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Albizia zygia (DC.) J.F. Macbr. (Leguminosae-Mimosoideae) root extract exhibits anti-nociceptive and antipyretic activities in murine models

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ABSTRACT

Ethnopharmacological relevance: The root extract of *Albizia zygia* (DC.) J.F. Macbr. (Leguminosae-Mimosoideae) is traditionally used in the management of pain and fever. However, little scientific data exists in literature to support its use.

Aim of study: The present study evaluated the anti-nociceptive and antipyretic properties of the hydroethanolic extract of the roots of *Albizia zygia* in animal models.

Materials and methods: The analgesic effects were investigated in chemical (acetic acid-induced abdominal writhing and formalin tests), thermal (tail-immersion test) and mechanical (carrageenan-induced hyperalgesia) pain models. Possible mechanisms of anti-nociception were also assessed with antagonists in the formalin test. The anti-pyretic effect was evaluated using the baker yeast-induced pyrexia model in young rats.

Results: The extract (30–300 mg/kg, *p.o.*) and positive controls, diclofenac (3–30 mg/kg, i.p.) and morphine (1–10 mg/kg, i.p.), significantly (at least $P < 0.01$) attenuated acetic acid-induced visceral pain, formalin-induced paw pain (both neurogenic and inflammatory), thermal pain as well as carrageenan-induced mechanical hyperalgesia in animals. The anti-nociceptive effect of the extract was reversed (at least $P < 0.05$) by the pre-emptive administration of naloxone and atropine; the administration of theophylline, however, exhibited no significant ($P > 0.05$) inhibition of anti-nociception. The extract (30–300 mg/kg, *p.o*) and paracetamol (15–150 mg/kg, *p.o.*) both reversed yeast-induced pyrexia in rats with ED_{50} values of 48.59 ± 2.59 and 26.19 ± 1.33 mg/kg respectively.

Conclusion: The findings indicate that the extract possesses significant anti-nociceptive and antipyretic effects which justify its traditional use in the management of pain and fever. Also, anti-nociceptive effect of the extract involves opioidergic and muscarinic cholinergic mechanisms.

1. Introduction

Pain and fever are ubiquitous. They are everyday symptoms of ailments, and as such, medications possessing analgesic and antipyretic activity are one of the widespread medicines used in clinical conditions by patients (Southey et al., 2009). According to the National Institutes of Health (NIH), pain is one of the most important national public health problems, a silent epidemic (Lippe et al., 2010). Fever and pain are frequent in infants and children of all ages, and represent more than 30% of all of the complaints referred to paediatricians (Raffaeli et al., 2016). The common use of analgesics and antipyretics reveal their general acceptance and effectiveness (Southey et al., 2009). However, their usage is accompanied by various side effects such as gastro-intestinal intolerance, liver and renal impairment (Rang et al., 2015). There is, therefore, an unmet medical need for safe and effective analgesic and antipyretic drugs. Medicinal plants offer an alternate source of drug discovery and development (Verpoorte, 1998).

The use of medicinal plants in traditional medicine furnishes new and essential leads in pharmacological managements (Balunas and Kinghorn, 2005). *Albizia zygia* (D.C.) Macbr (Leguminosae-Mimosoideae) is one of the plant species traditionally used in the management of pain and fever. It is also referred to as *Albizia brownei* (Walp.) Oliv., Red Nango or West African Walnut (Ashton et al., 1975). It is an indigenous plant of tropical Africa with native distribution in West and Eastern Africa as well as India and Australia. The plant is locally called “Okuro” (Ghana), “Nyie avu” (Igbo), “Ayinre weere” (Yoruba), “Red Nongo” (Uganda) and “Nongo” (Swahili). It is a deciduous tree with a spreading canopy which can grow up to 30 m.

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It buds in January to March as well as August and September. The fruits ripen between November and April (Kokila et al., 2013; Orwa et al., 2009). *A. zygia* is traditionally used in the management of waist pain, feverish conditions and eczema (Arbonnier, 2004; Ndjakou Lenta et al., 2007). The roots are crushed and applied to treat wounds, cut and injury (Bouquet and Debray, 1974). Ground roots are added to food to treat cough and as an expectorant (Apetorgbor, 2007). A number of scientific studies have been conducted on various parts of the plant. The powdered bark of *A. zygia* is used in Sudan, either alone or as a decoction, for the management of malaria and other parasites; specific activity has been attributed to the presence of flavonoids (including 3′,4′,7-trihydroxyflavone) and lupeol (Abdalla and Laatsch, 2012). The methanol stem bark extract of *A. zygia* possesses analgesic effects (Abere et al., 2014) and is also very active against *Plasmodium falciparum* K1 strain and *Trypanosoma brucei rhodesiense*, with respective IC_{50} values of 1.0 μg/ml and 0.2 μg/ml. (Ndjakou Lenta et al., 2007). The aqueous and hydroethanolic root extracts possess anticancer activity with high selective toxicity against Jurkat cells (Appiah-Opong et al., 2016). The gum from the bark of the plant has been widely investigated for its chemical and physical properties in comparison with other mucilages (Ashton et al., 1975; Mital et al., 1978; Odeku, 2005).

Based on the traditional use of the plant in the management of pain and fever associated with various conditions (Bouquet and Debray, 1974), the present study examined the anti-nociceptive and antipyretic properties of the hydroethanolic extract of the roots of *A. zygia* in animal models. The acute oral toxicity of the plant extract was also evaluated.

2. Materials and methods

2.1. Plant material collection

The roots of *A. zygia* were collected from the campus of Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana (6°40′31.8⌢N 1°34′44.1⌢W) in September 2013. The root sample was authenticated by Dr. George H. Sam of the Department of Herbal Medicine, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, KNUST. A voucher specimen (No.: KNUST/H/M/2016/R001) was kept at the herbarium of the Faculty. The plant name was also checked with the plant list website, www.theplantlist.org (accessed 20.06. 2016).

2.2. Preparation of extract

The roots were room dried for 2 weeks, and then pulverized into fine powder. The powder was cold macerated with 70% ($^{v}/_{v}$) ethyl alcohol. The hydro-alcoholic supernatant was filtered and then concentrated to a brown syrupy mass under reduced pressure at 50 °C in a rotary evaporator (R-210, BUCHI, Switzerland). The extract was further dried in a hot air oven at 50 °C and stored at 4 °C until use. The final product, of yield 9.03% ($^{w}/_{w}$), is subsequently referred to as AZE or extract in this study.

2.3. Phytochemical screening

Preliminary phytochemical tests were performed on AZE using methods described by Trease and Evans (1989) and Sofowora (1993).

2.4. Animals

Male ICR mice (20–25 g) and Sprague-Dawley rats (100–200 g) were obtained from Noguchi Memorial Institute of Medical Research (NMIMR), University of Ghana, Accra, and housed in the vivarium of the Department of Pharmacology, Kwame Nkrumah University of Science and Technology (KNUST), for acclimatization until use. The animals were kept in groups of 5–6 in stainless steel colony cages (34 cm×47 cm×18 cm) with soft wood shavings as bedding. Animals had free access to chow (Agricare Ltd, Kumasi, Ghana), were given water *ad libitum* and maintained under laboratory conditions (temperature 24–28 °C, relative humidity 60–70% and 12 h light-dark cycle). All procedures and techniques used in this study were in accordance with principles regarding the protection of animals used for experimental purposes (Directive 2010/63/EU). Ethical approval was granted by the Departmental Ethics Committee.

2.5. Drugs and chemicals

The following drugs and chemicals were used: formalin, acetic acid, theophylline (BDH, Poole, England); diclofenac (Troge, Hamburg, Germany); paracetamol, morphine hydrochloride (PhytoRiker, Accra, Ghana); atropine, naloxone, carrageenan sodium salt (Sigma-Aldrich Inc., St. Louis, MO, USA); commercially available dried baker's yeast (*Saccharomyces cerevisiae*, Saf do Brasil Produtos Alimentícios Ltd, Brazil).

2.6. Acute toxicity test

Mice were divided into five groups (n=5) and fasted overnight, but provided with water *ad libitum*. On the test day, mice were orally treated with AZE (0.3, 1, 3 and 5 g/kg) or vehicle (10 ml/kg). Animals were then monitored for gross behavioural changes and mortality at 0, 15, 30, 60, 120 and 180 min, and also at 24 h post-extract administration. The mice were also observed daily for up to 14 days to detect any possible delayed deaths.

2.7. Anti-nociceptive activity

2.7.1. Acetic acid-induced writhing assay

This test was carried out as described earlier (Koster et al., 1959; Woode and Abotsi, 2011) with modifications. Intraperitoneal injection of 0.6% acetic acid (10 ml/kg) induces a nociceptive behaviour, characterized by abdominal contractions known as writhing (an exaggerated extension of the abdomen combined with the outstretching of the hind limbs). Mice were divided into seven groups (n=5). They were then administered vehicle (10 ml/kg; *p.o.*), AZE (30, 100 and 300 mg/kg, *p.o.*) or diclofenac (3, 10 and 30 mg/kg; i.p.) 30 min (*i.p.*) or 1 h (*p.o.*) before administration of the acetic acid, and placed individually in a testing chamber (a Perspex chamber 15 cm×15 cm ×15 cm). A mirror inclined at 45 ° below the floor of the chamber allowed a complete view of the mice. The total number of writhes were captured for 30 min (5 min blocks) by a camcorder (Everio™, model GZ-MG1300), and tracking of the behaviour was done using a public domain software JWatcher™ Version 1.0 (University of California, Los Angeles, USA and Macquarie University, Sidney, Australia; available at http://www.jwatcher.ucla.edu/.) to obtain the total number of writhes per 5 min, starting 5 min after acetic acid administration.

2.7.2. Tail Immersion test

The test was performed according to the method described by Sewell and Spencer (1976) with modifications. This involved measuring the tail withdrawal latency (TWL) i.e. the time a mouse takes to withdraw the tail from a water bath maintained at a temperature of 49 ± 0.5 °C. A cut-off time of 10 s was imposed to prevent tissue damage. Animals were divided into seven groups (n=5–6) and baseline TWLs were determined on the test date. Mice were then treated as follows: vehicle (10 ml/kg, *p.o.*), AZE (30, 100 and 300 mg/kg; *p.o.*) and morphine (1, 3 and 10 mg/kg; i.p.). The TWL for each study group was then taken at 0.5, 1, 2, 3, 4 and 5 h intervals after a latency period of 30 min (i.p.) or 1 h (*p.o.*) following the administration of the drugs or extract. Anti-nociceptive activity was defined as an increase in TWL and calculated as percentage maximal possible effect (MPE). The %