

Full Length Research Paper

In-vivo* anti-inflammatory activity of different parts of *Adansonia Digitata

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The aim of the study is to investigate the anti-inflammatory property of the different parts of *Adansonia digitata* (Malvaceae) extracts. *A. digitata* is an important medicinal plant to West Africa including Ghana. The plant is used effectively in folk medicine to treat inflammatory diseases such as joint disorders, asthma, toothache and painful swelling. Carrageenan-induced pedal oedema in 7-day old chicks was the model used to determine the anti-inflammatory property of the extracts obtained from six different parts of *A. digitata*. The extracts were also assessed for their acute toxicity. The results from the acute toxicity test showed there were no behavioural changes, toxic signs, or death in the rats when given the highest dose (3000 mg/kg) of the extracts orally. The six extracts demonstrated varying degrees of anti-inflammatory effects, in a dose-dependent manner; with the stem extract giving the most potent activity with an ED₅₀ of 145.3 ± 7.6 mg/kg, followed by the flower (167.5 ± 10.42 mg/kg), leaves (169.7 ± 8.76 mg/kg), root bark (187.8 ± 11.2 mg/kg), fruit pulp (218.8 ± 6.86 mg/kg), and the seed (267.1 ± 12.3 mg/kg) as compared to the positive control (diclofenac, ED₅₀ = 55.08±6.11 mg/kg) (p < 0.0001).

Key words: *Adansonia digitata*, carrageenan-induced pedal oedema, anti-inflammatory activity, traditional medicine, acute toxicity.

INTRODUCTION

The focus on useful plant-based medicines and their application in traditional medicine has received global attention. This is due to the fact that the plants are readily available, accessible, cheap and accepted by over 80% of countries in Africa and Asia who rely on them for the

management of many diseases and disorders including inflammation (Amponsah et al., 2013; Boakye-Gyasi et al., 2008, Adebayo et al., 2015). Inflammation remains one of the body's immediate response to the invasion by foreign bodies such as parasites, viruses, and toxins.

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This response is an important protective reaction to injury, irritation, or infection. Inflammation has been found to be linked to many disease conditions (Kunnumakkara et al., 2018; Oguntibeju, 2018). Though this process may be protective, it tends to be very destructive to an organism's system when it is not brought under check, by intensifying many diseases including allergies, asthma, inflammatory bowel disease, tuberculosis, rheumatoid arthritis, autoimmune diseases and even cancer (Zhu et al., 2018). The process of inflammation involves inflammatory cells and mediators like pro-inflammatory cytokines (1L-1 β , 1L-6, 1L-18 and TNF α). It initiates and amplifies the inflammatory process, and anti-inflammatory cytokines (IRA, 1L-10 and TGF- β), which modulate the process of inflammation negatively (Calixto et al., 2004, Abdulkhaleq et al., 2018).

Many classes of medicines including opioids, Disease Modifying Anti-Rheumatic Drugs (DMARDs), steroidal and non-steroidal anti-inflammatory agents, and corticosteroids are known to have the ability to manage and sometimes treat inflammatory diseases and disorders. However, due to the high cost of treatment and undesirable adverse effects experienced with prolonged use of most of these medicines, their use is usually associated with non-compliance with medication. Over the years, many medicinal plants have been used to provide relief to inflammatory disorders. The growing intolerance to the gastric- and cardiovascular-related side- and adverse effects associated with the orthodox medicines has renewed the interest of scientists to identify safe alternative approaches (Amponsah et al., 2013). It is for this reason that medicinal plants have been widely explored scientifically, especially in Africa, as safer and cost-effective alternative options of anti-inflammatory agents (Essel et al., 2017).

In Ghana, many medicinal plants are considered for the treatment and management of inflammatory disorders, either alone or in combination with orthodox medicines. *Adansonia digitata* (Malvaceae), an iconic tree of African origin known as the "Small Pharmacy" or the "Chemist tree", is one of such plants which possesses important medicinal properties in all its parts (flower, fruits, leaves, seeds, stem bark and root bark extract) (De Caluwé et al., 2010; Braca et al., 2018). The different parts of *A. digitata* are used traditionally to manage inflammatory disorders such as joint diseases, painful swelling, toothache, asthma. They are also used in promoting wound healing and treating worm infestations, microbial infections, anaemia, and dysentery (Braca et al., 2018; Lisao et al., 2017). Though several biological effects of the plant have been reported in folklore medicine, only few scientific works (such as anti-plasmodial, anti-microbial, anti-sickling, anti-diabetic, analgesic and anti-pyretic activity) have been carried out to verify the uses of the plant (De Caluwé et al., 2010; Ismail et al., 2019). This research therefore seeks to provide a scientific basis for the traditional use of the different parts of the plant in

managing inflammatory disorders by comparatively evaluating the *in-vivo* anti-inflammatory effects using carrageenan-induced pedal oedema in chicks.

MATERIALS AND METHODS

Drugs and chemicals

Diclofenac (Denk-Pharm, Germany) and Carrageenan sodium salt (Sigma chemicals, St. Louis, MO, USA) were employed in the study.

Plant materials

The plant samples, including leaves, fruit pulp, flowers, seeds, stem bark and root bark were obtained from Miotso in the Greater Accra Region of Ghana (5°46'10.812" N 0°4'58.4112" E) with the help of a local herbalist between November and January 2015. The collected plant samples were identified and certified by Dr. George Sam of the Department of Herbal Medicine, Faculty of Pharmacy and Pharmaceutical Sciences (FPPS), Kwame Nkrumah University of Science and Technology (KNUST); voucher numbers were assigned to each sample (Table 1). The samples were placed at the Herbarium in the Herbal Medicine Department of FPPS, KNUST, Kumasi, Ghana.

Animals

Day old post-hatch cockerels (*Gallus gallus*; strain Shaven 579) and Sprague-Dawley rats (female and male) were obtained from Akropong Farms, Kumasi Ghana and Noguchi Memorial Institute for Medical Research, Accra, Ghana, respectively. The animals were held in separate stainless-steel cages and kept in the Animal house at the Pharmacology Department of FPPS, KNUST, Ghana. They were maintained under approved laboratory environments (temperature 25 \pm 2°C, 12 h light-dark cycle), provided with feed (chick mash (GAFCO, Tema, Ghana)), solid pellet diet (Agricare Ltd, Kumasi, Ghana) and clean water *ad libitum*. The chicks and rats were allowed to acclimatize to the laboratory environment for seven days pending the start of testing. A sample size of five (n=5) was used during the study. The animals were handled in harmony with the National Institute of Health Guidelines (NIH, 2011) for the care and use of laboratory animals and their use was approved by the Animal Ethics Committee (FPPS-AEC/CA04/16) of the Department of Pharmacology, FPPS, KNUST.

Sample preparation and extraction

Each of the plant samples was processed separately. The stem and root barks were washed, chopped into pieces and dried while the leaves and flowers were washed and air-dried for fourteen days. The dried fruit pulp and seeds were separated from the husk. A hammer mill (Christy Labmill, England) was used to mill the dried samples separately into powders. The powdered samples were kept in an air-tight container, labelled, and stored for subsequent work. 200 g each of the powdered plant samples was cold macerated using 500 ml of methanol for five consecutive seventy-two-hour period. The mixture from each sample was filtered through a No. 1 Whatman filter paper and evaporated to dryness using a rotary evaporator (R-114, Buchi, Switzerland). The semi solid masses obtained were further dried, labelled and stored in a desiccator until needed for biological screening (anti-inflammatory activity and acute toxicity).

Table 1. Plant parts and voucher specimen numbers with the dates of collection.

Parts of plant	Voucher specimen numbers	Dates
Leaves	KNUST/HM/2015/L016	November, 2015
Fruit's pulp	KNUST/HM/2015/FR001	December, 2015
Flowers	KNUST/HM/2016/F002	January, 2016
Seeds	KNUST/HM/2015/S008	December, 2015
Stem bark	KNUST/HM/2015/ST019	November, 2015
Root bark	KNUST/HM/2015/R012	November, 2015

Dose preparation and administration

For the anti-inflammatory assay, three doses (30, 100 and 300 mg/kg) were prepared for each of the 6 extracts using normal saline as vehicle. The standard drug diclofenac (10 mg/kg) was also prepared using normal saline. The actual doses of the extracts and standard drug were calculated using the individual weights of the cockerels. Solutions of the extracts and the standard drugs were administered orally. For the acute toxicity tests, 300, 1000 and 3000 mg/kg doses were prepared from each extract and administered orally.

Acute toxicity test

The acute toxicity test was done to ascertain the safe doses of the extracts (flower, fruits, leaves, seeds, stem bark and root bark extract) that could be administered to rats without causing any adverse effect or death. The assay was carried out based on the method described by Abotsi et al (2017). Female and male Sprague-Dawley rats weighing 150-210 g were categorized into four groups, with each group having five rats (n = 5). The rats were fasted overnight after which they were orally given either of the test sample doses (that is, 300, 1000 and 3000 mg/kg) depending on the test group or normal saline (0.9%; 10 ml/kg) as negative control. The rats were then observed closely at 0, 15, 30, 60, 120, 180 min, 24 h and 14 days after the extracts were given for changes in their behaviour and if possibly, mortality.

Carrageenan-induced pedal oedema test

One of the most common tests used in screening newer anti-inflammatory agents is carrageenan-induced paw oedema. This method measures how much an agent (extract/drug) is able to reduce oedema caused by injecting carrageenan (an irritant agent) into the paw of an animal (chicks, mice or rats) (Roach and Sufka, 2003; Ofori-Baah and Borquaye, 2019).

The anti-inflammatory effects of the extracts were evaluated using the above-mentioned model, as described by Boakye-Gyasi et al. (2008). Briefly, the 7-day old cockerels were randomly grouped into twenty (20) groups, with each group containing five cockerels: three groups for each of the six extracts, one group for positive control (diclofenac) and another group for negative control (normal saline). The cages were labelled A to U, respectively. The right footpad of each cockerel was measured using an electronic vernier caliper (Z 22855, Milomex Ltd, Bedfordshire, UK) as the basal reading. Inflammation was induced by sub-plantar injection into the right footpad of the cockerel with 10 μ l of 2% carrageenan in normal saline using the protocol for the curative studies. The test groups were treated one and hour after oedema induction with the test sample doses (that is, 30, 100 and 300 mg/kg p.o). The positive

control group was treated with 10 mg/kg (p.o) of diclofenac and the negative group received 5 ml/kg (p.o) of normal saline.

The thickness of the edematous foot was measured at hourly interval for six hours, after carrageenan injection using an electronic caliper. The anti-inflammatory activity of an extract was determined by how much the extract was able to reduce the oedema of the footpad of the chick measured with the electronic caliper. The values obtained (inhibition of inflammation) were expressed as percentage change in footpad size using Equation 1.

$$\% \text{ Change in footpad size} = \left[\frac{F_t - F_0}{F_0} \right] \times 100 \quad (1)$$

Where F_0 is footpad size before carrageenan was injected (at time 0), F_t is footpad size at the hourly time interval (at time t)

The raw score values for the footpad thickness obtained were normalized individually as percentage change from the values at time 0 and then the average for each treatment group. The total footpad oedema was expressed in arbitrary units as the area under the curve (AUC) for each group to obtain the percentage inhibition of oedema, as shown in Equation 2.

$$\% \text{ Inhibition of oedema} = \frac{AUC(\text{control}) - AUC(\text{test sample})}{AUC(\text{control})} \times 100 \% \quad (2)$$

Where AUC is area under the curve.

Statistical analysis

Statistical analysis was carried out using GraphPad prism version 7 for windows (GraphPad software, San Diego, CA, USA). The results were presented as the mean \pm SEM (n = 5) of the extract effect on the time course curve which was analyzed by one-way ANOVA followed by Dunnett's test. The total footpad oedema effects recorded over 6 hour period for all the extracts were analyzed by two-way ANOVA followed by Bonferroni's *post hoc* test.

RESULTS

Acute toxicity

No behavioural changes, toxic signs (such as lachrymatory, shedding furs, unusual vocalization, diarrhea, abnormal urination, convulsions, and other unusual locomotory and respiratory activities) or death were observed in the animals even when they were given

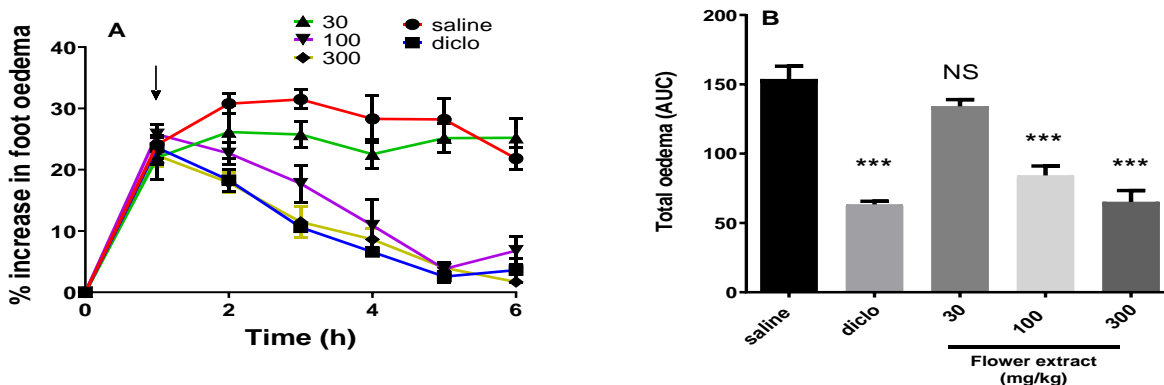


Figure 1. Effect of flower extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n=5).***p<0.001 compared to negative control (saline) (One way ANOVA followed by Dunnett's *post hoc* test)

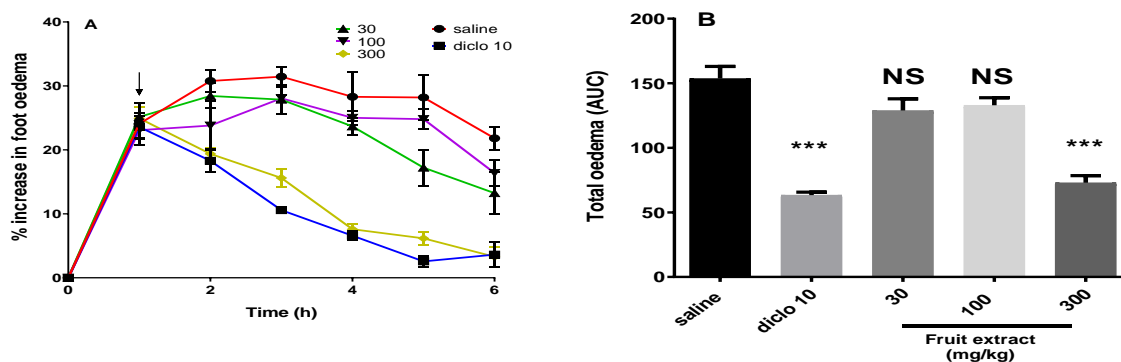


Figure 2. Effect of fruit extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n = 5), ***P < 0.001 compared to negative control (saline) (One way ANOVA followed by Dunnett's *post hoc* test)

the highest dose (3000 mg) of the extracts during the 14 days' observation period.

Carrageenan-induced pedal oedema test

The time course curves as seen in Figures 1A to 6A showed an increase in oedema between 1 and 2 h and a gradual decrease in oedema between 3 and 6 h for all six extracts and positive control (diclofenac) after carrageenan injection (100 μ l of 2%^{w/v}). After the administration of the extracts, the mean maximal swellings observed over 6 h period were reduced to about 50% for all the extracts at 300 mg/kg dose as compared to the negative control (inflamed control 5 ml/kg). However, the untreated or inflamed control (negative control/inflamed control indicated in red line) produced an increase in oedema from 1-5 h and a slight decrease in oedema in the 6th hour.

The total oedema and the percentage inhibition of oedema were calculated by using the area under the curve (AUC). The results as seen with the graphs in

Figures 1B to 6B showed a dose-dependent effect for all six extracts. Thus, an increase in the dose of the extract showed a higher percentage inhibition of oedema and a decrease showed a lower percentage inhibition of oedema. The ED₅₀ value, which is the dose of a drug that produces 50% of the maximum response was calculated for all the six extracts and diclofenac using a non-linear regression analysis of the dose-response curves (Figures 1A to 6A). The results of the ED₅₀ as seen in Table 2 showed that the stem bark extract produced the lowest ED₅₀ of 145.3 \pm 7.6 mg/kg and was about 3 times less potent than the positive control (diclofenac, ED₅₀ = 55.08 \pm 6.11 mg/kg) (p < 0.0001); while that of the seed extract which gave the highest ED₅₀ of 267.1 \pm 12.3 mg/kg was 5 times less potent than diclofenac (p < 0.0001).

DISCUSSION

The different parts of *A. digitata* have been used traditionally for the treatment of inflammation and some inflammatory related conditions, including asthma,

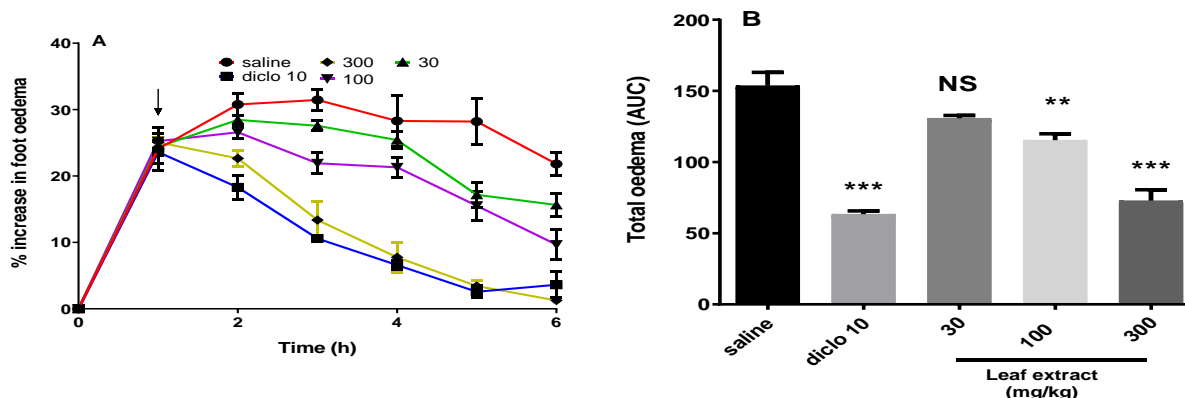


Figure 3. Effect of leaf extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n=5) ** $P < 0.01$, *** $P < 0.001$ compared to negative control (saline) (One way ANOVA followed by Dunnett's *post hoc* test).

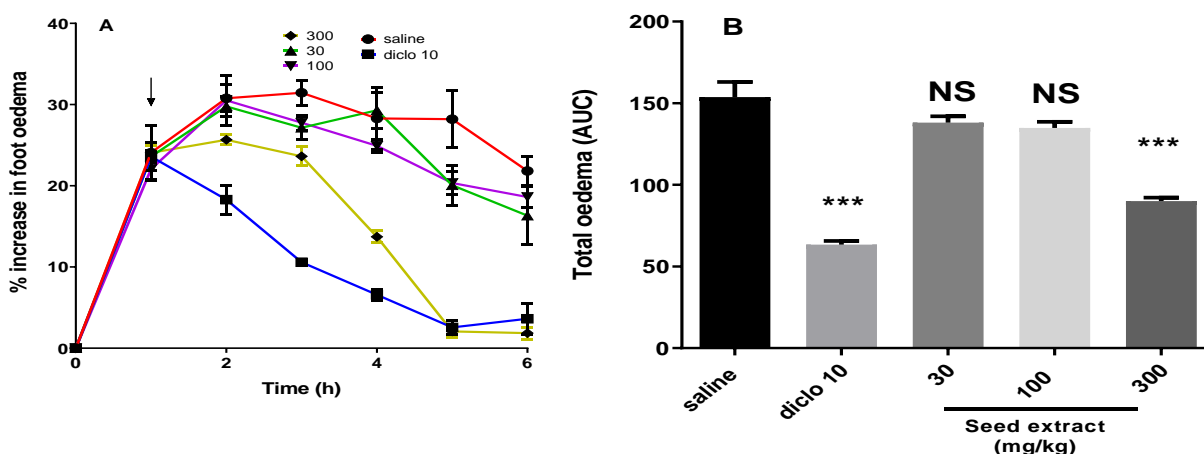


Figure 4. Effect of seed extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n=5) *** $p < 0.001$ compared to negative control (saline) (One way ANOVA followed by Dunnett's *post hoc* test).

gingivitis, painful swelling, labor pains, tuberculosis, toothache, kidney disease, microbial infection, fever, measles, and smallpox (Sharma et al., 2015; Braca et al., 2018; Lisao et al., 2017). The acute toxicity studies on the six extracts from the plant showed that there were no behavioural changes, toxic signs, or death in the animals even when given the highest dose of 3000 mg/kg for the 14-day study period. This indicates that the extracts are safe for use and may have LD₅₀ values above 3000 mg.

In evaluating their anti-inflammatory effects, the carrageenan-induced paw oedema assay in day-old chicks (cockerels) was employed because of its sensitivity in testing new oral anti-inflammatory candidates (Roach and Sufka, 2003; Ofori-Baah and Borquaye, 2019). The intra-plantar injection of carrageenan causes the release of inflammatory markers. This results in a biphasic phenomenon which involves different inflammatory

mediators that work in sequence to produce the inflammatory response (Ofori-Baah and Borquaye, 2019). This biphasic phenomenon begins with the early phase (first phase) that ensues from the 0th to 2nd hour post-carrageenan injection. It mainly involves the activities of histamine, serotonin (5-hydroxytryptamine (5-HTP) and increased synthesis of prostaglandins. This phase is non-responsive to non-steroidal anti-inflammatory drugs (NSAIDs) (Ravi et al., 2009). The latter phase (second phase or prostaglandin phase) is marked by a continuous release of prostaglandins (PGs), leukotrienes, polymorphonuclear cells, proteases, and lysosomes and the phase lasts from 2 to 6 hours. The production of the prostaglandins is associated with the movement of leucocytes into the inflamed area (Obiri and Osafo, 2013). It is this phase that is suppressed by NSAIDs as its introduction suppresses the ability of

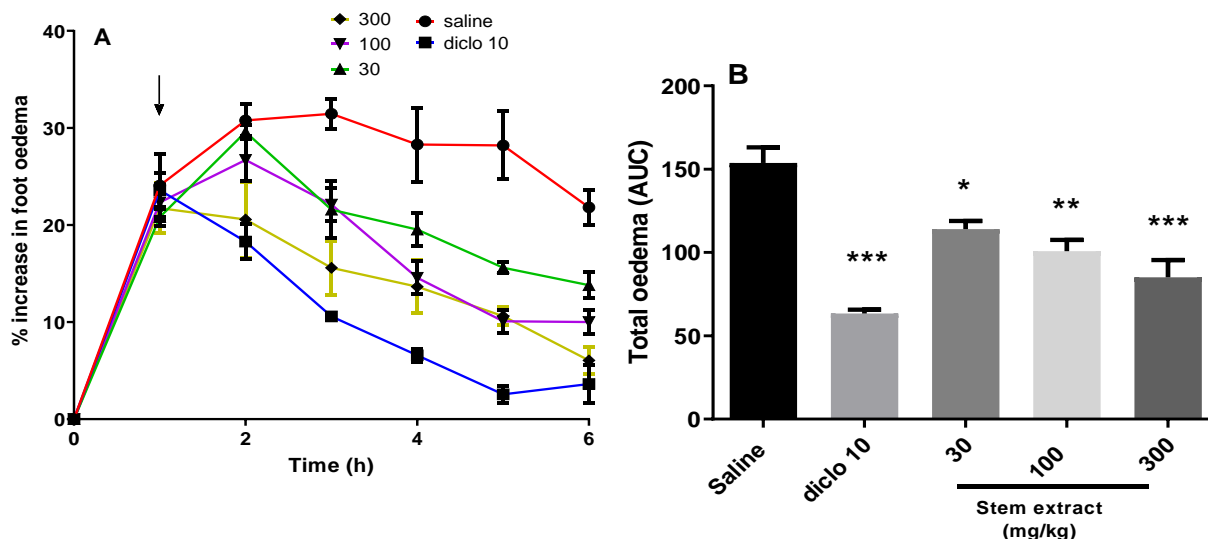


Figure 5. Effect of stem extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n=5) * p <0.05, ** p <0.01, *** p <0.001 compared to negative control (saline) (One way ANOVA followed by Dunnett's post hoc test).

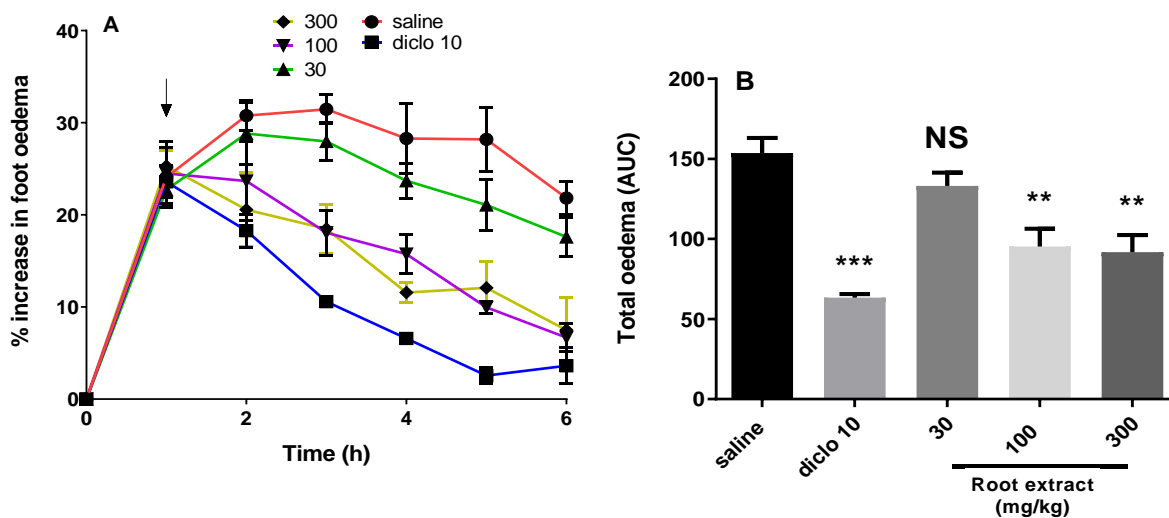


Figure 6. Effect of root extract and diclofenac sodium (diclo) on time course curve (A) and the total oedema response (AUC) (B) in carrageenan-induced oedema in chicks. Data are expressed as mean \pm SEM, (n=5) ** p <0.01, *** p <0.001 compared to negative control (saline) (One way ANOVA followed by Dunnett's post hoc test)

mononuclear leucocytes from migrating to the inflamed area (Abdulhaleq et al., 2018; Abotsi et al., 2017).

The varied anti-inflammatory activity of these six extracts may be attributed to the differences in the composition of the phytochemical principles present in the various plant parts. Some phytochemicals with anti-inflammatory properties include saponins (frutesaponins B and kalopanaxsaponin A), flavonoids (galangin, quercetin, baicalin, wogonin and luteolin), alkaloids (capsaicin, tetrandrine, fangchinoline and piperlactam),

triterpenes and terpenes (lupeol, celastrol, parthenolide oleanolic acid, catalpol, reynosin and tingene and ursolic acid), coumarins (furanocoumarins), phytosterol (β -sitosterol), glycosides (gigenoside) among others (Asante-Kwatia et al., 2019; Amponsah et al., 2013; Calixto et al., 2004). Many of the above-mentioned phytochemicals have been found to exhibit anti-inflammatory activity by inhibiting cytokine, chemokine or adhesion molecule synthesis which are known to show a major part in the pathophysiology of several inflammatory

Table 2. ED₅₀ results of the various parts of *A. digitata*.

Extract	ED ₅₀ (mg/kg)
Stem bark	145.3 ± 7.6****
Flowers	167.5 ± 10.42****, §§
Leaves	169.7 ± 8.76****, §§
Root bark	187.8 ± 11.2****, §§§§
Fruits	218.8 ± 6.86****, §§§§
Seeds	267.1 ± 12.3****, §§§§
Diclofenac	55.08 ± 6.11§§§§

One-way ANOVA analysis was carried out to test for differences among the ED₅₀ of the different parts of the plant. Dunnett *post-hoc* tests were conducted by comparing the ED₅₀ of the parts to that of Diclofenac and Stem bark and labelled as *0.05 < p < 0.01, **0.01 < p < 0.001, *** 0.001 < p < 0.0001, ****p < 0.0001 and §0.05 < p < 0.01, §§0.01 < p < 0.001, §§§0.001 < p < 0.0001, §§§§p < 0.0001, respectively.

related conditions such as asthma, rheumatoid arthritis, bronchitis, atopic dermatitis among others (Calixto et al., 2004; Calixto, 2019).

Although the probable mechanism of the various *A. digitata* extracts is not yet known, their effects could partly be attributed to their inhibition of the synthesis and/or release of chemical markers known to play a major role in the carrageenan-induced footpad oedema. While the first phase of the carrageenan model is mainly mediated by pro-inflammatory mediators from the injured tissue, the second phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorphonuclear cells and prostaglandins produced by leucocytes (Vasudevan et al., 2007). Therefore, the findings from this study show that the extracts are effective in both phases of the induced inflammation. This implies that the extracts may possibly be involved in attenuating the actions of 5-HT, histamine, and arachidonic acid metabolites (PGS) which rely on the mobilization of polymorphonuclear neutrophils (PMN) cells or inhibition of the synthesis of prostaglandins (PGs) through cyclooxygenase activation (Obiri and Osafo, 2013; Abotsi et al., 2017).

Conclusion

The different parts of *A. digitata* extracts possess *in-vivo* anti-inflammatory effect. The extracts produced no toxic effects in the acute toxicity studies. This present study provides a scientific justification for the use of *A. digitata* in managing inflammatory conditions. The stem bark, flowers and leaves are more effective than the other parts for such traditional purposes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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