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Acute toxicity and anti-inflammatory properties of *Fadogia agrestis* Schweinf. ex Hiern (Rubiaceae) extract in mice and rats.

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Abstract

Objective: Plants are widely used in alternative medicine for the treatment of various diseases. The aim of this study was to evaluate the anti-inflammatory properties of the hydroalcoholic extract of *Fadogia agrestis* leaves.
Methodology: The acute toxicity study was performed by oral administration of *Fadogia agrestis* hydroalcoholic extract at a single dose of 2000 mg/kg in NMRI mice. Then, the anti-inflammatory activity of *Fadogia agrestis* extract was studied on several models of acute and subacute inflammation in mice. The effects of the extract at

different concentrations (100, 200, and 300 mg/kg), administered orally, were compared to the effects of 1% carrageenan, 1% histamine, 1% serotonin, and 2% formalin injected into the plantar surface of the hind paw.
Results: The hydroalcoholic extract of *Fadogia agrestis* leaves at the dose of 2000 mg/kg did not cause the death of mice. The results also indicate that hydroalcoholic extract of *Fadogia agrestis* leaves strongly inhibited ($p<0.01$) carrageenan-induced edema formation at the fifth hour of inflammation. These maximum inhibitions were 47.45%, 50.87%, and 47.03% for extract doses of 300, 200, and 100 mg/kg, respectively. The hydroalcoholic extract of *Fadogia agrestis* leaves also inhibited formalin-induced edema formation. The inhibitions were highly significant ($p<0.01$) on the first day of induction. In addition, in rats treated with the extract at all doses, a highly significant ($p<0.01$) decrease in leukocyte count was observed compared to the control.
Conclusion: The results of the present study show that the hydroalcoholic extract of the leaves of *Fadogia agrestis* administered orally possesses an anti-inflammatory activity without toxic effects.

Keywords: *Fadogia agrestis*, Acute toxicity, Anti-inflammatory, Edema, Rats, Mice.

1. Introduction

The inflammatory reaction is a biological response of the organism to various aggressions. It can result from burns, irritations, or an invasion of the body by pathogens (Touitou, 2000). Inflammation is characterized by pain, heat, redness, and tumor at the tissue level (Chen et al., 2018). In most cases, inflammatory pathologies are relieved in modern medicine by non-steroidal anti-inflammatory drugs and steroidal anti-inflammatory drugs. However, the long-term therapeutic use of these drugs is often associated with adverse effects such as gastrointestinal ulcers and renal failure in addition to being expensive and inaccessible to certain social classes (Bindu et al., 2020). In such a context, in Africa and specifically in the Republic of Benin, many patients resort to traditional medicine which is related to a cultural dimension. Numerous recipes based on medicinal plants are thus proposed in traditional medicine against inflammatory pathologies. However, traditional recipes used in communities are challenged due to lack of scientific evidence (Oguntibeju, 2018). Scientific research in this field is therefore necessary and essential, in order to valorize and promote traditional medicine and pharmacopoeia (Ozioma and Chinwe, 2009). The use of natural resources, and more particularly medicinal plants, is becoming an important alternative path to explore in order to discover effective drugs with fewer side effects. Among these plants, *Fadogia agrestis* is recognized as an aphrodisiac in tropical African countries (Yakubu et al., 2005). In the traditional African medicine, it possesses diuretic and febrifuge effect, and is used to treat stomach and toothache (Avula et al., 2019; Raman et al., 2018). In Burkina Faso, stem barks and roots are used for the treatment of malaria, gastrointestinal pain, rickets, dysentery, kidney pain, seizures, anorexia, and fractures (Sanon et al., 2003). In the Republic of Benin, the leaves are utilized as an infusion in combination with other plant species for the treatment of musculoskeletal disorders (Vissiennon et al., 2011). The anti-inflammatory effect as well as cell toxicity in liver and kidney of male rats was studied for the aqueous extract of *Fadogia agrestis* bark (Yakubu et al., 2009; Oyekunle et al., 2009). However, information on the anti-inflammatory effect of the leaf extract of this plant species is still missing. The aim of this study was to assess the anti-inflammatory properties of the hydroalcoholic extract of *Fadogia agrestis* leaves. Specifically, the acute toxicity of the extract was studied and its effect on acute and subacute inflammation models in rats was evaluated.

2. Materials and Methods

2.1 Plant material collection and preparation of the plant extract

The leaves of *Fadogia agrestis* (Schveinf. ex Hiern) were collected in the savannah of Bassila in the center area of the Republic of Benin. The plant species was authenticated by the botanist Dr. Pierre O. Agbani of the university of Abomey-Calavi and preserved under the ID-

number AP 2290. The leaves of *Fadogia agrestis* were dried away from dust in the laboratory under artificial ventilation and reduced to a fine powder. The powdered material (100 g) was defatted with petroleum ether. The defatted plant material (91.6 g) was then extracted with water: ethanol (1L, 1:1*v/v*) three times for 10 minutes with the Ultra Turrax® (IKA T25, Staufen, Germany) at 13,000 rpm for 10 minutes. The supernatants were collected and lyophilized after evaporation of ethanol to obtain the hydroalcoholic extract (yield: 13.3g *w/w*) of *Fadogia agrestis* leaves (EHFA).

2.2 Experimental animals

Rats and mice of both genders from the Laboratory of Animal Physiology of Joseph KI-ZERBO University were used for experimentation. Rats and mice weighed an average of respectively 115g and 25g. They were kept in typical habitat settings (temperature: 22 ± 3°C, relative humidity: 50 ± 10 % and 12 h light/12 h dark cycle) with unlimited access to food and water.

2.3 Toxicity studies

The acute toxicity study of the hydroalcoholic extract of *Fadogia agrestis* leaves was performed according to OECD (2001) guideline 423. Six female mice were randomized into two groups of three mice each. They were fasted 4 hours before the experiment. Group1 (control group) received orally distilled water and group 2 (test group) was fed with hydroalcoholic extract of *Fadogia agrestis* at a single dose of 2000 mg/kg. Then, mice were refed two hours after the treatment. Observations were made at 1h, then 24h, 48h, 72h and 14 days and included mortality, sleepiness, food intake, bristly hair, muzzle color, lethargy and mobility, eye color, convulsions, and salivation.

2.4 Anti-inflammatory activities

2.4.1. Carrageenan, histamine and serotonin induced edema tests

The effects of *Fadogia agrestis* extract were tested on edema induced by different inflammatory agents such as carrageenan, histamine, and serotonin. Tests were performed on male mice according to the protocol of Lanher et al. (1991) for the carrageenan and serotonin tests. The histamine test was performed according to the protocol of Mandal et al. (2000). These mice were fasted for 12 hours before the experiment. For each experiment, five groups of five mice were used. Group 1 (control group) received orally 0.9% NaCl (1 mL/100g). Group 2 (reference group) was treated orally with diclofenac for carrageenan test, prozac for serotonin test and promethazine for histamine test at the dose of 20 mg/kg. Groups 3, 4, 5 (treatment groups) were treated orally with *Fadogia agrestis* hydroalcoholic leaf extract at doses of 100, 200, and 300 mg/kg respectively. One hour (1h) after these treatments, inflammation was induced in the hind paw by injection of 0.1 ml carrageenan (1%), histamine (1%), or serotonin (1%). Prior to edema induction, paw volume (Vo) was measured using a plethysmometer (Ugo Basile, 37140, Italy). The volume of paw edema was then measured at time intervals of 0.5 h, 1 h, 3 h, and 5 h after carrageenan injection. For the serotonin injection and histamine injection, the paw edema volume was respectively assessed after 0.5 and 1h. The percentage of plantar edema inhibition (Pi) was calculated using the formula:

$$Pi\ (\%) = [(Vt - Ve) / Vt].100;$$

where Vt represents the increase in the paw volume in the control group; Ve represents the increase in the paw volume in the test groups.

2.4.2 Formalin-induced leukocyte migration test

Thirty (30) male and female rats were divided into six (6) groups of five (5) rats each. These rats were fasted for 12 hours before the experiment. Group 1 (neutral control) did not receive any treatment; Group 2 (negative control) received 0.9% NaCl (10 ml/100g); Group 3 (positive control) received diclofenac 20 mg/kg; Groups 4, 5, and 6 (test groups) received orally the extract of *Fadogia agrestis* at the doses of 100, 200, and 300 mg/kg, respectively.

Inflammation was induced in the hind paw by injection of 0.1 ml of 2% formalin one hour after the different treatments. The inflammation was maintained the third day by a second injection of 2% formalin. Rats were treated with NaCl, diclofenac, and extract at different doses for 10 days at the frequency of a single daily administration (Vasudevan et *al.*, 2007). The volume of paw edema was measured using a plethysmometer (Ugo Basile, 37140, Italy) on the first day after formalin injection, then every two days for ten days. After ten days of treatment, the animals were anesthetized by intraperitoneal injection of ketamine (10 mL/kg) and lidocaine (2 mL/kg). Blood from each rat was collected by decapitation for hematological analysis.

2.5 Assessment of haematological parameters

The blood samples for haematology were collected in bottles containing Ethylenediaminetetraacetic acid (EDTA) as anticoagulant. Haematological analyses were performed at the "Centre hospitalier universitaire pédiatrique Charles De Gaulle (CHUP-CDG)", Ouagodougou, Burkina Faso. Parameters analysed include total and differential leukocyte (WBC), erythrocyte (RBC), Haemoglobin (HGB), Haematocrit (HCT), platelet count (PLT).

2.6 Statistical Analysis

Statistical analysis for animal experiments was carried out by one-way ANOVA following Dunnet's post hoc test using GraphPad Prism® Version 5.03. Data were presented as Mean ± SEM. The results obtained were compared with the control group. $p < 0.05$, $p < 0.01$, and $p < 0.001$ were statistically significant, highly significant, and very highly significant respectively.

3. Results

3.1 Acute toxicity of *Fadogia agrestis* extract

The single dose of 2000 mg/kg body weight of the extract showed no signs of toxicity in mice. No behavioral changes and no death were observed.

3.2 Effects of the extract on carrageenan, histamin and serotonin induced inflammation

3.2.1. Effects of the extract on carrageenan-induced inflammation

Thirty minutes later, no significant difference ($p>0.05$) in paw volume change was observed between the extract and control. All doses of the extract showed a significantly ($p<0.05$) inhibition of edema volume at the fifth hour. These inhibitions were maximal with percentages of 47.45 %, 50.87 %, 47.03 % for 300, 200, 100 mg/kg respectively. Diclofenac highly significantly ($p<0.05$) inhibited edema volume throughout the five hours, with a maximum percentage inhibition at the fifth hour of 52.54 % (Figure 1).

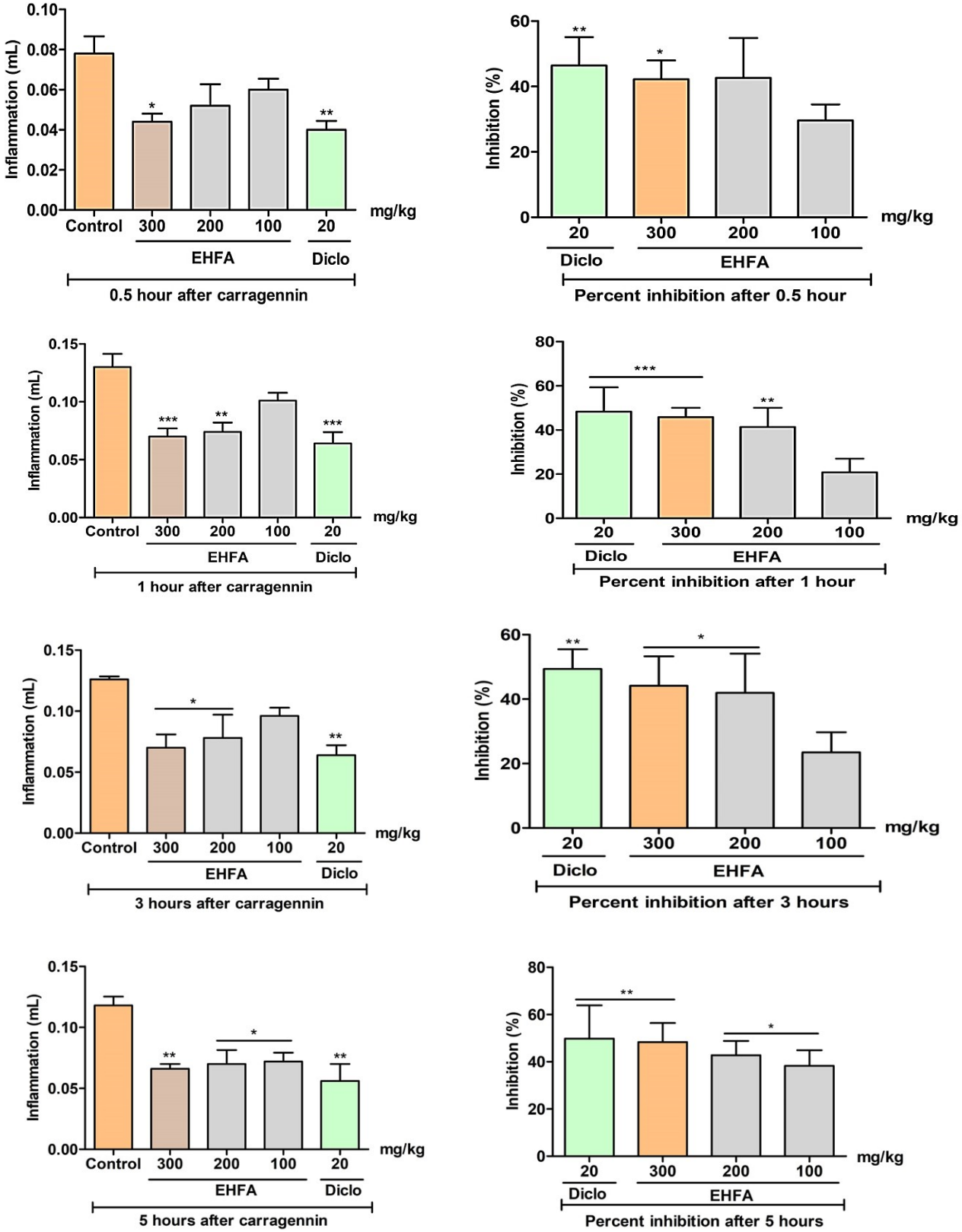

Fig. 1: Anti-inflammatory activity of the hydroalcoholic extract of *Fadogia agrestis* leaves in the carrageenan-induced acute inflammation in mice. Each bar represented the mean ± esm, (n=5). *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ significant difference from negative control mice.

3.2.2. Effects of the extract on serotonin-induced inflammation

The extract at 100, 200 and 300 mg/kg indicated a non-significant inhibition ($p>0.05$) of serotonin-induced edema (Figure 2).

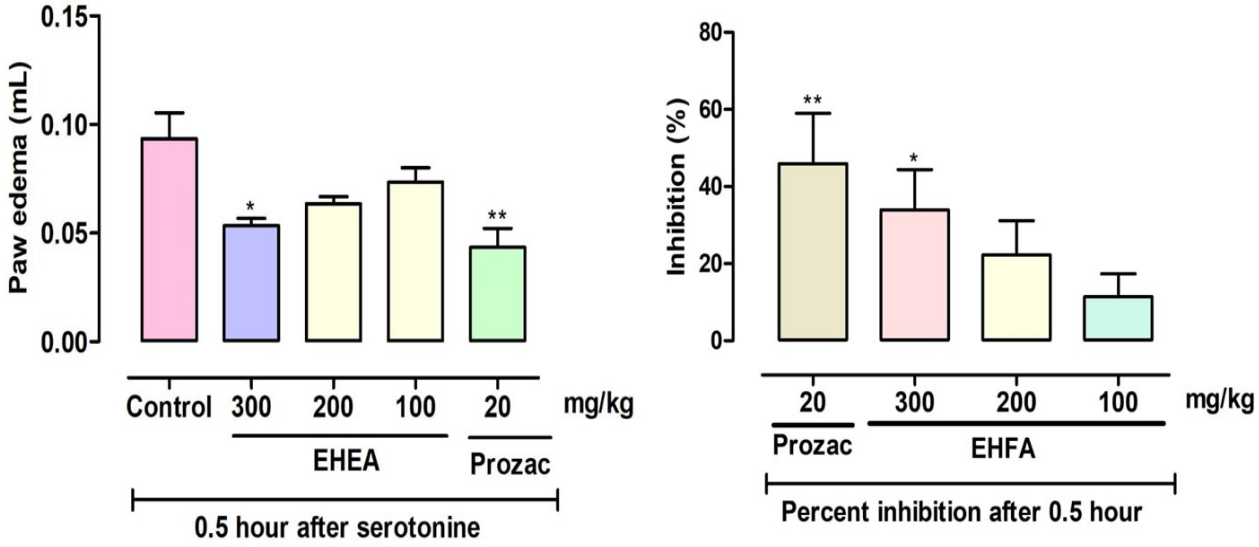

Fig. 2: Effects of hydroalcoholic extract of *Fadogia agrestis* leaves on serotonin-induced acute inflammation in mice. Each bar represented the mean ± esm, (n=5).

3.2.3. Effects of the extract on *histamin*-induced inflammation

In mice treated with *Fadogia agrestis* extract at 300 mg/kg the volume of edema was inhibited highly significantly ($p<0.01$). This percentage of inhibition was 38.46% (Figure 3).

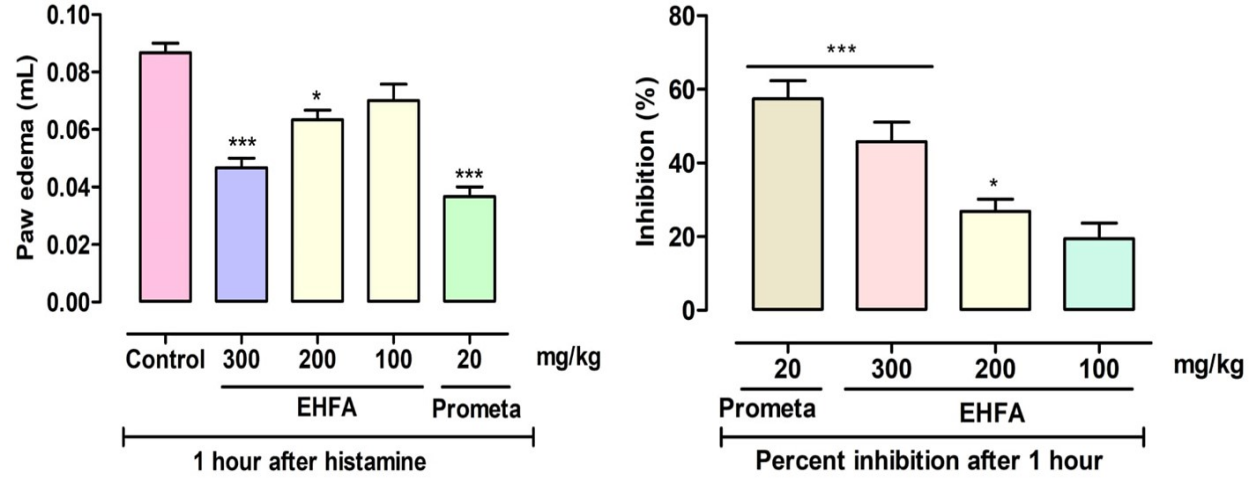

Fig. 3: Effects of hydroalcoholic extract of *Fadogia agrestis* leaves on histamine-induced acute inflammation in mice. Each bar represented the mean ± esm, (n=5). **: $p<0.01$; ***: $p<0.001$ significant difference from negative control mice.

3.3 Effects of the extract on formalin-induced inflammation

3.3.1. Effects of the extract on formalin-induced leukocyte migration

At the sixth hour of the first day of the experiment, extract at 200 mg/kg inhibited very significantly ($p<0.01$) the volume of edema. This inhibition percentage was 45%. Extract at 300 mg/kg inhibited very significantly ($p < 0.01$) edema volume. From day 3 to day 9, extracts had no significant ($p>0.05$) action on edema volume (Table I).

Table I: Effects of *Fadogia agrestis* extracts on formalin-induced subacute inflammation in rats.

Treatments (mg/kg)	Days				
	1	3	5	7	9
Control	1.155 ± 0.04	0.678 ± 0.02	0.766 ± 0.04	0.698 ± 0.03	0.558 ± 0.04
Diclo 20	0.64 ± 0.05 (44.58) ***	0.424 ± 0.06 (37.46)	0.412 ± 0.04 (46.21) **	0.45 ± 0.02 (35.53)	0.344 ± 0.07 (38.35)
EHFA 100	0.844 ± 0.1 (26.92)	0.582 ± 0.08 (14.15)	0.694 ± 0.03 (9.39)	0.522 ± 0.03 (25.21)	0.42 ± 0.03 (24.73)
EHFA 200	0.64 ± 0.08 (44.58) ***	0.554 ± 0.11 (18.28)	0.63 ± 0.02 (17.75)	0.484 ± 0.09 (30.65)	0.442 ± 0.04 (20.78)
EHFA 300	0.754 ± 0.08 (34.71) **	0.504 ± 0.04 (25.66)	0.64 ± 0.09 (16.44)	0.494 ± 0.03 (29.22)	0.398 ± 0.04 (28.67)

Each value represents the mean ± esm, (n=5). **: $p < 0.01$; ***: $p < 0.001$ significant difference from negative control mice. Values in parentheses represent percent inhibition of paw edema.

3.3.2. Effects of the extracts on some hematological parameters

In rats treated with the extract at all doses, a highly significant ($p<0.01$) decrease in the number of leukocytes was observed compared to the control (Table II).

Table II: Effects of *Fadogia agrestis* extract on hematologics parameters.

Hematologics parameters	Treatments (mg/kg)					
	Control	Formalin 2%	EHFA 100	EHFA 200	EHFA 300	Diclofenac 20
WBC x 10^3/µl	5.60 ± 0.02	8.92±0.12 ###	5.8±0.53 **	5.92±0.28 **	5.96±0.48 **	5.95±0.6 **
LYM (%)	57.21 ±1.7	86.43±0.9###	75.5±0.6 ***	76.67±0.48 ***	72.87±0.85***	64.8±2.3 ***
GRA (%)	10.3 ± 0.33	26.40 ±0.8###	16.7±0.48***	15.43±0.52 ***	18.53±1.0 ***	13.9±0.8***
RBC x 10^6/µl	7.84 ± 0.01	7.34 ± 0.14	7±0.40	7.17 ±0.13	7.02± 0.12	6.95±0.06
HGB (g/dl)	12.4 ±1.35	12.43±0.33	12.80±0.46	12.70±0.38	11.97±0.32	12.27±1.16
PLT (10^3/µL)	771.33 ± 24	662.33±18.85	842.00±52.44	767.33±46.48	837.33±10.17	890.67±16.46
HCT (%)	46.6 ± 0.87	42.40 ±1.39	43.60±1.62	39.50±1.33	43.97±2.41	43.47±2.40

Values were expressed as mean ± esm, (n=5). ###: significant difference from control rats. **: $p<0.01$; ***: $p<0.001$ significant difference from control-negative rats (formalin). WBC: White blood cell, RBC: Red blood cell, LYM: Lymphocyte, GRA: Granulocyte, HGB: Hemoglobin, PLT: Platelet, HCT: Hematocrit

Discussion

In the present study, the anti-inflammatory properties of the hydroalcoholic extract of *Fadogia agrestis* leaves was assessed. This extract at the dose of 2000 mg/kg did not cause the death of mice. The results also indicate that hydroalcoholic extract of *Fadogia agrestis* leaves strongly inhibited ($p<0.01$) carrageenan-induced edema formation at the fifth hour of inflammation. These maximum inhibitions were 47.45%, 50.87%, and 47.03% for extract doses of 300, 200, and 100 mg/kg, respectively. The hydroalcoholic extract of *Fadogia agrestis* leaves also inhibited formalin-induced edema formation. These inhibitions were highly significant ($p<0.01$) on the first day of induction. In addition, in rats treated with the extract at all doses, a highly significant ($p<0.01$) decrease in leukocyte count was observed compared to the control.

Inflammatory response induced by carrageenan injection occurs in three phases. The initial phase lasts about one hour after induction and is attributed to the release of histamine and serotonin (Dongmo et *al.*, 2003). The second phase, which lasts from the second hour to the third hour, is due to the release of kinins, which accelerates the formation of edema. The third phase begins three hours after carrageenan injection and is due to the synthesis of prostaglandins and leukotrienes (Adeolu et al., 2009).

The results of the anti-inflammatory effects of the hydroalcoholic extract of *Fadogia agrestis* exhibited intense inhibitions according to the paw edema during the early phase of acute inflammation, compared to the control group. *Fadogia agrestis* extract would therefore have an anti-inflammatory effect that opposes the release or action of endogenous pro-inflammatory mediators (serotonin, histamine, bradykinin) responsible for the development of the early phase of inflammation (Gobiannand et *al.*, 2010). These results are similar to those reported by Dimo et al. (2006) on the study of the anti-inflammatory effects of the aqueous extract of *Kalanchoe crenata*. The extract weakly inhibited the second phase of carrageenan-induced edema. Only the reference product diclofenac significantly inhibited the volume of edema during this phase. These results show that *Fadogia agrestis* extract would have no effect on the conversion of hepatic kininogen by kalikrein to kinins. The third phase of carrageenan-induced edema was significantly inhibited by all doses of the extract. The extract of *Fadogia agrestis* would thus be able to block the degradation of arachidonic acid by the cyclooxygenase or lipo-oxygenase pathway. It would thus oppose the production of prostaglandins, thromboxane A2 and leukotrienes (Khalil et al., 2006).

From these results, it can be suggested that the hydroalcoholic extract of *Fadogia agrestis* leaves contains secondary metabolites likely to inhibit the mediators of the first and third phase but without effect on the mediators of the second phase of the inflammation induced by carrageenan. In variable proportion, these metabolites could be alkaloids, saponins, anthraquinones and flavonoids revealed in the aqueous extract of *Fadogia agrestis* stems (Sumalatha et al., 2010). Oyekunle et al. (2009) reported similar results on the evaluation of the anti-inflammatory activity of an aqueous extract obtained from the stems of *Fadogia agrestis* and this activity was attributed to flavonoids and saponins found in the plant. Saponins are potent inhibitors of prostaglandins (Chattopadhyay et *al.*, 2004; Arula et *al*., 2005; Araico et al., 2007). Moreover, a recent study on quality control of different parts (leaves, barks, roots) of *Fadogia agrestis* based on chemical fingerprinting revealed the presence of a variety of phenolic compounds (Avula et al.,2019). Their role as compounds with analgesic and anti-inflammatory properties has been reported in the extracts of various plant species, through the inhibition of cyclooxygenase and lipoxygenase (Chagas et al., 2022). These constituents could be responsible for the anti-inflammatory activity of our extract.

The histamine and serotonin edema induction tests confirmed the anti-inflammatory properties of *Fadogia agrestis* extract during the first phase of inflammation. In the histamine test, the extract

significantly inhibited inflammation at a dose of 300 mg/kg as well as promethazine, the reference antihistamine used. The extract of *Fadogia agrestis* would possess compounds capable of reducing inflammation by acting like promethazine and therefore by competitively inhibiting the histamine H1 and H2 receptors.

All three doses of the extract were found to be effective against edema formation six hours after formalin injection, confirming the anti-inflammatory properties of our extract. Hematological analysis revealed a significant increase in the number of leukocytes in rats treated with formalin alone. Indeed, during inflammation, hyperleukocytosis is usually observed (Zerbato, 2010). Toxins stimulate the production of interleukin I (IL-1) which acts on the bone marrow to increase the production of neutrophils (PNN), the young forms of which are released into the blood. Some chemokines have a targeted effect on certain blood cell lines interleukin 8 (IL-8) on PNN, eotaxin on eosinophils, MCP-1 (monocyte chemo attractant) on monocytes. The hydroalcoholic extract of *Fadogia agrestis* could inhibit the production of interleukins thus reducing the number of PNN in the inflammatory focus. The extract would prevent the probable action of chemokines.

5. Conclusion

Herbal medicine represents an alternative to traditional drugs for the treatment of inflammatory diseases. The acute toxicity study conducted on mice for *Fadogia agrestis* hydroalcoholic extract was proved to be non-toxic when administered orally. Anti-inflammatory studies performed on acute and subacute inflammation models induced in mice show satisfactory results of the hydroalcoholic extract of *Fadogia agrestis* leaves. Our results confirm the traditional therapeutic indication of *Fadogia agrestis* leaves as an anti-inflammatory agent. However, anti-inflammatory studies of the extract in a chronic inflammation model, subacute toxicity and an in-depth phytochemical study will be necessary to conclude on the toxicity and anti-inflammatory properties of the hydroalcoholic extract of *Fadogia agrestis* leaves.

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Conflict of interest statement

We declare that we have no conflict of interest

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