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Original Research Article

Assessment of the antipyretic, and anti-inflammatory effects of *Zanthoxylum Zanthoxyloides* stem bark aqueous extract on Wistar rats

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This present study was aimed at investigating the antipyretic and anti-inflammatory effects of *Zanthoxylum zanthoxyloides* stem bark aqueous extract on albino Wistar rats at doses of 400 and 800 mg/kg body weight. Oedema was induced using 0.2 mL of 1% egg albumin and 2% formalin in rats treated with the extract and standard drugs (diclofenac and aspirin respectively). Paw circumference was measured in the experimental groups with Vernier caliper at different times. Fever was induced by subcutaneous injection of 20 ml/kg with brewer's yeast suspension in normal saline at 20% (w/v) to each rats and treated with the extract and paracetamol. The rectal temperatures were taken hourly for four hours. Significant oedema reduction was observed from the 90th minute after induction with egg albumin and from the 150th minute after induction with formalin. The extract administration provoked significant rectal temperature reduction from the second hour of fever induction until the fourth hours of the experiment. This present study reveals the antipyretic, and anti-inflammatory properties of the stem bark aqueous extract of *Zanthoxylum zanthoxyloides*.

Keywords: *Zanthoxylum zanthoxyloides*, stem bark, aqueous, anti-inflammatory, antipyretic, oedema, rectal temperature, Wistar rats

INTRODUCTION

Fever is an inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature. Fever is a ubiquitous component of inflammation across the animal kingdom,

Figure 1: Stem bark of *Zanthoxylum zanthoxyloides* (source: google.fr)

and enhances the host response. Fever is normally regulated by the hypothalamus but certain bacterial or viral infections can result in the production of pyrogens, chemicals that effectively alter the ''thermostat setting'' of the hypothalamus to elevate body temperature and cause fever. Pyrogens may be endogenous or exogenous (Walter et al., 2016).

Herbal medicine plays a major role in the health of thousands of people worldwide mostly in developing countries. Traditional and alternative medicines are extensively practiced in the prevention, diagnosis and treatment of various illnesses including infectious diseases, allergies and hypertension. It has attracted increasing public attention over the years, as these types of medicines are easily accessible in some regions (Girish et al., 2009). In the most developed countries, such as the United States and Europe, many people are going back to the use of herbal medicines despite great advancement in health care (Adegbolagun and Olukemi, 2010). According to the World Health Organization, over 80% of the world population use herbal medicines to treat diseases. Nowadays with substances derived from higher plants that constitute about a quarter of all prescribed medicines, plants appear to be the most exclusive source of drugs for the majority of the world's population (Adesina, 2005). Many developing countries are endowed with vast resources of natural products. There are several medicinal plants, one of which is *Z. zanthoxyloides*, belonging to the Rubiaceae family (Figure 1). It is used traditionally across the African region to treat various illnesses such as malaria, fever, sickle cell anaemia, oedema and general body weakness. The root and stem bark are used traditionally to treat malaria in Mali (Diarra et al., 2015), and in Guinea (Traore et al., 2013). Traditional healers in Togo use the stem, stem bark and leafy stem to treat malaria (Denou et al., 2016; Kantati et al., 2016). In Togo, the maceration of the root bark is used to treat central nervous system disorders such as epilepsy and paralysis (Kantati et al., 2016). Some studies were conducted using different parts of *Z. zanthoxyloides* to elucidate the biological activities of this plant. A study on the root and fruits of *Z. zanthoxyloides* showed that these parts possess antimicrobial activity (Anne et al., 2013; Wouatsa et al., 2013). The leaves have shown effects on blood glucose, lipid profile and some enzymes in alloxan induced diabetic rats (Aloke et al., 2012), and have anti-inflammatory and analgesic activities (Diatta et al., 2014). A study on the root, leaves and stem bark showed antiplasmodial activity (Goodman et al., 2019; Kassim et al., 2005). *Z. zanthoxyloides* fruits, leaves and stem bark showed high radical scavenging and ferric reducing properties (Tine et al., 2017).

To the best of our knowledge, few or no pharmacological studies have been reported out on the stem bark of this plant. This present study aimed to assess the antipyretic and anti-inflammatory activities of the stem bark aqueous extract of *Z. zanthoxyloides*.

MATERIALS AND METHODS

Plant material

Z. zanthoxyloides stem bark was collected in the northern part of Togo (Pya) in February 2019. Botanists from the

Botany and Vegetal Ecology Department (University of Lomé) and National Herbarium Unit respectively identified and authenticated the plant and a voucher specimen has been deposited in the herbarium with reference number Togo 15491. The stem bark was air-dried and reduced into powder in Biochemistry Department (University of Jos, Nigeria) using a mortar and pestle.

Preparation of the aqueous extract

500 g of the powder was macerated with 1.5 L of distilled water for 24 hours at room temperature and the mixture was filtered after 24 hours. The same procedure was performed with the substrate from the first maceration two more times. The whole filtrate was concentrated to dryness in an oven at 70 ºC. The dry extract was stored at -4 ºC in the refrigerator.

Animal material and ethical considerations

The Animal House Unit of the University of Jos, Nigeria, provided Wistar rats weighing between 150-200 g. The animals were kept under ambient temperature, with 12h light and 12h dark cycle and had free access to food and water *ad libitum*. All animal procedures were performed in accordance with the recommendations of the proper care and use of laboratory animals after approval (No. UJ/FPS/F17-00379) from the Ethics Committee of the University of Jos, Nigeria. Before each experiment, the animals were separated into five per cage based on their body weights, acclimatized for 7 days. The animals were then fasted overnight with free access to water *ad libitum*.

Anti-inflammatory evaluation

Egg albumin induced oedema model

Animals were randomly grouped in to four of five rats each (3 males and 2 females) and treated as follows: the Normal saline (10 mL/kg) *per os* (group I / control group); Diclofenac at 20 mg/kg *i.p* as standard group (group II); extract at 400 and 800 mg/kg (groups III and IV, respectively, *per os*). Diclofenac and the extract were administered 15 and 30 minutes, respectively, before induction of the inflammation. Inflammation was induced in rats by the injection of 1% egg albumin (0.2 mL) into the sub plantar tissue of the right hind paw as described by Okokon and Nwafor (2010) and Zhao et al. (2018). The linear circumference of the injected paw was measured before (baseline) and 0, 30, 60, 90, 120, 150 and 180 minutes after the administration of the egg albumin. The average (mean) oedema was assessed by measuring the paw diameter with Vernier calipers.

Formalin induced oedema model

The chronic anti-inflammatory activity of the extract was evaluated by using the formalin induced hind paw oedema model described by Arzi et al. (2015) and Soyocak et al. (2019). Animals were divided into four groups of five rats each (3 males and 2 females). The treatment was done orally as follows: Group I, Control group received Normal saline (10 mL/kg); Group II, Standard group received acetylsalicylate of DL-Lysine (ASP) at 200 mg/kg; Groups III and IV, received extract at 400 and 800 mg/kg, respectively. Thirty minutes after drugs administration, the paw oedema was induced by injecting 0.2 mL of 2 % formalin into sub-plantar tissues of the rat's right paw in all groups. The paw diameter was measured before (baseline) and after formalin injection at 0, 30, 60, 90, 120, 150, 180 min and at 24 and 48 h) using Vernier caliper. The average feet swelling in test as well as standard groups were compared with that of control.

Antipyretic evaluation

Fever was induced by injecting 20 ml/kg (subcutaneous) of 20% (w/v) suspension of brewer's yeast dissolved in 0.9% normal saline below the nape of the neck (Panda et al., 2009). The rectal temperature was measured before and 18 hours after fever induction. Animals that showed an increase of 0.5 to 1ºC in rectal temperature were selected. Twenty albino Wistar positive to fever induction were randomly divided into four groups and treated as follows: Group I, Control group was given 1 mL of 0.9% normal saline; Group II, Standard group was treated with paracetamol at 150 mg/kg; Groups III and IV received the extract at 400 and 800 mg/kg, respectively. After drug and extract administration, the rectal temperature of all animals in the groups were recorded at 0, 1, 2, 3, 4 hours as described by Ghule et al. (2007) and Vinod and Malgi (2019).

Statistical analysis

GraphPad Prism 8.0.1 was used and results expressed as mean ± SEM. The level of significance was determined using the one-way ANOVA followed by Tukey's multiple comparisons test. A *p*-value less than 0.05 was considered to be statistically significant.

RESULTS

Anti-inflammatory evaluation

Effect of the extract on egg albumin induced oedema on rats

Acute inflammation was induced in Wistar rats using 1% egg albumin. During the first 30 minutes after induction, no significant reduction of the oedema was observed in all groups ($p > 0.05$). Sixty minutes after induction, only the standard group showed significant reduction of the oedema ($p < 0.05$). From the 90th minute until 3 hours after induction, all groups showed significant reduction of the oedema ($p < 0.05$) (Figure 2). The reduction was at

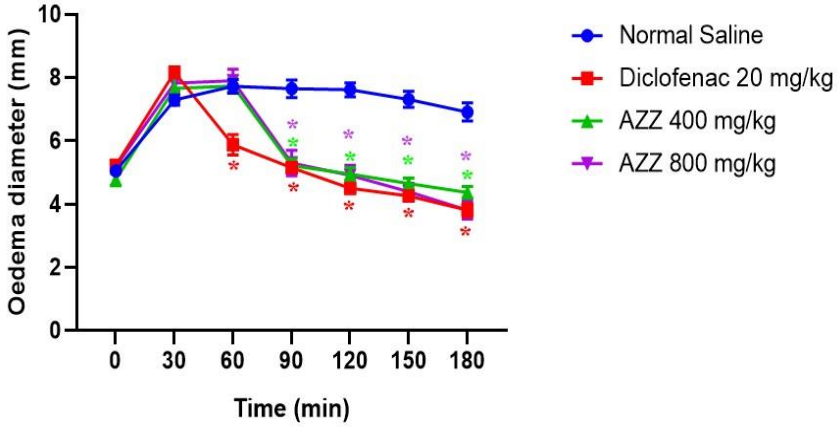

Figure 2 : Anti-inflammatory effect of AZZ (400 and 800 mg/kg, *p.o*) and Diclofenac (20 mg/kg, i.p) in egg albumin induced oedema in rats. AZZ: aqueous stem bark extract of *Zanthoxylum zanthoxyloides*. The data were analysed by ANOVA one eay followed by Tukey's multiple comparisons test. The results are expressed as mean ± SEM (n=5). *$p < 0.05$ (treated groups compared to control).

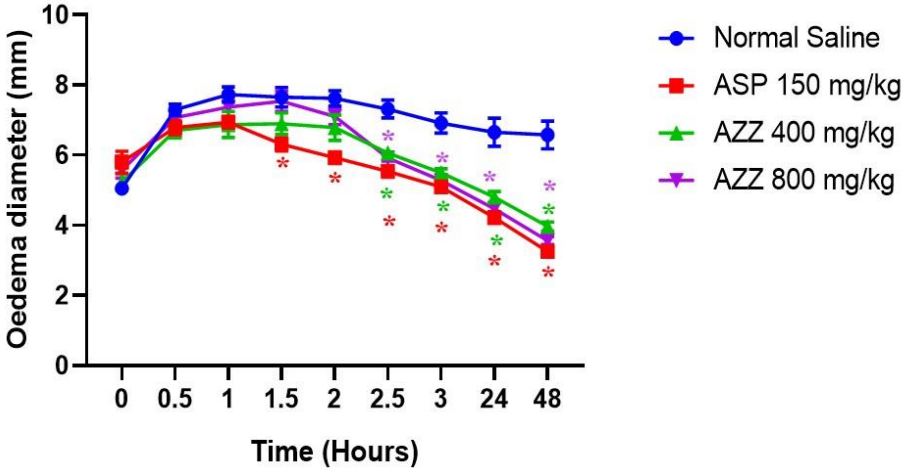

Figure 3: Anti-inflammatory effect of AZZ (400 and 800 mg/kg, p.o) and Aspirin (150 mg/kg, p.o.) in Formalin-induced oedema in rats. AZZ: aqueous stem bark extract of *Zanthoxylum zanthoxyloides*. The Data were analysed by ANOVA one way followed by Tukey's multiple comparisons test. The results are Expressed as mean ± SEM (n=5). *$p <$ 0.05 (treated groups compared to control).

31.76%, 34.95%, 36.38% and 36.75% for AZZ at 400 mg/kg and 30.71%, 35.47%, 39.94% and 44.86% for AZZ at 800 mg/kg at 90, 120, 150 and 180 minutes, respectively. The standard displayed an oedema reduction of 23.83%, 32.67%, 40.86%, 41.72% and 44.86% at 60, 90, 120, 150 and 180 minutes.

Effect of the extract on formalin induced oedema on rats

Chronic inflammation was induced in Wistar rats using formalin 2%. During the first 60 minutes after induction, no significant reduction of the oedema was observed in all groups ($p > 0.05$). In the standard group, significant reduction of the oedema was observed from the 90th minute until the end of the experiment ($p < 0.05$). In the groups treated with the extract, significant reduction was observed after 150 minutes ($p < 0.05$) (Figure 3). The reduction was 17.09%, 20.54%, 27.81% and 39.57% for AZZ at 400 mg/kg, whereas 19.15%, 23.58%, 32.78% and 46.62% for AZZ at 800 mg/kg respectively at 2.5, 3, 24 and 48 hours. However, for the standard drug, it was 24.35%,

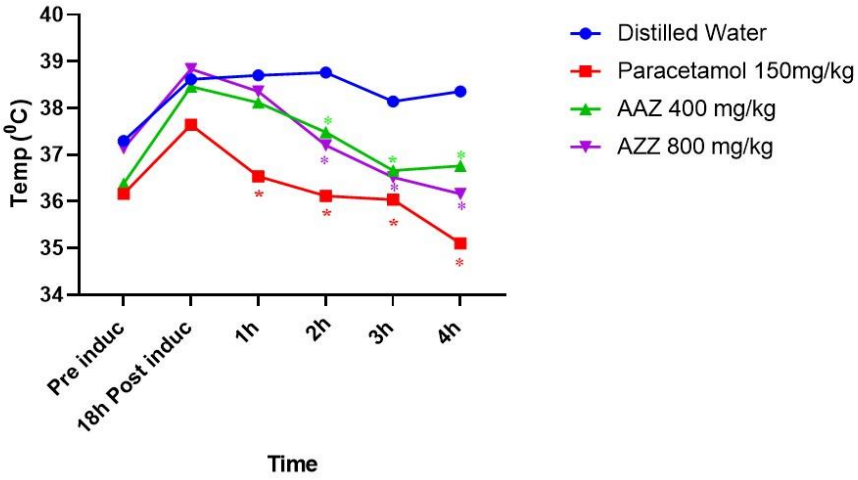

Figure 4: Antipyretic effect of AZZ (400 and 800 mg/kg, p.o) and Paracetamol (150 mg?kg, p.o) in fever Induced by 20% brewer's yeast. AZZ: Aqueous stem bark extract of *Zanthoxylum zanthoxyloides*. The data were analysed by ANOVA one way followed by Tukey's multiple comparisons test. The results are expressed as mean (n=5). *p < 0.05 (treated groups compared to control).

26.33%, 36.69% and 50.53% at the same time intervals measured.

Antipyretic effect of the extract on brewer's yeast induced fever on rats

Fever was induced in male Wistar rats using brewer's yeast at 20 % (w/v) dissolved in 0.9% normal saline. Animals with a rectal temperature rise of up to 1°C were chosen and randomly grouped into four groups of five animals each. One-hour after drugs administration, only the standard drug group showed a significant reduction in the rectal temperature at p < 0.05 when compared to control. However, from the second to the fourth hour, the animals administered with the standard drug and the extract at different doses showed significant reduction of the rectal temperature when compared to control at p < 0.05 (Figure 4).

DISCUSSION

Tissue damage and injury are always associated with pain and inflammation (Arzi et al., 2015). Inflammation is an important biological response of the vascular tissues to harmful stimuli, such as pathogens and damaged cells or irritants (Deshpande et al., 2011). The onset of the inflammation process is closely associated with arachidonic acid (AA) metabolites. For new drugs research and development, the arachidonic acid metabolic pathways are one of the important targets (Meirer et al., 2014). During the egg albumin-induced oedema, the extract displayed significant reduction (p < 0.05) of the oedema at all doses from the 90th minute to the 3rd hour. However, the standard drug (diclofenac 20 mg/kg *i.p*) displayed significant reduction (p < 0.05) from the first hour of the experiment. In the same manner, during the formalin-induced oedema, the extract at all doses displayed significant effects after 150 minutes until the end of the experiment. The standard drug (Aspirin 200 mg/kg *per os*) group showed significant reduction (p < 0.05) after 90 minutes. Arachidonic acid has two metabolic pathways, which are catabolized prostaglandin (PGs) by cyclooxygenase (COX), and catalysis generated leukotrienes (LTs) by 5-lipooxygenase (5-LO) (Zhao et al., 2018). AZZ significantly inhibited the activities of COX-2 and 5-LO and the extract played an anti-inflammatory role by influencing the metabolic pathways of arachidonic acid. In fact, the inhibition of COX and LO has vital significance for the treatment of inflammation. COX-1 is a constitutive enzyme that maintains the body's normal physiological function. On the other hand the expression of COX-2 can be significantly increased after stimulation by factors of inflammation (Yu et al., 2016). Our results were in accordance with an earlier study which found that the administration of the hydroethanolic extract of *Zanthoxylum zanthoxyloides* leaves to rats reduced carrageenan induced oedema. (Diatta et al., 2014). Prempeh and Mensah-Attipoe (2008) used the aqueous root extract of *Z. zanthoxyloides* during their work and found significant reduction of the prostaglandins E_2 (PGE_2) induced by the carrageenan injection. Our previous published work on the phytochemical screening of the extract showed the presence of components such flavonoids, tannins, saponins (Tougoma et al., 2021). This effect might be attributed to the presence of these components. Previous work done on plant extracts showed that the flavonoids and tannins have anti-inflammatory activity. Tanko et al. (2008) showed that the ethanolic

flower extract of *Newbouldia laevis*, which contains tannins has significant anti-inflammatory activity at doses 25, 50 and 100 mg/kg in oedema induced by formalin in rats at $p < 0.05$. One study showed the anti-inflammatory effect of the methanolic rhizome extract of *Sambucus ebulus* containing flavonoids and steroids (Ahmadiani et al., 1998), while Tannin-enriched fractions from the stem bark of *Myracrodruon urundeuva* at 5 and 10 mg/kg have shown potent anti-inflammatory action in carrageenan-induced oedema (Souza et al., 2007).

Fever is known to be caused by several endogenous pyrogens such as prostaglandin, interleukin-1β, interleukin-6, interleukin-8, tumour necrosis factor-α and macrophage protein-1. Prostaglandin synthesis may be activated by tumor necrosis factor-α and phospholipase A_2. Brewer's yeast induces both TNF-α and prostaglandin synthesis (Gege-Adebayo et al. 2013; Ridtitid et al., 2008) and causes pathogenic fever. Prostaglandin E_2 is currently accepted as the final fever mediator in the brain, specifically in the preoptic area of the anterior hypothalamus (Li et al., 2008). After 18 h of induction, the normal saline (control), extract (400 and 800 mg/kg) and paracetamol (standard, 150 mg/kg) were administered to rats which rectal temperature raise up to 1 °C. The rectal temperature was recorded each hour after administration. When compared to the control, the treated groups showed significant reduction of rectal temperature. The standard drug displayed a reduction in rectal temperature from the first hour while the extract displayed a reduction in rectal temperature from the second hour. Antipyretics such as non-steroidal anti-inflammatory drugs (NSAIDs) are known to reduce body temperature. NSAIDs typically COX-2 expression to reduce PGE_2 biosynthesis which is mostly produced in increased or elevated temperatures (Annan et al., 2013; Sharma et al., 2010). From our results, it can be considered that AZZ might inhibit the synthesis of prostaglandins. The link between circulating cytokines and fever is well established with a number of these mediators, most prominently IL-1β, IL-6 and TNF, implicated in triggering the central mechanisms that regulate the fever response (Conti et al., 2004; Konsman et al., 2002). These cytokines contribute to the activation of the central mechanisms involved in regulating the fever response. The cytokines have been regularly assessed by measuring the activation degree of transcription factors such as NF-kB, which are in turn activated by both TNF and IL-1β, and STAT-3, which is activated by IL-6 (Lebel et al, 2000). Both pathways lead to the transcription and induction of COX-2 (Inoue et al., 2008). Our results are in accordance with those from the experiment conducted by Souza et al. (2007). According to them, methanolic leaf extract of *Ocimum gratissimum* at doses of 200 and 300 mg/kg showed significant reduction ($p < 0.05$) of brewer's yeast-induced fever in rats after 1h of administration, and this antipyretic activity was observed up to 4h after administration. On the hand, methanolic and aqueous leaf extract of *Abutilon indicum* have been shown to exhibit significant antipyretic effect shortly after the administration and the effect was maintained for four hours (Vinod and Malgi, 2019). The efficacy of the antipyretic effect of AZZ was observed to be in a dose dependent manner. Therefore, augmentation of the concentration of the components in the extract exhibit increased antipyretic effects. In this study, the extract's antipyretic effect may be attributed to its phytochemical components, which include flavonoids. Plants containing flavonoids such as *Palisota hirsuta* and *Jasminum trichotomum* have been found to possess antipyretic properties (Achuta et al., 2011; Boakye-gyasi et al., 2011). During their work, Hämäläinen et al. (2011) and O'Leary et al. (2004) found that a variety of flavonoids inhibit production and transcription of COX-2 and exhibit antipyretic effect by suppressing TNF-α (Chang et al., 2007).

It can be concluded from the above results that the stem bark aqueous extract of *Zanthoxylum zanthoxyloides* possess antipyretic and anti-inflammatory activities**.** These activities might be attributed to the chemical components of the extract such as flavonoids and tannins. Further studies are needed to elucidate the mechanism of action of the different activities observed and to isolate the components responsible for these activities.

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Conflict of Interests

The authors state that there is no conflict of interest in the paper's publication.

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