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Full Length Research Paper

Evaluation of anti-inflammatory activities of root extracts of *Stephania dinklagei* (Engl.) Diels

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The hexane, chloroform, ethyl acetate and methanol extracts of *Stephania dinklagei* were screened for anti-inflammatory activities using carrageenan, kaolin-carrageenan and formaldehyde-induced paw edema models of inflammation. The extracts showed dose dependent anti-inflammatory activity with 300 mg/kg of the extracts being more potent. At 1 and 4 h, post carrageenan injection, the paw edema in the 100 and 300 mg/kg hexane and ethyl acetate treated mice was significantly lower than the paw edema in the control group. Treatment of mice with 100 and 300 mg/kg hexane and ethyl acetate extracts significantly suppressed the progression of edema post kaolin-carrageenan injection. The paw edema induced by formaldehyde in the 300 mg/kg hexane and ethyl acetate treated groups was significantly lower than edema in the other treatment groups on day 1, 4 and 8 post formaldehyde injections. The result of the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) assay showed that the hexane, chloroform and methanol extracts at 400 µg/ml exhibited 77.5, 58.4 and 51.7% activity, respectively. The ethylacetate extract showed maximum scavenging activity of 70.6% at 50 µg/ml. The results suggested that the hexane and ethyl acetate extracts of *S. dinklagei* possessed potent anti-inflammatory properties with the ethyl acetate extract showing the best activity.

Key words: *Stephania dinklagei*, carrageenan, kaolin, formaldehyde, edema, 1, 1-diphenyl-2-picrylhydrazyl (DPPH).

INTRODUCTION

Stephania dinklagei (Engl.) Diels is a slender climber which grows in dense humid rain forests in West Africa (Grace, 2008). This plant belongs to the genus *Stephania* of the family Menispermaceae (Semwal et al., 2010). Several plants in this genus have been found to have medicinal effects and are used traditionally in the treatment of asthma, dysentery, wounds, hyperglycemia, cancer, fever, intestinal disorders, sleep disorders and inflammation (Akubue et al., 1983; Gaur, 1999; Kirtikar and Basu, 2004). In Southern Nigeria, the leaves of *S. dinklagei* are used to prepare decoctions used in the treatment of impotence, dysentery, diarrhea, cough and mental illness (Grace, 2008). The stems of this plant are also used to prepare medicines for hypnosis, sedation and analgesia (Semwal et al., 2010). In Nsukka area, Southeast Nigeria, the roots are used to prepare ethno medicines used in the treatment of mental illness, pain and inflammatory conditions.

Scientific studies have shown that the aqueous stem extract of *S. dinklagei* has hypnotic, sedative and central analgesic effect (Akubue et al., 1983). Despite studies suggesting that plants in the genus *Stephania* possess anti-inflammatory property, there is yet no scientific report authenticating the ethno medicinal use of *S. dinklagei* roots in the management of inflammatory disorders. This study aimed to investigate the anti-inflammatory activities of *S. dinklagei* using different experimental inflammatory

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models.

MATERIALS AND METHODS

Experimental animals

Mature male albino mice weighing between 22 to 28 g were used for the experiments. They were maintained under standard experimental conditions and allowed free access to standard rodent diet and clean drinking water. All experiments carried out were approved by the Animal Ethics Committee, University of Nigeria, Nsukka. Each experimental group consisted of six mice each.

Plant material

Fresh roots of *S. dinklagei* were collected from Orba in Udenu L.G.A. in April, 2010. They were identified and authenticated by Mr. A.O. Ozioko, a taxonomist with the International Centre for Ethnomedicine and Drug Development, Nsukka. Voucher specimen (INTERCEED, 916) was deposited in the herbarium of the centre for future reference.

Preparation of extract

The roots were washed, cut into small pieces and dried at room temperature. They were pulverized into coarse powder and extracted successively using n-hexane, chloroform, ethyl acetate and methanol,respectively. The solvents were allowed to evaporate in a rotary evaporator at 40°C and the extracts obtained stored in a refrigerator at 4°C. The yields of the hexane, chloroform, ethyl acetate and methanol extracts were 1.43, 7.53, 6.28 and 7.82 % (w/w), respectively. At the time of use, the extracts were prepared as suspension in 10% Tween 20 at the required concentrations.

Acute oral toxicity

The extracts (hexane, chloroform, ethyl acetate and methanol) were administered per os (p.o.) at doses of 250, 500 and 1000 mg/kg, respectively to mice as described by Lorke (1983). The control received distilled water (1 ml/kg). The mice were observed for 24 h for behavioural signs of toxicity or mortality. Based on the results of this toxicity test and preliminary anti-inflammatory tests, the dose for the study was decided to be 100 and 300 mg/kg**.**

Phytochemical screening

The hexane, chloroform, ethyl acetate and methanol extract were tested for the presence of alkaloids, flavonoids, tannins, terpenoids, glycosides, arthroquinones and saponins as described by Harborne (1984).

Carrageenan-induced paw edema test

This test was performed as previously described (Winter et al., 1962). The initial left hind paw thickness of each mouse was measured with a vernier caliper (Udegbunam et al., 2011). The extracts (100 and 300 mg/kg) were administered p.o to mice in the extract treated groups. Aspirin (100 mg/kg) was used as standard. Control animals were treated with normal saline (1 ml/kg, p.o.). Acute inflammation was induced 1 h later by sub plantar injection of 0.02 ml carrageenan. The paw thicknesses were re-measured at 1, 2, 3 and 4 h post edema induction. Paw edema was calculated as described by Zhang et al. (2008).

Kaolin-carrageenan induced hind paw edema

A mixture of kaolin (20%) and carrageenan (1%) was injected into the hind paw of mice to induce edema (Hajare et al., 2001). At 18 h post edema induction, the extracts (100 and 300 mg/kg, p.o.) and aspirin (100 mg/kg, p.o.) were administered to the mice. The treatments were repeated at 3 and 7 h after the first dosing. The paw thicknesses were measured before the first dose and at 3, 6 and 24 h after the first dose. Paw edema was calculated (Zhang et al., 2008).

Formaldehyde-induced paw edema

The effect of the extracts on chronic inflammation was evaluated using formaldehyde induced paw edema test (Chau, 1989). Chronic inflammation was induced by sub plantar injection 0.1 ml of 2.5% freshly prepared formaldehyde solution. The extracts (100 and 300 mg/kg) and dexamethasone (3 mg/kg) were administered p.o. to mice 1 h prior to formaldehyde injection and continued daily for a period of 7 days after induction of edema. Control animals were treated with normal saline (1 ml/kg, p.o.). The paw thickness of each mouse was measured on day 0 and once every day for 7 days. The paw edema was calculated (Zhang et al., 2008).

1, 1-Diphenyl-2-hydrazyl (DPPH) assay

The *in vitro* anti-oxidant activity of the extracts was performed according to the methods of Mensor et al. (2001). The extracts were tested at 10, 50, 100, 200 and 400 µg/ml concentrations. 1 ml of methanol plus 2 ml of the extract was used as blank while 1 ml of 0.5 mM DPPH solution plus 2 ml of methanol was used as control. Ascorbic acid was used as reference standard. Absorbance at 517 nm was taken after 30 min incubation in the dark at room temperature. The concentrations were prepared in triplicates. The percentage anti-oxidant activity was calculated as previously described (Hsu, 2006).

Statistical analysis

The data were statistically analyzed using analysis of variance (ANOVA) followed by Duncan multiple range tests. P values less than 0.05 were accepted as significant.

RESULTS

Acute oral toxicity

No behavioral changes or mortality were noted post administration of the extracts at 250, 500 and 1000 mg/kg.

Phytochemical screening

Phytochemical screening revealed the presence of

Table 1. Effect of *S. dinklagei* extracts on paw edema induced by carrageenan.

Treatments	Doses(mg/kg)	Paw edema (mm)	
		1 h	4 h
Carrageenan	-	0.12 ± 0.02^{c}	0.22 ± 0.03 ^{c}
Aspirin	100	0.04 ± 0.02^{a}	0.06 ±0.01^{a}
Hexane extract	100	0.07 ± 0.02^{b}	0.12 ± 0.01^{b}
Chloroform extract	100	0.11 ±0.03^{c}	0.16 ±0.02^{d}
Ethyl acetate extract	100	0.04 ± 0.01^{a}	0.09 ± 0.03^{ab}
Methanol extract	100	0.09 ± 0.04^{bc}	0.13 ± 0.04^{b}
Hexane extract	300	0.03 ± 0.01^{a}	0.08 ± 0.02^{ab}
Chloroform extract	300	0.10 ± 0.02^{cd}	0.18 ± 0.02^{cd}
Ethyl acetate extract	300	0.02 ± 0.01^{e}	0.07 ± 0.01^{a}
Methanol extract	300	0.06 ± 0.02^{b}	0.12± 0.04^{b}

Different superscript across a column show significant difference $p < 0.05$.

Table 2. Effect of *S. dinklagei* extracts on paw edema induced by kaolin- carrageenan.

Treatments	Doses (mg/kg)	Paw edema (mm)		
		3 h	6 h	24 h
Kaolin-carrageenan	-	0.35±0.04^{a}	0.29 ± 0.06^{b}	0.22 ± 0.04^{b}
Aspirin	100	0.19 ± 0.04^{c}	0.15 ± 0.03^{a}	0.13 ± 0.02^{a}
Hexane extract	100	0.31 ± 0.02^{ab}	0.22 ± 0.01^{c}	0.16 ± 0.02^{ab}
Chloroform extract	100	0.34 ± 0.03^{a}	0.30 ± 0.05^{b}	0.24 ± 0.02^{d}
Ethyl acetate extract	100	0.30 ± 0.01^{b}	0.21 ± 0.01^{c}	0.15 ± 0.02^{ab}
Methanol extract	100	0.33 ± 0.02^{ab}	0.26 ± 0.03^{d}	0.20 ± 0.01^{bc}
Hexane extract	300	0.21 ± 0.01^{c}	0.17 ± 0.01^{a}	0.15 ± 0.02^{ab}
Chloroform extract	300	0.25 ± 0.02^{d}	0.24 ±0.02^{cd}	0.19 ±0.03^{ab}
Ethyl acetate extract	300	0.20 ± 0.02^{c}	0.16 ±0.02^{a}	0.12 ± 0.02^{a}
Methanol extract	300	0.23 ± 0.02^{d}	0.22 ± 0.03^{c}	0.17 ± 0.02^{ab}

Different superscript across a column show significant difference $p < 0.05$.

alkaloids in all the extracts. The ethyl acetate and methanol extracts contained tannins while flavonoids were seen in the hexane, ethyl acetate and methanol extracts. The chloroform and methanol extracts contained terpenoids.

Carrageenan-induced paw edema

At 1 and 4 h, post carrageenan injection, the paw edema in the 100 and 300 mg/kg hexane and ethyl acetate treated mice were significantly ($p < 0.05$) lower than paw edema in the control group (Table 1). The effect of the hexane and ethyl acetate extracts were similar to the control drug. At 4 h, the order of edema inhibition by the extracts was ethyl acetate > hexane > methanol > chloroform respectively.

Kaolin- carrageenan induced hind paw edema

Treatment of mice with 100 and 300 mg/kg hexane and ethyl acetate extracts significantly suppressed the progression of edema post kaolin-carrageenan injection at 3, 6 and 24 h (Table 2). The effects of both extracts on kaolin-carrageenan induced edema were similar to that of aspirin.

Formaldehyde-induced paw edema

The paw edema induced by formaldehyde in the 300 mg/kg hexane and ethyl acetate treated groups were significantly lower than edema in the other treatment groups on days 1, 4 and 8 post formaldehyde injection (Table 3). The ethyl acetate extracts showed the best activity.

Table 3. Effect of *S. dinklagei* extracts on paw edema induced by formaldehyde.

Treatments	Doses (mg/kg)	Paw edema (mm)		
		Day 1	Day 4	Day 8
Formaldehyde	-	0.23 ± 0.01^{a}	0.24 ± 0.02^{c}	0.22 ± 0.03^{d}
Dexamethasone	3	0.12 ± 0.04^{c}	0.10 ± 0.01^{a}	0.09 ± 0.03^{a}
Hexane extract	100	0.21 ± 0.01^{ab}	0.17 ± 0.02^{b}	0.11 ± 0.01^{a}
Chloroform extract	100	0.22 ± 0.01^{a}	0.25 ± 0.01^{c}	0.21 ± 0.01^{d}
Ethyl acetate extract	100	0.19 ± 0.01^{ab}	0.16 ± 0.01^{b}	0.09 ± 0.01^{a}
Methanol extract	100	0.21 ± 0.03^{ab}	0.20 ± 0.01^{d}	0.15 ± 0.01^{b}
Hexane extract	300	0.11 ± 0.02^{c}	0.07 ± 0.03^{e}	0.05 ± 0.01^{c}
Chloroform extract	300	0.19 ± 0.01^{ab}	0.20 ± 0.04^{dc}	0.18 ± 0.02^{de}
Ethyl acetate extract	300	0.13 ± 0.03^{c}	0.05 ± 0.03^{e}	0.03 ± 0.02^{c}
Methanol extract	300	0.20 ± 0.01^{ab}	0.14 ± 0.04^{b}	0.07 ± 0.02^{a}

Different superscripts across a column show significant difference $p < 0.05$.

Table 4. Percentage DPPH scavenging activity of *S. dinklagei* extracts.

Extracts	DPPH scavenging activity (%)				
	10 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml
Hexane	76.1	77.1	77.4	77.0	77.5
Chloroform	14.4	31.3	39.5	55.2	58.4
Ethyl acetate	70.0	70.6	65.8	64.3	63.4
Methanol	5.4	43.4	48.7	49.9	51.7
Ascorbic acid	73.6	73.8	74.6	77.2	79.1

DPPH free radical scavenging assay

The result of the DPPH scavenging assay of the extracts are shown in Table 4. As shown in the Table, the hexane, chloroform and methanol extracts showed concentration dependent DPPH scavenging activity with highest activity of hexane (77.5%), chloroform (58.4%) and methanol (51.7%) seen at 400 µg/ml. The ethylacetate extract showed maximum scavenging activity of 70.6% at 50 µg/ml.

DISCUSSION

The hexane and ethyl acetate extracts of *S. dinklagei* inhibited both phases of acute inflammation induced by carrageenan. Carrageenan is often injected to induce acute paw inflammation in experimental animals. Carrageenan-induced edema is a sensitive tool for investigating systemic anti-inflammatory agents. Most clinically effective anti-inflammatory drugs have been shown to inhibit the development of paw edema post carrageenan injection (Ruangsang et al., 2010). The edema post carrageenan occur biphasically and lasts up to 6 h. The initial phase occurs within 2 h of its injection while the latter phase occur 3 to 5 h post carrageenan injection. The early phase of inflammation is triggered by the release of histamine, 5-hydroxytryptamine, and bradykinin in the inflamed tissues (Ruangsang et al., 2009). The release of algogens (kinins and prostaglandins) in these tissues is believed to be responsible for the second phase of inflammation (Jothimanivannan et al., 2010). The results obtained in this study suggest that these extracts may inhibit the release of inflammatory mediators post carrageenan injection. A similar plant *Stephania tetrandra* S. Moore has been proved by *in vitro* and *in vivo* experiments to possess anti-inflammatory activities (Teh et al., 1990; Kang et al., 1996; Xue et al., 2008).

The kaolin-carrageenan and formaldehyde- induced paw edema tests are used to evaluate the effect of drugs on sub acute and chronic inflammation respectively. Injection of kaolin-carrageenan induces sub acute inflammation, which lasts up to 72 h, while formaldehyde induces chronic inflammation with articular changes similar to those seen in rheumatoid arthritis (Okoli et al., 2008). Edema post injection of the aforementioned substances results due to release of inflammatory

mediators (Northover and Subramanian, 1961; Bonta and DeVos, 1965; Wheeler-Aceto and Cowan, 1991). The hexane and ethyl acetate extracts on continued administration were effective in reducing the paw edema induced by kaolin-carrageenan and formaldehyde. This shows their ability to inhibit the activity of inflammatory mediators involved in sub acute and chronic inflammatory response.

The inflammatory process involves the activity of inflammatory mediators such as neutrophil-derived free radical, reactive oxygen species (ROS), nitric oxide (NO·), prostaglandins, and cytokines (Syahida et al., 2006; Valko et al., 2006). These free radicals play important roles in the pathogenesis of many inflammatory diseases (Valko et al., 2006). The hexane and ethyl acetate extracts showed the most pronounced DPPH scavenging activity. Similar studies showed that extracts of *Stephania rotunda* Lour and *Stephania hernandifolia* (Willd) Walp strongly scavenged DPPH radicals (Gulchin et al., 2010; Sharma et al., 2010). The ability of these extracts to scavenge free radicals released during inflammation might be responsible for their inhibitory effect on the progression of acute, subacute inflammatory reaction in the paw of mice.

The potent anti-inflammatory activity exhibited by the hexane and ethyl acetate extracts shows that they contain phytochemical compound with anti-inflammatory properties. In this study we did not characterize the compound in the hexane and ethyl acetate extracts responsible for this activity. However, the phytochemical screening showed that both extracts contained flavonoids. We ascribe the anti-inflammatory activity of both extracts to the presence of flavonoids in these extracts. Previous *in vitro* and *in vivo* studies have shown that flavonoids isolated from medicinal plants possess anti inflammatory and antioxidant properties (Duke, 1992; Ahmadiani et al., 2002; Sawadogo et al., 2006; Musa et al., 2007). Isolation and characterization of the active constituent (s) of both extracts of *S. dinklagei* will be the subject of further study.

In conclusion the present study showed that the hexane and ethyl acetate extracts of *S. dinklagei* possessed potent anti-inflammatory properties. However the ethyl acetate extract showed the best anti-inflammatory activity.

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