in different sites of carrageenan and turpentine. J. Pathology, 1971;104: 15-29. DOI: 10.1002/path.1711040103

Dongaonkar R.M., Laine GA, Stewart RH, and Quick CM. Balance point characterization of interstitial fluid volume regulation. Am. J. Physiol., 2009; 297: R6-R16.

Dongaonkar R.M., Quick CM, Stewart RH, Drake RE, Cox CS Jr, and Laine GA. Edemagenic gain and interstitial fluid volume regulation. Am. J. Physiol., 2008; 294: R651-R659.

Doucet A., G. Favre, G. Deschenes. Molecular mechanism of edema formation in nephritic syndrome: therapeutic implications. Paediatr. Nephrol. 2007;22(12):1983-1990.

Edge J., M. Hawkins, D. Winter and D. Dunger. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch. Dis. Child, 2001;85: 16-22. DOI: 10.1136/adc.85.1.16

Fiorucci S., O. Menezes de Lima, A. Mencarelli, B. Palazzetti and E. Distrutti *et al*. Cyclooxygenase-2-derived lipoxin A4 increases gastric resistance to aspirin-induced damage. Gastroenterology, 2002;123: 1598-1606. DOI: 10.1053/gast.2002.36558

Friedman N.J., Kaiser P.K. Essentials of ophthalmology. Elsevier Health Sciences, 2007; pp 29.

Gbolade A.A. Inventory of antidiabetic plants in selected districts of Lagos state, Nigeria. J. Ethnopharmacol., 2009;121: 135-139. DOI: 10.1016/j.jep.2008.10.013

Green R.E., Newton I., Shultz S., Cunningham A.A., Gilbert M., Pain D.J. and Prakash V. Diclofenac poisoning as a cause of vulture population declines across the Indian subcontinent. J. Appl. Ecol., 2004;41: 793–8

Greenwald R.A. Animal models for evaluation of arthritic drugs. Meth. Find Clin. Pharmacol., 1991 13:75-*83*.

Gupta M., U.K. Mazumder, P. Gomathi and V. Thamil Selvan. Anti-inflammatory evaluation of leaves of *Plumeria acuminate***.** BMC alternative and complementary medicine, 2006; 6:36 doi: 10.1186/1472-6882-6-36.

Gupta M., U.K. Mazumder, P. Gomathi, Y. Rajeshwar, B.B. Kakoti and V.T. Selven. Anti-inflammatory, analgesic and antipyretic effects of methanol extract from leaves *Bauhinia racemosa* stem bark in animal models. J. Ethnopharmacol., 2006; 98:267-273.

Iwalewa E.O., L.J. McGaw, V. Naidoo and J.N. Eloff. Inflammation: The foundation of diseases and disorders. A review of phytomedicines of South African origin used to treat pain and inflammatory conditions. Afr. J. Biotechnol., 2007;25: 2868-2885.

Kaner R.J. and R.G. Crystal. Pathogenesis of high altitude pulmonary edema: Does alveolar epithelial lining fluid vascular endothelial growth factor exacerbate capillary leak. High Altitude Med. Biol., 2004; 5: 399-409. DOI: 10.1089/ham.2004.5.399

Khan C.M. The Merck Veterinary Manual 9th ed. Merck and C. Inc. NJ. USA. 2005; Pp. 2125-2136.

Kyei S., G. A. Koffuor1 and J. N. Boampong. The efficacy of aqueous and ethanolic leaf extracts of *Pistia stratiotes* Linn. in the management of arthritis and fever. Journal of Medical and Biomedical Sciences, 2012; 1(2): 29-37

Li M.H., K.L. Huang and S.Y. Wu. Baicalin attenuates air embolism-induced acute lung injury in rat isolated lungs. British J. Pharmacol., 2009;157: 244-251. DOI: 10.1111/j.1476-5381.2009.00139.x

Lin J., T.P. Mvelase and T. Puckree Anti-diarrhoeal evaluation of some medicinal plants used by Zulu traditional healers. J. Ethnopharmacol., 2002;79: 53-56.

Lorke, D. A new approach to practical acute toxicity testing. Arch. Toxicol., 1983;54: 275-287. DOI: 10.1007/BF01234480

Modi C.M., S.K. Mody, H.B. Patel, G.B. Dudhatra, A. Kumar and M. Avale. Toxicopathological overview of analgesic and anti-

inflammatory drugs in animals. Journal of Applied Pharmaceutical Science, 2012; 2 (1): 149-157.

Muhammad N., Muhammad Saeed and Haroon Khan. Antipyretic, analgesic and anti-inflammatory activity of *Viola betonicifolia* whole plant. BMC alternative and complementary med., 2012;12:592:59 http://www.biomedcentral.com/1472-6882/12/59

Ndip R.N., A.E. Malange, A.E. Tarkang, S.M. Mbullah and H.N. Luma *et al*. *In vitro* anti-*Helicobacter pylori* activity of extracts of selected medicinal plants from North West Cameroon. J. Ethnopharmacol., 2007;114: 452-457. DOI: 10.1016/j.jep.2007.08.037

Nwaehujor C.O. and Udeh N.E. Screening of ethyl acetate extract of *Bridelia micrantha* for hepatoprotective and anti-oxidant activities on Wistar rats. Asian Pacific Journal of Tropical Medicine, 2011;796-798

Nwaehujor C.O., M.I. Ezeja, N.E. Ude, D.N. Okoye, R.I. Udegbunam. Anti-inflammatory and antioxidant activities of *Mallotus oppositifolius* (Geisel) methanol leave extract. Arabian Journal of Chemistry, 2012; http://dx.doi.org10.1016/jarabjc

Okeleye B.I., Bessong P.O., Ndip R.N. Preliminary phytochemical screening and *In vivo* Anti-Helicobacter pylori activity of extracts of the stem bark of *Bridelia micrantha* (Hochst., Baill., Euphorbiaceae) Molecules , 2011;16, 6193-6205

Rang H.P., M.M. Dale and J.M. Ritter. *Pharmacology*. 4th Eds., Guanabara-Koogan, Rio de Janeiro, 2001 pp: 174-188.

Rao V., R. Kartik, S.K. Ojha, Amresh and G.M.M. Rao. Antiinflammatory and antinociceptive activity of stem juice powder of *Tinospora cordifolia* Miers. in experimental animals. Hamdard Med, 2005; XLVIII, 102-106.

Rao V., S.K. Ojha, S. Amresh and P. Mehrotra. Analgesic, anti-inflammatory and antiulcerogenic activity of unripe fruits of *Aegle marmelos*. Acta Pharmaceutica Turcica, 2003;45: 85-91.

Reed R.K., Liden A., and Rubin K. Edema and fluid dynamics in connective tissue remodeling. J. Molec. Cell Cardiol., 2010;48: 518-523.

Rocca G.D., Chiarandini P. and Pietropaoli P. Analgesia in PACU: non-steroidal anti-inflammatory drugs. Curr. Drug targets. 2005;6 (7): 781-787.

Rondon-Berrios H. New insights into the pathophysiology of oedema in nephritic syndrome. Nefrologia, 2011;32(2):148-154.

Runyon B.A. Ascites and Spontaneous Bacterial Peritonitis. Sleisenger & Furdtran's Gastrointestinal and Liver Disease, edited by Feldman M, Scharschmidt BF, and Sleisenger MIT, and Saunders WB, 1993;78:1310

Samie, A., C.L. Obi, P.O. Bessong and L. Namrita. Activity profiles of fourteen selected medicinal plants from rural Venda communities in South Africa against fifteen clinical bacterial species. Afr. J. Biotechnol., 2005;4: 1443-1451.

Schriner S.E., A. Avanesian, Y. Liu, H. Luescha ndd M. Jafari. Protection of human cultured cells against oxidative stress by *Rhodiola rosea* without activation of antioxidant defenses. Free Radical Biol. Med., 2009;47: 577-584. DOI: 10.1016/j.freeradbiomed.2009.05.025

Seibert K., Y. Zhang, K. Leahy, S. Hauser, J. Masferrer, W. Perkins, L. Lee and P. Isakson, Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci USA, 1994;91:12013–7.

Sen T. and A.K. Nag-Chaudhari. Anti-inflammatory evaluation of *Plunchea indicia* roots extract. J. Ethnopharmacol., 1991; 33: 135-141. DOI: 10.1016/0378-8741(91)90172-A

Singh G., Ramey D.R., Morfeld D., Shi H., Hatoum H.T., Fries J.F., Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. Arch. Internal. Med., 1996;156(14): 1530–1536.

Singh, R.K. and B.L. Pandey. Anti-inflammatory activity of seed extracts of *Pongamia pinnata* in rats. Ind J Physiol Pharmacol., 1996;40: 355-358.

Ssegawa P. and J.M. Kasenene. Medicinal plant diversity and uses in the Sango bay area, Southern Uganda. J. Ethnopharmacol., 2007;113: 521-540. DOI: 10.1016/j.jep.2007.07.014

Steenkamp V. Traditional herbal remedies used by South African women for gynaecological complaints. J. Ethnopharmacol., 2003;86: 97-108. DOI: 10.1016/S0378-8741(03)00053-9

Suryakumar J.G. and D. Shukla. Modulation of hypoxia-induced pulmonary vascular leakage in rats by sea buckthorn (*Hippophae rhamnoides* L.). Evidence-based Complementary Alternative Med., 2011.

Svendsen S., Reed R.K., Wilg H. The interstitium and lymphatics have an important role in edema generation in sepsis. Annual update in intensive care and emergency medicine, 2011; 1:297-306

Swingle K.F. Anti-inflammatory agents. Chemi. Pharmacol., 1974; 2: 33.

Tripathy S., Ashaa M.A., Pradhana D. Acute and chronic anti-inflammatory evaluation of *Crateva religiosa* in rats. Int. J. Pharmacol. Ther., 2010;2(4):1270-1279

Udegbunam R.I., I.U. Asuzu, R.O.C. Kene, S.O. Udegbunam, C.O Nwaehujor. Anti-nociceptive, anti inflammatory and anti-oxidant effects of the methanol leave extract of *Sterculia tragacantha* Lindl. Journal of Pharmacology and Toxicology, 2011; 6(5):515-524.

Vane J. and R. Booting. Inflammation and mechanism of action of anti-inflammatory drugs. FASEB J., 1987;1: 89-96.

Wallace J.L., A. Bak, W. Mcknight, S. Asfaha, K.A. Sharkey and W.K. Macnaughton. Cyclooxygenase1 contributes to inflammatory responses in rats and mice: Implications for gastrointestinal toxicity. Gastroenterology, 1998; 115:101–109.

Watt, J.M. and M.G. Breyer-Brandwijk. The Medicinal and Poisonous Plants of Southern and Eastern Africa. 2nd Eds., Livingstone, London, 1992.

Wheeler-Aceto, H. and A. Cowan. Neurogenic and tissue mediated components of formalin-induced edema: Evidence for supraspinal regulation. Agents Action, 1991;34: 264-269. DOI:10.1007/BF01993299

Winter C.A., E.A. Risley and G.W. Nuss. Carrageenan induced edema in the hind paw of the rat as an assay for anti-inflammatory drugs. Proc. Soc. Exp. Biol. Med., 1962;111: 544-547. DOI: 10.3181/00379727-111-27849

Yuen, N., S.E. Anderson, N. Glaser, D.J. Tancredi and M.E. O'Donell, 2008. Cerebral blood flow and cerebral edema in rats with diabetic ketoacidosis. Diabetes, 57: 2588-2594. DOI: 10.2337/db07-1410

Yuh-Fung C., T. Huei-Yann and W. Tian-Shung. Anti-inflammatory and analgesic activities from roots of *Angelica pubescens*. Planta Med., 1995; 61: 2-8. DOI: 10.1055/s-2006-957987

How to cite this article:

Nwaehujor Chinaka O, Igile Godwin O, Ode Julius O. and Udegbunam Rita I. Anti-Inflammatory Activities of Methanol Leaf Extract of *Bridelia micrantha* (Hochst) Baill. (Euphorbiaceae) In Wistar Rats. J App Pharm Sci, 2014; 4 (06): 068-073.