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Full Length Research Paper

Anti-inflammatory and anti-ulcerogenic activity of the ethanol extract of ginger (*Zingiber officinale*)

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The acute toxicity test carried out on the ginger extract gave the LD_{50} value as 1000 mg/kg. The anti-inflammatory and anti-ulcerogenic effects of the ethanol extract of ginger (*Zingiber officinale*) in adult Wistar rats were studied using values below the lethal dose. Inflammation was induced by injecting 0.1 ml undiluted fresh egg albumin (philogistic agent) into the subplantar surface of the right hind paw of the rats. Ethanol extract of ginger with doses of 100, 200 and 400 mg/kg and indomethacin 100 mg/kg were administered intraperitoneally to separate groups of the rats. Control group received 1 ml of normal saline (vehicle). All the doses of the extract (100, 200 and 400 mg/kg) significantly ($p < 0.05$) reduced the fresh egg albumin induced rat paw oedema, though not in a dose dependent manner. The oedema reductions were more than that obtained for indomethacin, the standard anti-inflammatory drug used. The ginger extract also showed good protective effect against indomethacin – induced gastric ulcer in the rats. Administration of the extract doses (100, 200 and 400 mg/kg) evinced a significant ($p < 0.05$) reduction in the indomethacin – induced gastric erosion in all the experimental groups when compared to control. The percent ulcer inhibition by the extract doses was comparable with that of ranitidine (100 mg/kg), the reference drug. These results show that ginger possess good potential as an anti-oedema and anti-ulcer agent.

Key words: Ginger extract, inflammation, oedema reduction, gastric ulcer, indomethacin, ulcer inhibition.

INTRODUCTION

In recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show immense potential of medicinal plants used in various traditional systems (Dahanuka et al., 2002). *Zingiber officinale* (ginger) which belongs to the family Zingiberaceae is a slender perennial plant that reaches the height of 2 feet and has greenish yellow flowers resembling orchids. The rhizome of ginger has an aromatic pungent taste. Its exact country of origin is uncertain, but it was thought to be originally native of tropical South East Asia before it spread to Africa. It is now grown abundantly in Northern Nigeria.

Ginger has extensive medicinal history. It is used as spice in food and beverages and in traditional medicine as carminative, antipyretic and in the treatment of pain, rheumatism and bronchitis (Afzal et al., 2001). Its extracts have been extensively studied for a broad range of biological activities including antibacterial (Mahady et al., 2003; Azu et al., 2007), analgesic and anti-inflammatory (Raji et al., 2002; Grzanna et al., 2005), anti-angiogenesis and antitumor (Surn et al., 1999; Kim et al., 2005). It is also used for the treatment of gastrointestinal disorders including gastric ulcerogenesis (Agrawal et al., 2000; Mohsen et al., 2006). It performs the above role by eliminating the bacteria *Helicobacter pylori* whose secretions of ammonia in the stomach are responsible for many ulcers, especially of the duodene and for other stomach problems like gastritis. The plant also neutralizes the excess gastric acid in the stomach which causes other forms of ulcers. Ginger has also been reported to be an effective anti-emetic, used in the treatment of both motion sickness and the nausea and vomiting associated with pregnancy (Backon, 1991; Ernest and Pittler, 2000). It reduces the stickiness of blood platelets, hence may help reduce the risk of artherosclerosis and heart attacks (Verma et al., 2004). On the basis of these common uses of *Z. officinale* in ethnomedicine, this work was therefore aimed at assessing the effect of the ethanol extract of ginger on induced inflammation and ulcer.

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MATERIALS AND METHODS

Animals

Swiss Albino mice (22 – 28 g) and adult Wistar rats (120 – 200 g) of both sexes obtained from the animal house of the Faculty of Biological Sciences, University of Nigeria, Nsukka were used for the studies. They were acclimatised for seven days before the experiment and maintained *ad libitum* on water and growers mash (Pfizer Feeds, Aba) bought from Nsukka market. The research was conducted in accordance with the ethical rules on animal experimentation approved by the ethical committees of the Faculty of Biological Sciences, University of Nigeria, Nsukka.

Chemicals

All chemicals used in this study were of analytical grade. They were products of May and Baker, England and Merck, Darmstadt, Germany.

Plant materials

The ginger plant material (*Z. officinale*) was purchased from the Nsukka local market and identified by Mr. Ugwuozor of Botany department, University of Nigeria, Nsukka. Voucher specimen was deposited in the herbarium unit of the department of Botany, University of Nigeria, Nsukka. The plant was peeled, chopped into tiny bits, air-dried for 2 weeks and ground with a mechanical grinder. The ground plant (500 g) was macerated in absolute ethanol for 24 h, filtered with a white cloth and the filtrate concentrated using a rotary evaporator at an optimum temperature of 40 -50°C. The dried yield of the extract was 5 g.

Phytochemical analysis

Preliminary phytochemical tests were carried out on the ethanol extract of ginger using the methods of Harborne (1984) and Trease and Evans (1989). Tests for the presence or absence of phytochemical compounds using the above methods involve the addition of an appropriate chemical agent to the extract of the plant in a test tube. The mixture was shaken vigorously or gently as the case may be. The presence or absence of phytochemicals such as saponnins, flavonoids, alkaloids, tanninis, trepenoids, steroids etc was observed.

Test for carbohydrate (Molisch's test)

A known weight of 0.1 g of the ginger extract was boiled with 2 ml of water and filtered. To the filtrate, few drops of naphtol solution in ethanol (Molisch's reagent) were added. Concentrated sulphuric acid was then gently poured down the side of the test tube to form a lower layer.

Test for alkaloids (General tests)

Sulphuric acid (20 ml of 5%) in 50% ethanol was added to about 2 g of the ginger extract sample and heated on a boiling water bath for 10 min, cooled and filtered. Filtrate (2 ml) was tested with a few drops of: Mayer's reagent (Potassium mercuric iodide solution), Dragendorff's reagent (Bismuth potassium iodide solution), Wagner's reagent (Iodide in potassium iodide solution) and Picric acid solution (1%). The remaining filtrate was placed in 100 ml separating funnel and made alkaline with dilute ammonia solution. The aqueous alkaline solution was separated and extracted with two 5 ml portions of dilute sulphuric acid. The sample was tested with a few drops of Mayer's, Wagner's and Dragendorff's reagent.

Test for glycosides (Fehling's test)

A quantity of 5 ml of a mixture of equal parts of Fehling's solution I and II were added to 5 ml of the ginger extract sample and then heated on a water bath for 5 min.

Test for Saponnins (Fehling's method)

Water (20 ml) was added to 0.25 g of the ginger extract in 100 ml beaker and boiled gently on a hot water bath for 2 min. The mixture was filtered hot and allowed to cool and the filtrate used for the following test: Fehling's Test: To 5 ml of the filtrate was added 5 ml of Fehling's solution (equal parts of I and II) and the content heated. A reddish precipitate indicated the presence of saponnins. It was then heated further with sulphuric acid.

Test for tannins (Ferric chloride method)

Ginger extract (1 g) was boiled with 50 ml of water, filtered and used for the Ferric Chloride test: To 3 ml of the filtrate, few drops of ferric chloride were added.

Test for flavonoids (Ammonium test method)

Ethylacetate (10 ml) was added to 0.2 g of the ginger extract sample and heated on a water bath for 3 min. The mixture was cooled, filtered and the filtrate used for the Ammonium test: About 4 ml of the filtrate was shaken with 1 ml of dilute ammonia solution. The layers were allowed to separate.

Test for resins (Precipitation test)

The ginger extract (0.2 g) was extracted with 15 ml of 95% ethanol. The alcoholic extract was then poured into 20 ml of distilled water in a beaker.

Test for proteins (Million's test)

Two drops of million's reagent were added to the filtrate in a test tube.

Test for oils

The ginger extract (0.1 g) material was pressed between a filter paper and the paper was put under serious observation.

Test for steroids and terpenoids

Ethanol (9 ml) was added to 1 g of the ginger extract sample and refluxed for a few minutes and filtered. The filtrate was concentrated to 2.5 ml on a boiling water bath and 5 ml of hot water was added. The mixture was allowed to stand for 1 h and the waxy matter filtered off. The filtrate was extracted with 2.5 ml of chloroform using separating funnel. To 0.5 ml of the chloroform extract in a test tube was carefully added to 1 ml of concentrated sulphuric acid to form a lower layer.

Acute toxicity study

The acute toxicity test was carried out by a modified method of Lorke (1983) to define the range of lethal dose and safe dose for the extract. Swiss albino mice were starved of food but allowed access to water prior to the study and were then grouped (three mice per group). They were treated intraperitoneally with different doses of the extract (50, 100, 400, 600, 1000 and 1500 mg/kg). The animals were then observed for 24 h for nervousness, dullness, in-coordination or death.

Anti-inflammatory test

The anti-inflammatory test was carried out using a philogistic agent - induced rat hind paw oedema as a model for acute inflammation (Winter et al., 1962). The philogistic agent employed in this study was fresh egg albumin (Akah and Nwambie, 1994). Twenty five (25) adult wistar rats of either sex (120 – 200 g) were divided into five experimental groups of five rats each. They were fasted and deprived of water for 18 h before the experiment. Deprivation of water was to ensure uniform hydration and to minimize variability in oedematous response (Winter et al., 1963).

Various extract doses (100, 200 and 400 mg/kg) suspended in normal saline were administered intraperitoneally into groups I, II and III of the rats. Control group received equivalent amount of normal saline and the reference group was administered 100 mg/kg indomethacin. One hour post treatment, inflammation of the hind paw was induced by injecting 0.1 ml of undiluted fresh egg albumin (philogistic agent) into the subplantar surface of the right hind paw. This treatment was found to cause swelling of the paw which retained about the same degree of oedema for 3 h. The right hind paw volumes of the rats were taken on the principle of volume displacement using LETICA Digital Plethysmometer (LE 7500) immediately before the experiment (zero time) and at 1 h intervals after the injection of egg albumin for a period of 5 h. Average oedema at every interval was assessed in terms of difference in volume displacement after injecting the philogistic agent and zero time volume displacement of the injected paw ($V_t - V_0$). Percent inhibition of oedema was also calculated for each dose (Akah and Njike, 1990) using the relation (Perez, 1996);

$$\% \text{ inhibition of oedema} = 1 - \left(\frac{a-x}{b-y}\right) \times 100$$

Where;
a = Mean paw volume of treated rats after egg albumin injection.
x = Mean paw volume of treated rats before egg albumin injection.
b = Mean paw volume of control rats after egg albumin injection.
y = Mean paw volume of control rats before egg albumin injection.

Indomethacin induced ulcer

This assay was carried out using the method of Urushidani et al. (1979). Twenty five adult rats randomly divided into 5 groups of 5 rats each were deprived of food for 18 h and treated per orally with normal saline and varying doses of the ginger extract. The extract and drugs used were freshly prepared as a suspension in normal saline and administered per orally (p.o) to the animals in 5 ml/kg doses. Group 1 (normal control) was administered normal saline (5 ml/kg). Groups II, III and IV were treated with 100, 200 and 400 mg/kg of the ginger extract respectively. Group V (reference group) was administered 100 mg/kg of ranitidine (standard anti ulcer drug).

Thirty minutes later, 50 mg/kg of indomethacin was administered (p.o) to the rats. After 8 h, each animal in the groups was sacrificed by chloroform anaesthesia and the stomach removed and opened along the greater curvature, pinned flat on a board, examined and scored for ulcer. Erosions formed on the glandular portions of the stomach were counted and the ulcer index calculated as described by Main and Whittle (1975).

The ulcer was counted and scored as 0 = no ulcer; 1 = superficial ulcer; 2 = deep ulcer and 3 = perforations. The sum of all the lesions/ulcer in all the animals for each group (Total ulcer score) was used to calculate the ulcer index. Percent ulcer inhibition was calculated relative to control.

Table 1. Result of phytochemical analysis of the ginger extract.

Plant constituent	Bioavailability
Alkaloid	++
Glycosides	-
Steroids	+++
Terpenoids	+++
Flavonoids	++++
Tannins	-
Acidic compounds	-
Fats and oil	+
Resins	+++
Carbohydrate	+++
Saponnins	-

Key:
- = Not present.
+ = Present in low concentration.
++ = Present in moderately high concentration.
+++ = Present in very high concentration.
++++ = Abundantly present.

Statistical analysis

This was done using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA). All values are expressed as mean ± SD. Data were analysed by one-way ANOVA and difference between means was assessed by a two-tailed Student's T-test. $P < 0.05$ was considered statistically significant.

RESULTS

Phytochemical analysis of the ethanol extract of ginger (Table 1) showed the presence of phytochemicals such as alkaloids, resins, steroids, flavonoids and terpenoids. Other constituents like saponnins, tannins, glycosides and acidic compounds were absent.

The LD_{50} of the crude ethanol extract was calculated to be 1000 mg/kg. All the doses used in this study were therefore carefully chosen to exclude the lethal range. Data from Table 2 show the mean paw volumes for the various groups at different time intervals. On the control rats, fresh egg albumin induced paw oedema which was sustained for 3 h after which it started reducing significantly. The mean paw volumes of groups administered 200 and 400 mg/kg of ginger significantly reduced ($p < 0.05$) from the first hour after oedema induction and that

Table 2. Effect of ethanol extract of ginger on egg albumin induced rat paw oedema.

Groups	Δ paw volume (oedema) ml and % inhibition of oedema				
	1 h	2 h	3 h	4 h	5 h
Control	0.76 ± 0.05	0.68 ± 0.16	0.56 ± 0.23	0.44 ± 0.19	0.3 ± 0.12
100 mg/kg	0.64 ± 0.11 (15.79)	0.4 ± 0.19* (41.18)	0.3 ± 0.14* (46.43)	0.17 ± 0.1* (63.04)	0.11 ± 0.05* (63.33)
200 mg/kg	0.6 ± 0.14* (21.05)	0.46 ± 0.09* (32.35)	0.3 ± 0.07* (46.43)	0.22 ± 0.04* (52.17)	0.1 ± 0* (66.67)
400 mg/kg	0.46 ± 0.09* (39.47)	0.31 ± 0.11* (54.41)	0.2 ± 0.07* (64.29)	0.13 ± 0.06* (71.74)	0.07± 0.03* (76.67)
100 mg/kg Indomethacin	0.7 ± 0.07 (7.89)	0.5 ± 0.12 (26.47)	0.36 ± 0.09* (35.71)	0.27 ± 0.08* (41.3)	0.16 ± 0.05* (46.67)

*Reduction in oedema significant at $p < 0.05$ compared to control. Values of oedema shown are mean ± SD (n = 5). Values in parenthesis are percent inhibition of oedema calculated relative to control.

Table 3. Effect of ginger extract on indomethacin induced gastric ulcer in rats.

Treatment	Dose (mg/kg)	Total ulcer scores	Magnification X 1/10	Ulcer index	% Ulcer inhibition
Control (normal saline)	5 ml/kg	204	20.4	4.08 ± 1.61	-
Extract	100	58	5.8	1.16 ± 0.66*	71.56
Extract	200	105	10.5	2.1 ± 1.23*	48.53
Extract	400	98	9.8	1.9 ± 0.63 *	53.4
Ranitidine	100	44	4.4	0.88 ± 0.33*	78.4

Values shown are mean ± SD. (n = 5). *Significantly different from control at $p < 0.05$.

of group administered 100 mg/kg significantly reduced from the second hour. The paw oedema reduction increased with time but not in a dose dependent manner. The percent inhibition of oedema for the group treated with 100 mg/kg of ginger was 15, 41, 46, 63 and 63% for the 1st, 2nd, 3rd, 4th and 5th hour respectively. That of groups treated with 200 and 400 mg/kg were 21, 32, 46, 52, 66, 39, 54, 64, 71 and 76% respectively.

The oedema reduction for the ginger treated groups was more than that observed for the standard anti-inflammatory drug, indomethacin, which had 7, 26, 35, 41 and 46% inhibition of oedema for the 1st, 2nd, 3rd, 4th and 5th hour respectively. The mean oedema and percent inhibition of oedema in the ginger extract treated rats are shown in Table 2. Data from Table 3 show that indomethacin induced gastric ulcer in all experimental groups. Groups treated with ginger had a significant reduction ($p < 0.05$) in the gastric erosions formed, when compared to control as is shown from the reduced ulcer indices. The reduction in the ulcer was also not dose dependent. Ginger extract dose of 100 mg/kg showed 71% inhibition of ulcer, which was comparable to that of ranitidine, the anti-ulcer drug used, which had 78% inhibition, while 200 and 400 mg/kg doses showed 48 and 53% inhibition respectively.

DISCUSSION

The present study revealed some of the pharmacological basis for the ethnomedicinal use of ginger in the treatment of inflammation. The ethanol extract of ginger showed a good anti-inflammatory activity against acute inflammation, suppressing the rat paw oedema both at the early and later phases, though not dose dependently. Oedema results from the action of inflammatory mediators such as histamine, serotonin and bradykinin at the site of a local inflammatory insult (Harriot et al., 2004).

The early phase of oedema, beginning from 1 h after the administration of the irritant, is due to the release of histamine and serotonine, while the later phase, occurring from 3 to 5 h after the administration of the irritant is induced by bradykinin, protease, prostaglandin and lysosome (Wallace, 2002; Harriot et al., 2004). The reduction in oedema evinced by ginger extract in this study suggests that it contains active constituents which block the release of histamine and serotonin from mast cells and inhibit the activity of other inflammatory media-

tors. This report agree with earlier reports of Suekewa and Yuasa (1986) which showed that (6)-shogaol isolated from ginger extract inhibited experimentally- induced swelling of the hind paw in rats. This, they reported may be due to the ability of (6)-shogaol to inhibit cyclooxygenase enzyme.

Sharma and Srivastava (1994) also reported that ginger inhibited paw oedema in an experimentally induced arthritis in the right knee and paw of rats. Srivastava and Mustafa (1992) reported that 75% of patients suffering from arthritis, osteoarthritis or muscular discomfort experienced relief in pain and swelling to varying degrees after powered ginger treatment for 3 months to 2.5 years. Shen et al. (2005) also reported the anti-inflammatory effect of ginger roots on osteoarthritic cow chondrocytes showing its strong inhibition of COX-2 enzyme, pro-inflammatory cytokines and prostaglandins which are all components of the inflammatory response. Middleton and Kandaswami (1992) and Read (1995) reported that plant flavonoids, apart from their many pharmacological actions, also have potent anti-inflammatory activities. Phytochemical results of this study showed that ginger is abundantly rich in flavonoids. This suggests that the flavonoids in ginger may be one of its main active anti-inflammatory constituents.

From this study, ginger extract had significant ($p < 0.05$) protective effect against indomethacin - induced gastric ulcer for all the doses. Some drugs such as indomethacin, ibuprofen and aspirin known to have effective anti-inflammatory activity (NSAIDs); inhibiting the various changes leading to inflammation are associated with some side effects such as gastric erosions and abdominal ulcers after prolonged use (Ogbru, 2006). This is believed to be due to the inhibition by these drugs of the cyclooxygenase 1 enzyme which synthesises prostaglandin (PG) needed for haemostasis and the maintenance of the gastric lining of the stomach (Wallace, 2002). The concern over the severe side effects of these anti-inflammatory drugs have led to the search for new anti-inflammatory agents from plants and plant products with low toxicity and minimal side effects.

In this study, the ethanol extract of ginger exhibited anti-ulcerogenic effect against indomethacin induced gastric ulcer, with percent ulcer inhibition comparable with that obtained for ranitidine, an antiacid used to neutralize intraluminal acid, improve gastric microcirculation and reduce the absorption and concomitant adverse drug interactions of many NSAIDs (Derle et al., 2006). Earlier reports by Agrawal et al. (2000) and Mohsen et al. (2006) on the anti-ulcerative activities of ginger suggest that ginger extract possess its anti-ulcerative properties through a mechanism related to acid and pepsin secretory inhibition. Although the exact mechanism of action of the anti-ulcer activities of ginger has not been clearly delineated, the plant contains some active constituents whose ulcer protective properties have been identified (Yamahara et al., 1988). The results of this present study show that ginger extract possess good potential as an antioedema and antiulcer agent. This suggests that the extract of ginger is both anti-inflammatory and anti-ulcerogenic.

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