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Xylopia aethiopica (Annonaceae) fruit extract suppresses Freund's adjuvant-induced arthritis in Sprague-Dawley rats

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ABSTRACT

Ethnopharmacological relevance: Xylopia aethiopica is used in a decoction of the dried fruit to treat bronchitis, asthma, arthritis, rheumatism, headache, neuralgia and colic pain. The aim of the study is to evaluate the anti-arthritic effects of a 70% aqueous ethanol extract of the fruit of *Xylopia aethiopica* in a chronic inflammatory model.
Materials and methods: Adjuvant arthritis was induced in Sprague-Dawley rats by intraplantar injection of Complete Freund's Adjuvant into the right hind paw. Foot volume was measured by water displacement plethysmometry. The oedema component of inflammation was evaluated as the percentage change in paw swelling and the total oedema induced calculated as area under the time course curves. In addition to X-ray radiography, histopathology of ankle joints supported by haematological analysis was used to assess the anti-arthritic action of the extract of *Xylopia aethiopica* (XAE).
Results: Xylopia aethiopica extract (100, 300 and 600 mg kg^{-1}) modified the time course curve significantly reducing hind paw oedema in the ipsilateral paw at all dose levels when administered both prophylactically and therapeutically. In addition XAE significantly suppressed the systemic spread of the arthritis from the ipsilateral to the contralateral limbs. The radiological pictures of the joints particularly metatarsal, phalanges and the ankle joint space of rats in the XAE-treated group showed protective effect against adjuvant-induced arthritis while histopathology revealed significant reduction in mononuclear infiltration, pannus formation and bone erosion. The haematological analysis in the test animals revealed significant improvement relative to the CFA model group.
Conclusion: Xylopia aethiopica XAE suppresses joint inflammation and destruction in arthritic rats
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1. Introduction

Xylopia aethiopica [Dunal] A. Rich the "African guinea pepper" as it is commonly called is a tropical evergreen tree with seeds that are aromatic and contain bitter principles (Burkhill, 1985) and belongs to the Annonaceae family. Among the folkloric uses Igwe et al. (2003) report that a decoction of the plant is used to treat dysentery, bronchitis, ulceration, rheumatism, headache, neuralgia and colic pain. Results from the earlier and recent studies on extracts of the plant have shown that *Xylopia aethiopica* possess antibacterial (Asekun and Adeniyi, 2004; Fleischer et al., 2008; Kuete, 2010), antifungal (Tatsadjieu et al., 2003) and anti-plasmodial (Boyom et al., 2003) activities. Interestingly, while some extracts of *Xylopia aethiopica* reportedly exhibit antioxidant activity (Karioti et al., 2004) and protect rats from the adverse effects of irradiation (Adaramoye et al., 2010, 2011) some other extracts as reported by Ju et al. (2004) and Choumessi et al. (2012) demonstrate cytotoxic effects on a wide range of cancer cell lines through triggering DNA damage and accumulation of cells in the G1 phase of the cell cycle, followed by apoptosis. The constituent diterpenes called kauranes, notably kaurenoic acid (*ent*-kaur-16-en-19-oic acid) and xylopic acid [15β-acetoxy-(−)-kaur-16-en-19-oic acid] as elucidated by Ekong and Ogan (1968) account for the observed biological activities. In addition, kaurenoic acid exhibits analgesic (Block et al., 1998) diuretic, vasorelaxant, anti-inflammatory and anti-pyretic effects in rodents (Somova et al., 2001; Sosa-Sequera et al., 2010).

Abbreviations: DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; HGB, haemoglobin; HCT, haematocrit; IgG, immunoglobulin G; IL, interleukin; MAPK, mitogen activated protein kinase; NO, nitric oxide; NF-κB, nuclear Factor-κB; PG, prostaglandin; RBC, red blood cell; RA, rheumatoid arthritis; TNFα, tumour necrosis factor α; WBC, white blood cell; XAE, xylopia aethiopica extract

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Xylopia aethiopica possesses activities suggestive of benefit in a chronic inflammatory disorder such as rheumatoid arthritis (RA). For example, the constituent kauranes impair inflammation signalling through inhibition of the NF-κB signalling pathway (Castrillo et al., 2001) as a mechanism of anti-inflammatory action. In addition very recent *in vivo* studies demonstrating potent analgesic effects in three animal pain models; chemical (acetic acid-induced abdominal writhing and formalin tests), thermal (tail-flick and Hargreaves thermal hyperalgesia tests) and mechanical (Randall-Selitto paw pressure test) as reported by Woode et al. (2012) lend support to the potential utility of *Xylopia aethiopica* and its major constituent, xylopic acid in RA since pain is a cardinal sign of inflammation.

RA is a reported autoimmune disease characterised by chronic inflammation of multiple joints. The classical features of RA are associated with subsequent progressive, erosive destruction of articular bone and cartilage, mononuclear cell infiltration, pannus formation, and functional impairment. Rat adjuvant- and collagen-induced arthritis experimentally are the most widely used animal models of inflammatory polyarthritis and they present with clinical and pathological features typical of RA in human (Wooley, 2008; Bolon et al., 2011). Hoffmann et al. (1997) indicate that as in human RA, the prognosis of rat adjuvant-induced arthritis is divided into three phases; the induction phase which has no evidence of synovitis, followed by early synovitis, and finally late synovitis with progressive joint destruction. Although the initiating cause(s) of RA is not well established, Kishimoto et al. (1992) and Feldmann et al. (1996) report that elevated levels of pro-inflammatory cytokines notably TNFα and the activation of NF-κB signalling pathway are thought to be essential to the disease pathophysiology and progression. Thus, the reduction of pain, inflammation, and joint damage is the focus of drug treatment of RA.

The anti-rheumatic drugs in clinical use are associated with severe adverse reactions and potential toxic effects (Amoroso et al., 2003). For instance at doses that would result in maximum efficacy, long-term use of the disease modifying anti-rheumatic drugs for the treatment of RA cause serious toxicities. The non-steroidal anti-inflammatory drugs (NSAIDs) as reported by Wolfe et al. (1999) have little potential for modification of the disease progression at the doses that are generally safe for prolonged use in humans due to their associated gastrointestinal side effects. However, Sanghi et al. (2006) report that even though the selective *cyclooxygenase* (COX)-2 inhibitors minimise this gastrointestinal associated risks they also present unwanted side effects on the kidney and cardiovascular system. The steroidal drugs (glucocorticoids) on the other hand when taken chronically in doses needed for RA leave the patients with the so-called Cushing syndrome (Dore, 2010). In sum these biologic agents may improve RA but in addition to the severe adverse and toxic effects expensive costs also further limit their clinical application (Katikireddi et al., 2010). Consequently, natural herbal therapies have widely attracted attention in recent years (Venkatesha et al., 2011; de Sousa et al., 2012).

As part of our on-going research into medicinal plants, we have recently reported that the aqueous ethanol extract of the dried fruit of *Xylopia aethiopica* has anti-allergic and anti-inflammatory actions in mice (Obiri and Osafo, 2013). In the present study we evaluate the effect of the dried fruit extract of *Xylopia aethiopica* on ameliorating arthritis in an experimental animal model of RA.

2. Materials and methods

2.1. Materials

2.1.1. Preparation of plant extract

Samples of the dried fruits of *Xylopia aethiopica* [Dunal] A. Rich were purchased from a commercial herb market in Kumasi in March, 2012. The identity was confirmed as the fruit of *Xylopia aethiopica* [Dunal] A. Rich by anatomical observation and direct comparison with the authentic specimens, stored in the Herbarium in the Department of Herbal Medicine, KNUST, Kumasi. A voucher specimen (No. FP/09/77) has been deposited in the same department. Dried fruit (2.7 kg) was ground using heavy duty blender (37BL85 (240CB6), WARING Commercial, USA) and extraction was done with 70% v/v ethanol (5 L) by maceration for 24 h. The ethanol filtrate was concentrated under reduced pressure at 45 °C by a vacuum rotary evaporator (R-210, BUCHI, Switzerland) and further dried in an oven (Gallenkamp OMT, SANYO, Japan) to yield a solid mass of weight 167 g. The dried extract, XAE was freshly emulsified with Tween-80 and prepared with normal saline before use.

2.2. Experimental animals

Purpose bred male Sprague-Dawley rats (200–250 g) were purchased from Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana and kept in the Animal facility of the Department of Pharmacology, College of Health Sciences, KNUST, Kumasi, Ghana. All animals were humanely handled throughout the experimental period in accordance with internationally accepted principles for laboratory animal use and care (EEC Directive of 1986: 86/609 EEC). Additionally all animal experiments were approved by the Department of Pharmacology, KNUST Ethics Committee. Therefore, animals were acclimated upon arrival for a week before assigned randomly to their respective group. Rats (5/cage) were housed in a polypropylene cage in a temperature-controlled room (22.2 °C) on a 12-h light-dark cycle with free access to commercial pellet diet (GAFCO, Ghana) and water *ad libitum*. All animals were euthanised at the end of each experiment. Each animal was therefore used only once.

2.3. Chemicals and reagents

Aspirin was purchased from Sigma-Aldrich (St Louis, USA). Paraffin oil was purchased from KAMA Pharmaceutical Industries (Ghana).

2.4. Microorganism

Heat-killed *Mycobacterium tuberculosis* [strains C, DT and PN (mixed)] was obtained from the Ministry of Agriculture, Fisheries and Food, UK.

2.5. Methods

2.5.1. Adjuvant-induced arthritis in rats

Adjuvant arthritis was induced as previously described by Pearson (1956). Briefly, right hind paw of rats were injected intraplantar with 100 μl of Complete Freund's Adjuvant (CFA) prepared as a suspension of 5 mg ml^{-1} of heat-killed *Mycobacterium tuberculosis* [strains C, DT and PN (mixed)] in paraffin oil while non-arthritic control group received only intraplantar injection of 100 μl sterile paraffin oil referred to as Incomplete Freund's Adjuvant (IFA). Foot volume measurements were taken with a plethysmometer (Ugo Basile, Comerio, Italy) for both the ipsilateral (injected) and the contralateral (non-injected) hind paws before intraplantar injection of CFA/IFA (day 0) and on every other day up to 28 days (Binder and Walker, 1998). The oedema component of inflammation was quantified by measuring the difference in foot volume between day 0 and the various time points.

Foot volumes were individually normalised as percentage of change from their values at day zero and then averaged for each

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