African Journal of Pharmacology and Therapeutics Vol. 5 No. 2 Pages 111-117, 2016
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Research Article

Antinociceptive and anti-inflammatory activities of root extract of *Zea mays*

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Background: *Zea mays* is used in Ibibio traditional medicine in Nigeria for the treatment of various ailments such as pains, malaria and hemorrhoids.

Objective: To evaluate the anti-inflammatory and analgesic activities of *Zea mays* ethanol root root extract in mice.

Methodology: The crude ethanolic extract (45 – 135 mg/kg) of *Zea mays* root was investigated for anti-inflammatory and analgesic activities in mice using various experimental models; acetic acid and thermal- induced pains and carrageenan, egg albumin and xylene – induced oedema. The activity of the extract was compared to that of standard drug, acetyl salicylic acid (100 mg/kg).

Results: The extract caused a significant ($p<0.05$ – 0.001) dose-dependent reduction of inflammation and pains induced by different phlogistic agents used. These effects were comparable to that of the standard drugs, acetyl salicylic acid (100 mg/kg) used in some models.

Conclusion: The anti-inflammatory and analgesic effects of this plant may in part be mediated through the chemical constituents of the plant and the results of the analgesic action suggest central and peripheral mechanisms. The findings of this work confirm the ethno medical use of this plant to treat inflammatory conditions.

Key words: *Zea mays,* antiinflammatory, analgesic

Received: April, 2016
Published: September, 2016

1. Introduction

Zea mays L. (Family- Poacae) known as maize or corn, is an annual grass plant cultivated for human consumption and rearing of animals. It was introduced to Nigeria in the 16th century (Osagie and Eka, 1998). It is tall with strong erect stalks and a fibrous root system. The plant has long narrow leaves that are spaced alternately on opposite side of the stem and bears ears that are enclosed in modified leaves known as husks (Simmonds, 1979).

Besides its nutritive values, maize grains, leaves, cornsilks, stalk, and inflorescence are also used in ethnomedicine for the treatment of several ailments. The corn silk is used as an antidiabetic or diuretic, and decoction of the silk is consumed for the treatment of urinary troubles and gallstones (Foster and Duke, 1990; Gill, 1992; Abo et al, 2008). The ash of the cob is used for the treatment of cough (Gill, 1992) as well as inflammatory diseases. The husks are used in the treatment of pains and arthritis (Owoyele et al, 2010). it is also taken as warm tea for the treatment of malaria in Ibibio traditional medicine. Biological activities reported on the leaf extract include; anticancer (Balasubramanian et al, 2014), antioxidant (Balasubramanian and Padma, 2012) and antioxidative stress (Balasubramanian and Padma, 2013; Balasubramanian et al, 2015) activities. Antiinflammatory and analgesic activities have been reported on the husk extract (Owoyele et al, 2010).

Eight phenolic compounds (gallic acid, protocatechuic acid, chlorogenic acid, cafeic acid, femlic acid, rutin, resveratrol, and kaempferol) have also been detected in ethanol husk extract of *Zea mays* (Dong et al, 2014). The

 ISSN 2303-9841

antifungal compounds, 6-methoxybenzoxazolinone and 6,7-dimethoxy benzoxazolinone, were isolated from an ethanol extract of *Zea mays* roots, and (6R)-7,8-dihydro-3-oxo-α-ionone and (6R; 9R)-7,8-dihydro-3-oxo- α - ionol were isolated from the root exudates (Park et al, 2004).

Information on the biological activities of the root extract is scarce. We report in this study the anti-inflammatory and antinociceptive activities of root extract of *Zea mays* to confirm and support its use in Ibibio ethnomedicine.

2. Materials and Methods

2.1 Plants collection

The plant material *Zea mays* (roots) were collected in a farmland in Uyo area, Akwa Ibom State, Nigeria in May, 2015. The plant was identified and authenticated by a Taxonomist in the Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria. Hebarium specimen (**DPNH 866**) was deposited at Department of Pharmacognosy and Natural Medicine Herbarium.

2.2 Extraction

The plant parts were washed and shade-dried for two weeks. The dried plants' materials were reduced to powder using mortar and pestle. The powdered material was soaked in 50% ethanol for 72 hours. The liquid filtrate was concentrated and evaporated to dryness *in vacuo* 40°C using rotary evaporator and stored in a refrigerator at - 4°C.

2.3 Phytochemical Screening

Phytochemical screening of the crude extract was carried out employing standard procedures and tests (Trease and Evans, 1989; Sofowora, 1993), to reveal the presence of chemical constituents such as alkaloids, flavonoids, tannins, terpenes, saponins, anthraquinones, reducing sugars, cardiac glycosides among others.

2.4 Animals

Albino Swiss mice (17-25g) of either sex were obtained from the University of Uyo animal house. They were maintained on standard animal pellets and water *ad libitum*. Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics committee, University of Uyo.

2.5 Determination of median lethal dose (LD_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice by intraperitoneal (i.p) route using the method of Lorke (1983). This involved intraperitoneal administration of different doses of the extract (100, 300, 400, 500, 600 and 1000 mg/kg) to groups of three mice each. The animals were observed for manifestation of physical signs of toxicity such as writhing, decreased motor activity, decreased body/limb tone, decreased respiration and death. The number of deaths in each group within 24 hours was recorded.

The LD_{50} was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b):

$$LD_{50} = \sqrt{ab}$$

2.6 Evaluation of antiinflammatory activity of the extract

Carrageenan – induced mice hind paw oedema

Adult albino male mice were used after 24 hours fast and deprived of water only during experiment. Inflammation of the hind paw was induced by injection of 0.1 ml of freshly prepared carrageenan suspension (1%) in normal saline into the sub planar surface of the hind paw. The linear circumference of the injected paw was measured before and 0.5, 1, 2, 3, 4 and 5 hrs after administration of carrageenan. The increase in paw circumference post administration of carrageenan was adopted as the parameter for measuring inflammation (Winter et al, 1962; Akah and Nwambie, 1994; Ekpendu et al, 1994, Besra et al, 1996; Nwafor et al, 2010). The difference in paw circumference between the control and 0.5, 1, 2, 3, 4 and 5 hrs after administration of phlogistic agent was used to assess inflammation (Hess and Milonig, 1992).

The extract (45, 90 and 135 mg/kg i.p) was administered to various groups of 6 mice each, 1 h before inducing inflammation. Control mice received 10 ml/kg of distilled water while reference group received ASA (100 mg/kg). The average (mean) oedema was assessed by measuring with Vernier calipers. Average inflammation/oedema ($C_t - C_0$) was calculated for each dose (Oriowo, 1982; Akah and Njike, 1990).

Egg-albumin induced inflammation

Inflammation was induced in mice by the injection of egg albumin (0.1ml, 1% in normal saline) into the sub planar tissue of the right hind paw (Akah and Nwambie, 1994; Okokon and Nwafor, 2010). The linear circumference of the injected paw was measured before and 0.5, 1, 2, 3, 4 and 5 hrs after the administration of the egg albumin. The root extract (45, 90 and 135 mg/kg i.p) and ASA (100 mg/kg orally) were administered to groups (n=6) of 24 h fasted mice 1 h before the induction of inflammation. Control group received 10 ml/kg of distilled water orally. Edema (inflammation) was assessed as the difference in paw circumference between the control and 0.5, 1, 2, 3, 4 and 5 hrs post administration of the egg albumin (Hess and Milonig, 1972). The average (mean) edema was assessed by measuring with vernier calipers. Average inflammation/oedema ($C_t - C_0$) was calculated for each dose (Oriowo, 1982; Akah and Njike, 1990).

Xylene – induced ear oedema

Inflammation was induced in mice by topical administration of 2 drops of xylene at the inner surface of the right ear. The xylene was left to act for 15 mins. *Zea mays* root extract (45, 90 and 135 mg/kg i.p), dexamethasone (4 mg/kg) and distilled water (0.2 ml/kg) were orally administered to various groups (n=6) of mice 1 h before the induction of inflammation. The animals were sacrificed under light anaesthesia and

the left ears cut off. The difference between the ear weights was taken as the oedema induced by the xylene (Tjolsen et al, 1992; Okokon and Nwafor, 2010).

2.7 Evaluation of analgesic potential of the extract

Acetic acid induced writhing in mice

Writhings (abdominal constrictions consisting of the contraction of abdominal muscles together with the stretching of hindlimbs) resulting from intraperitoneal (i.p) injection of 2% acetic acid, was induced according to the procedure described by Santos et al. (1994), Correa et al. (1996) and Nwafor et al, (2010). The animals were divided into 5 groups of 6 mice per group. Group 1 served as negative control and received 10 ml/kg of normal saline, while groups 2, 3 and 4 were pre-treated with 45, 90, and 135 mg/kg doses of *Z. mays* extract intraperitoneally, and group 5 received 100 mg/kg of acetyl salicylic acid. After 30 minutes, 0.2 ml of 2% acetic acid was administered intraperitoneally (i.p). The number of writhing movements was counted for 30 minutes. Antinociception (analgesia) was expressed as the reduction of the number of abdominal constrictions between control animals and mice pretreated with extracts.

Thermally induced pain in mice

The effect of extract on hot plate induced pain was investigated in adult mice. The hot plate was used to measure the response latencies according to the method of Vaz et al, (1996) and Okokon and Nwafor, (2010). In these experiments, the hot plate was maintained at 45±1^{o}C, each animal was placed into a glass beaker of 50 cm diameter on the heated surface, and the time(s) between placement and shaking or licking of the paws or jumping was recorded as the index of response latency. An automatic 30-second cut-off was used to prevent tissue damage. The animals were randomly divided into 5 groups of 6 mice each and fasted for 24 hours but allowed access to water. Group 1 animal served as negative control and received 10 ml/kg of normal saline. Groups 2, 3 and 4 were pre-treated intraperitoneally with 45, 90, and 135 mg/kg doses of *Z. mays* root extract respectively, while group 5 animals received 100 mg/kg of acetyl salicylic acid intraperitoneally, 30 minutes prior to the placement on the hot plate.

2.8 Statistical analysis and data evaluation

Data obtained from this work were analyzed statistically using Student's t-test and ANOVA (One-way) followed by a post test (Tukey-Kramer multiple comparison test). Differences between means were considered significant at 1% and 5% level of significance i.e. $P \leq 0.01$ and 0.05.

3. Results

3.1 Phytochemical screening

The phytochemical screening of the ethanolic extract of the root of *Zea mays* revealed the presence of alkaloids, cardiac glycosides, tannins, saponins, terpenes and flavonoids.

3.2 Determination of median lethal dose (LD_{50})

The various doses employed in the study produced different degrees of mortality (**Table 1**). The median lethal dose (LD_{50}) was calculated to be 447.21 mg/kg. The physical signs of toxicity included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death.

Table 1: Acute toxicity profile of ethanolic root extract of *Zea mays*

Doses (mg/kg)	Mortality
100	0/3
300	0/3
400	0/3
500	3/3
1000	3/3

3.3 Carrageenan-induced oedema in mice

The effect of ethanol extract of *Zea mays* root on carrageenan-induced oedema is as shown in **Table 2**. The extract (45 - 135 mg/kg) exerted a significant ($P<0.05 – 0.001$) anti-inflammatory effect in a dose – dependent manner at the later phase (3-5h). The activity of the highest dose was more than that of the standard drug, ASA, 100 mg/kg (**Table 2**).

Table 2: Effect of *Zea mays* root extract on carrageenan induced oedema in rats.

Treatment	Linear circumference of injected paw (mm) ± SEM					
	0.5hr	1hr	2hr	3hr	4hr	5hr
Control	1.53 ± 0.22	1.55 ± 0.23	2.66 ± 0.12	2.55 ± 0.13	2.55 ± 0.19	2.10 ± 0.26
Extract						
45 mg/kg	1.64± 0.28	1.81 ± 0.61	1.96 ± 0.25	1.75 ± 0.31	1.59 ± 0.30^{a}	1.38 ± 0.33
90 mg/kg	1.99± 0.22	2.22 ± 0.166	2.34 ± 0.05	1.62 ± 0.15^{a}	1.48 ± 0.13^{a}	1.27 ± 0.14^{c}
135 mg/kg	1.77 ± 0.20	1.76 ± 0.14	2.39 ± 0.08	1.56 ± 0.15^{a}	1.43 ± 0.21^{b}	0.85 ± 0.16^{C}
ASA 100 mg/kg	1.58±0.21	1.42 ± 0.80	1.63 ± 0.37^{a}	1.48 ± 0.33^{a}	1.22 ± 0.08^{b}	1.22 ± 0.29^{C}

Data are expressed as mean ± SEM. Significant at ^{a} $P<0.05$, ^{b} $P < 0.01$, ^{c} $P < 0.001$ when compared to control. n = 6

 ISSN 2303-9841

Table 3: Effect of *Zea mays* root extract on egg-albumin induced oedema in rats.

Treatment	Linear circumference of injected paw (mm) ± SEM					
	0.5hr	1hr	2hr	3hr	4hr	5hr
Control	3.43 ± 0.14	3.58 ± 0.10	3.44 ± 0.11	3.27 ± 0.14	3.23 ± 0.17	2.72 ± 0.06
Extract						
45 mg/kg	3.18 ±0.12	3.05 ± 0.11	3.16 ± 0.11	2.61 ± 0.18	2.52 ± 0.13	1.97 ± 0.10
90 mg/kg	3.38 ±0.12	3.40 ± 0.20	3.34 ± 0.20	3.08 ± 0.27	2.61 ± 0.19[c]	2.33 ± 0.24
135 mg/kg	2.35± 0.53[a]	2.22 ± 0.29[c]	2.18 ± 0.30[c]	1.91 ± 0.25[c]	1.62 ± 0.33[c]	1.68 ± 0.41[c]
ASA 100 mg/kg	3.33 ±0.07	2.78 ± 0.05[a]	2.56 ± 0.06[a]	2.37± 0.01[a]	2.02 ± 0.04[b]	1.60 ± 0.12[a]

Data are expressed as mean ± SEM. Significant at [a] P<0.05, [b] P < 0.01, [c] P < 0.001 when compared to control. n = 6

Table 4: Effect of *Zea mays* root extract on xylene-induced ear oedema in mice.

Treatment	Weight of right ear (g)	Weight of left ear (g)	Increase in ear weight (g)	% Inhibition
Control	0.053 ± 0.003	0.110 ± 0.005	(105.66) 0.056 ± 0.006	
Extract				
45 mg/kg	0.053 ± 0.003	0.090 ± 0.00	(67.92) 0.036 ± 0.003[a]	35.71
90 mg/kg	0.053 ± 0.003	0.080 ± 0.005	(49.05) 0.026 ± 0.003[b]	53.57
135 mg/kg	0.056± 0.003	0.070 ± 0.005	(35.71) 0.020 ± 0.00[c]	64.28
Dexamethasone 4.0 mg/kg	0.053 ± 0.003	0.060 ± 0.003	(24.52) 0.013 ± 0.003[c]	76.78

Figures in parenthesis indicate % increase in ear weight. Significant at [a] P<0.05, [b] P < 0.01, [c] P < 0.001 when compared to control. n = 6

3.4 Egg albumin- induced oedema

Administration of extract of *Zea mays* (45 - 135 mg/kg) on egg albumin - induced oedema in mice caused a significant (p<0.05 – 0.001) dose-dependent anti-inflammatory effect against oedema caused by egg albumin at the later phase (3 - 5h). The effect was weak compared to that of standard drug, ASA (100 mg/kg) (**Table 3**).

3.5 Xylene- induced ear edema

Anti-inflammatory effect of crude extract of *Zea mays* against xylene-induced ear oedema in mice is shown in **Table 4**. The extract exerted a dose-dependent anti-inflammatory effects that were significant (P<0.05 - 0.01) but weak compared to that of the standard drug, dexamethasone (4.0 mg/kg).

3.6 Effect of ethanol crude extract of *Z. mays* on acetic acid-induced writhing in mice

The administration of *Zea mays* extract (45 - 135 mg/kg) demonstrated a dose-dependent reduction in acetic acid-induced writhing in mice. The reductions were statistically significant (p<0.05 - 0.001) relative to control and the effect of the highest dose (135 mg/kg) at 30 min was ccomparable to that of the standard drug, ASA (**Table 5**).

3.7 Effect of ethanol root extract of *Z. mays* on thermally-induced pain in mice.

The extract (45 - 135 mg/kg) exhibited a dose - dependent effect on thermally-induced pain in mice. This inhibitions were statistically significant (p<0.001) relative to the control but weak compared to that of the standard drug, ASA (100 mg/kg) (**Table 6**).

Table 5: Effect of *Zea mays* root extract on acetic acid induced writhing in mice.

Treatment	Time intervals (hr)						
	5	10	15	20	25	30	Total
Control	6.66 ± 0.88	11.66 ± 1.20	24.66 ± 1.85	17.0 ± 0.57	13.00 ± 1.15	11.0 ± 1.00	83.98 ± 6.65
Extract							
45 mg/kg	4.33 ± 0.33	5.33 ± 1.45	13.0 ± 2.00[b]	12.66 ± 0.88[b]	11.66 ± 0.66	7.66 ± 0.33	54.64 ± 5.65[a]
90 mg/kg	3.33 ± 0.33	5.33 ± 2.96	9.00 ± 1.52[c]	9.66 ± 0.88[c]	8.33 ± 1.76	7.0 ± 1.00[a]	42.65 ± 8.45[c]
135 mg/kg	0.33 ± 0.33[c]	3.00 ± 0.57[b]	4.33 ± 1.20[c]	4.00 ± 0.57[c]	5.66 ± 0.88[b]	4.00 ± 0.57[c]	21.32 ± 4.12[c]
ASA 100 mg/kg	4.00 ± 0.57[a]	6.00 ± 0.57	8.33 ± 0.88[c]	8.66 ± 0.33[c]	7.66 ± 0.66[c]	4.00 ± 0.57[c]	38.65 ± 3.58[c]

Data are expressed as mean ± SEM. Significant at [a] P<0.05, [b] P < 0.01, [c] P < 0.001 when compared to control. n = 6

 ISSN 2303-9841

Table 6: Effect of *Zea mays* root extract on hot plate test

Treatment	Reaction time (sec) (mean ± SEM)	% inhibition
Control	4.92 ± 0.23	
Extract 45 mg/kg	5.97 ± 0.22	21.34
90 mg/kg	13.25 ± 0.50 [a]	169.30
135 mg/kg	20.51 ± 0.74[c]	316.86
ASA 100 mg/kg	29.53 ± 3.48[c]	500.20

Data are expressed as mean ± SEM. n = 6.
Significant at [a]P < 0.05, [b] P < 0.001, [c] P < 0.001 when compared to control.

4. Discussion

Zea mays root is used traditionally for the treatment of various illnesses such as malarial fever, pains and inflammatory conditions. In this study, the ethanol root extract was evaluated for analgesic and anti-inflammatory activities using different experimental models.

In the carrageenan-induced oedema, the extract (45-135 mg/kg) was observed to have exerted significant effect at the later stage of inflammation (3-5 hr) indicating insignificant effect on histamine, serotonin and kinins that are involved in the early stage of carrageenan-induced oedema (Vane and Booting, 1987). The extract caused significant reduction of the later stage of the oedema maybe due to its ability to inhibit prostaglandin which is known to mediate the second phase of carrageenan-induced inflammation (Vane and Booting, 1987). However, ASA (100 mg/kg) a prototype NSAID, a cyclooxygenase inhibitor whose mechanism of action involves inhibition of prostaglandin, produced a considerable inhibition of the paw swelling induced by carrageenan injection.

The extract also inhibited egg albumin-induced oedema, though at the later stage (3-5hr), demonstrating that it can inhibit inflammation by blocking the release of histamine and 5-HT, two mediators that are released by egg albumin (Nwafor et al, 2007). However, ASA, a cyclooxygenase inhibitor reduced significantly oedema produced by egg albumin.

The extract exerted a significant ($p<0.01$) inhibition of ear oedema caused by xylene only at all doses of the extract, suggesting the inhibition of phospholipase A_2 which is involve in the pathophysiology of inflammation due to xylene (Lin et al,1992). However, dexamethasone, a steroid antiinflammatory agent produced significant reduction in the mean right ear weight of positive control rats indicating an inhibition of PLA_2.

The extract significantly reduced acetic acid-induced writhing and delayed the reaction time of animals (mice) to thermally induced pain. Acetic acid causes inflammatory pain by inducing capillary permeability (Amico-Roxas et al.,1984; Nwafor et al., 2007), and in part through local peritoneal receptors from peritoneal fluid concentration of PGE_2 and $PGF_2\alpha$ (Deraedt et al,1980; Bentley et al,1983). The acetic acid-induced abdominal writhing is a visceral pain model in which the processor releases arachidonic acid via cyclooxygenase, and prostaglandin biosynthesis plays a role in the nociceptive mechanism (Franzotti et al, 2002). It is used to distinguish between central and peripheral pain. These results suggest that the extract may be exerting its action partly through the lipoxygenase and/or cyclooxygenase system.

The study also shows that the extract significantly delayed the reaction time of thermally- induced (hot plate) test. This model is selective for centrally acting analgesics and indicates narcotic involvement (Turner, 1995) with opioid receptors.

Phytochemical screening of the root extract revealed the presence of alkaloids, cardiac glycosides, tannins, saponins, terpenes and flavonoids. Flavonoids are known anti-inflammatory compounds acting through inhibition of the cyclo-oxygenase pathway (Liang et al, 1999). Some flavonoids are reported to block both the cyclooxygenase and lipoxygenase pathways of the arachidonate cascade at relatively high concentrations, while at lower concentrations they only block lipoxygenase pathway (Carlo et al, 1999). Some flavonoids exert their antinociception via opioid receptor activation activity (Suh et al, 1996; Rajendran et al, 2000; Otuki et al, 2005). Flavonoids also exhibit inhibitory effects against phospholipase A2 and phospholipase C (Middleton et al, 2000), and cyclooxygenase and/or lipoxygenase pathways (Robak et al, 1998).

Triterpenes have been implicated in anti-inflammatory activity of plants (Huss et al, 2002; Suh et al, 1998) and reports on their analgesic activities have also been published (Liu, 1995; Krogh et al, 1999; Tapondjou et al, 2003; Maia et al, 2006). Ursolic acid is a selective inhibitor of cyclooxygenase-2 (Ringbom et al, 1998). Oleanolic acid is known to exert its analgesic action through an opioid mechanism, and possibly, a modulatory influence on vanilliod receptors (Maia et al, 2006).

5. Conclusion

The results of this study demonstrated that *Zea mays* root possesses analgesic property. Further investigation is being advocated especially in elucidating cellular mechanisms and establishing structural components of the active ingredients with a view of standardizing them.

 ISSN 2303-9841

Conflict of Interest Declaration

The authors declare no conflict of interest.

Acknowledgements

Authors are grateful to Mr Enefiok Ukpong and Nsikan Malachy of Department of Pharmacology and Toxicology, University of Uyo for their technical assistance.

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 ISSN 2303-9841