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EFFECT OF *LEPTADENIA HASTATA* HEXANE LEAF EXTRACTS AGAINST HEAMOTOLOGICAL, BIOCHEMICAL AND INDOMETHACIN INDUCED ULCER IN RATS

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ABSTRACT

Objectives: This study was targeted at valuing a claim by traditional herbal practitioner that the leaves of *Leptadenia hastata* possess ulcer healing property by assessing the effect of *Leptadenia hastata* on ulcer induced rats. **Material and method:** The effects of an hexane leaf extracts of *Leptadenia hastata* were studied in 40 white albino rats over a period of 21days, to ascertain the claim of *Leptadenia hastata* has ulcerogenic properties, the rats were divided into eight groups those in group one served as control group, group two negative control (Indomethacin) ulcer induced with no treatment, while group three positive control (Omeprazole) and groups four to eight are dosed groups ranged from; 100mg/kg 200mg/kg, 300mg/kg, 400mg/kg and 500mg/kg extracts respectively, Microscopic examination was carried out and scored for the presence of lesion. The length and breadth of the lesion of the stomach was measured for ulcer index. Stomach and Blood sample were collected for Histological, hematological and biochemical analysis. The specimen of the stomach was taken for histopathological studies. **Results:** The study showed that the extracts of *Leptadenia hastata* caused increased in the weight of the rats compared to the negative control and the levels of packed cell volume, hemoglobin concentration, red blood cell, white blood cell, mean corpuscular volume and mean corpuscular hemoglobin. The changes in the biochemical parameter were all within the range of the control. Histologically, stomach degeneration was characterized by lesion and decrease number of lining cell of the epithelium. **Conclusion:** The study indicate that hexane leaves crude extracts of *Leptadenia hastata* possess ulcer healing activity.

KEYWORDS: *Leptadenia hastata*, ulcer, rats, histopathology, haematology, serum biochemistry.

INTRODUCTION

In the recent past many researchers of the world have been focusing on the provision of the empirical proof and relevance of use of tropical plants in traditional medicine with their curative potentials.[6] Many of this medicinal plant are used as spices, foods and medicinal purposes.[11] The medicinal value of these plants lies in some chemical substance that produce a definite physiological action on the human body. The most phytochemical constituents are alkaloids, tannins, phenolic and flavonoids compounds.[10]

In Nigeria and other parts of the world *Leptadenia hastata* the plants of the family Asclepiadaceae is widely used in the management of diverse diseases. The Decoction of the leaves of *Leptadenia hastata* with the bark of *Erythrina senegalensis* is either taken orally or used as a medicinal bath to treat onchocercosis in Mali.[37] In Chad, the roots are used to treat scabies.[38] This plant is commonly used in Hausa-speaking communities in Nigeria as a spice and used in sauces.[15] Also in Nigeria, local healers use the plant for hypertension, catarrh and skin diseases.[39] In Burkina Faso, locally it is used for sexual potency (chewing leaves), trypanosomiasis (decoction of leaves), skin diseases and wound-healing (application of latex).[40] In Senegal, the leaves have been reportedly used for lactation and as a purgative by Kerharo and Adam and Arbonnier.[41,42] Senegalese healers also use the *L. hastata* for prostate and rheumatism complaints.[43]

Ulcer is a chronic medical disorder, it is defined as a breach in the lining (mucosa) of the digestive tract produced by the digestion of the mucosa by pepsin and acid basically as the disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance, the peptic areas of the human body under normal circumstances are the stomach and the duodenum and the common medical disorder with the area is peptic ulcer disease.[12] Ulcer are commonly caused by *Helicobacter pylori* a bacteria that can cause a stomach infection and inflammation,

frequent use of analgesic, radiation therapy and other anti-inflammatory drugs can as while cause this medical disorder.[5] The aim of this study is to evaluate the effects of *Leptadenia hastata* in normal and induced ulcer rats. However, finding of this work will help in advancing in research for natural compound that can be incorporated into drugs for the disease treatment.

MATERIALS AND METHODS

Chemicals

Diagnostic kits for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin were purchased from Randox Laboratories Ltd, albumin from Sigma Diagnostic®, UK, which contain bromocresol green. Omeprazole and Indomethacin (reference drug) was obtained from a pharmacy shop in yola Adamawa State, Nigeria. Other chemicals and solvents were of the highest grade commercially available.

Extract Preparation

Freshly leaves of *Leptadenia hastata* were collected from the uncultivated farm land of the Federal University Wukari Taraba State, Nigeria and was authenticated at Ahmadu Bello University Zaria and Voucher No PU: 2 ABU Herbarium No 900220. The plant *Leptadenia hastata* (yadiya) was dried under room temperature. The plant *Leptadenia hastata* were washed with distilled water to remove the soil and dust particles they were thoroughly air dried and powdered using laboratory grinder machine (FGR-350, Quest Scientific) extraction using hexane by placing 150g of the powdered samples into an Erlenmeyer flask and hexane three times the weight of the extracts was added, the solution was covered and shaken at an interval of an hour and then allowed at room temperature to stand for 7days, the mixture were then filtered using whatman filter paper No.4 and the solvent was evaporated using a rotary evaporator (Heidolph Laborato 400) under reduced pressure below 50EC. It was then stored under a frozen condition until required.

Breeding of animals (Albino rats)

Forty male albino rats weighing between (150-190g) were obtained from the animal farm, National Research Institute Vom, Jos Plateau State Nigeria. They were put in cages at room temperature (20-27^{o}c) under 12/12 night/dark. They were maintained on a standard animal pellets (vital feeds, Grands cereals and oil meal Jos) and water ad libitum.

Experimental protocol

The albino rats were randomly divided into eight groups, this include normal group, negative and positive control group while five groups for extracts dosage, except the normal all the groups were induced with ulcer, the animals were starved from food 24hours and water 2hours before the commencement of the experiment.

Group 1: Normal control (diet/water)
Group 2: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water)
Group 3: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet/water + Omeprazole)
Group 4: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +100mg/kg/bwt extracts). Group 5: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +200mg/kg/bwt extracts)
Group 6: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +300mg/kg/bwt extracts)
Group 7: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +400mg/kg/bwt extracts)
Group 8: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +500mg/kg/bwt extracts)

Determination of ulcer lesion

The drug Indomethacin was administered intragastrically via the aid of an orogastric cannula. Four hours later, the rats were sacrificed using chloroform anesthesia; the stomach was removed and opened along the greater curvature. The tissue was fix with 10% formaldehyde in saline, microscopic examination was carried out and scored the presence of lesion using the method of Nwafor et al.[17] Ulcer lesion and weight of the rats were calculated.

Histopathology

The stomach Histopathology of all the animals were fixed in 10% buffered formalin in labeled bottles and processed routinely for histology examination. The tissue embedded in paraffin wax were sectioned in 5µm thick, stained with Haematoxylin and eosin, mounted on glass slides and then examined under a standard light microscope.

Blood collection

All the rats from the various groups were sacrificed using standard laboratory procedures and then blood sample were collected into heparinized and non-heparinized bottles for hematological and serum biochemistry studies respectively. Blood sample collected into a clean non-heparinized bottle could clot and serum was separated from the clot and centrifuged according to groups in a clean bottle for the biochemical analyses.

Determination of hematological parameters

Hematological parameter concentration was determined as described by Schalm, Jain and Carroll in 1975 using cyanomethaemoglobin method. Packed cell volume (PCV) was determined by conventional method of filling the capillary tubes with blood as described by[13] Schalm *et al*. The Erythrocyte count was however determined by the haemocrytometer method as described by[9] Coles. However, the Erythrocytes indices were determined from the values obtained from RBC count, hemoglobin and PCV values. Total leucocytes and differential leucocyte counts were also determined.

Determination of serum biochemical parameters

Albumin by colorimetric estimation using the Sigma Diagnostics albumin reagent, albumin was measured, and total protein was measured using biuret reaction. Globulin was estimated as the difference between total protein and albumin.

Alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (AL were determined on a photometric colorimeter (Gallenkamp and sons Ltd, England) as described by Toro and Ackermann[14] and Duncan, Prasse and Mahaffey.[9] Serum urea and creatinine levels were also determined on a photoelectric colorimeter (Gallenkamp and Sons Ltd England) as described by Toro and Ackermann[14] and Coles.[9]

Statistical analysis

Data are reported as Mean ± SD and were analyzed statistically using one-way ANOVA followed by student t-test and value of $p<0.05$ were considered significant.

RESULTS

Indomethacin-induced gastric ulceration

The effect of extracts on indomethacin-induced gastric ulceration showed a dose-dependent reduction in ulcer indices in pretreated groups relative to the control. The reduction was statistically significantly ($P<0.05$) compared to control (table 1) the effect of the extract is more than that exhibited by the standard drug omniprazole.

The weight of the albino rats showed a dose dependent increase in pretreated group compared to the negative control. The increase was statistically significantly ($p<0.05$). The effect of the extract on weight gain is close to the normal control at dose 25, and 100mg/kg/bwt but went higher at dose 200, 300 and 400mg/kg/bwt with 161.89± 10.87, 157.36 ± 8.06 and 161.89 ± 12.03 respectively when compared with the control. This agrees with the report of Bello, *et al*. which state that the extracts of *Leptadenia hastata* increase in body weights of treated diabetic compared to the diabetic untreated groups which may be due to protein sparing effect.[36]

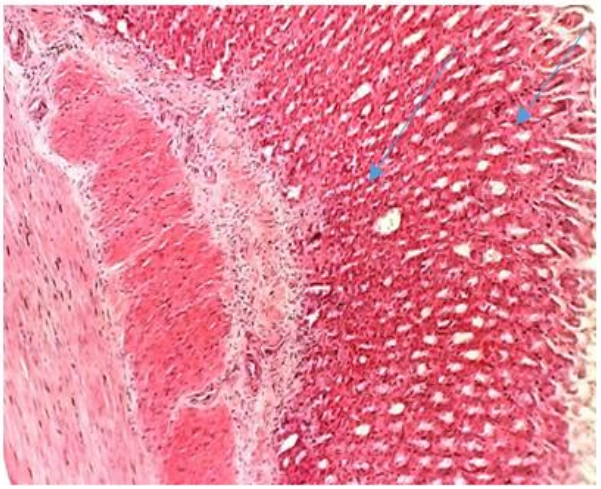
The Ulcer Area (UA) was calculated. The percentage (%) of protection (P%) availed to the animals through the various treatments were calculated using the formula:

$$P\% = \frac{\text{UA ulcer control - UA treatment}}{\text{UA ulcer control}} \times 100$$

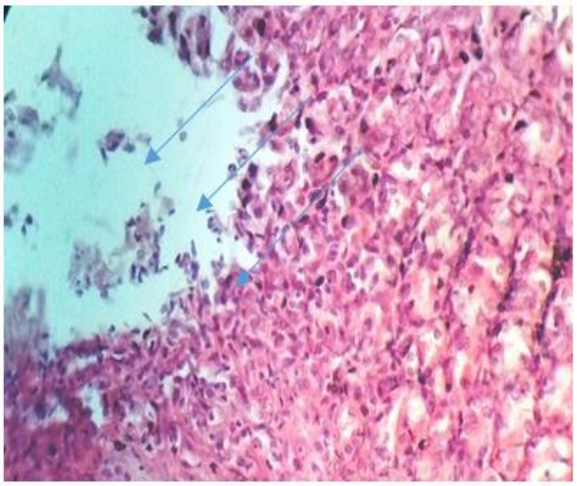
Histopathology

The stomach Histopathology of the animals were fixed in 10% buffered formalin in labelled bottles and processed routinely for histology examination. The tissue embedded in paraffin wax were sectioned in 5µm thick, stained with Haematoxylin and eosin, mounted on glass slides and then examined under a standard light microscope.

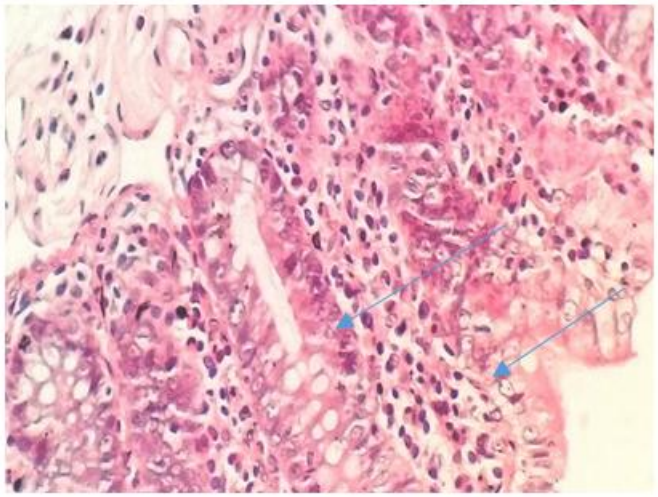
Haematoxylin/eosin



1 Control before induced by indomethacin.



2 After induced by indomethacin.



3 After 21 days post treatment.

Histological appearance of haematoxylin/eosin-stained full-thickness colonic samples in control rats (1) and animals with indomethacin induced (2). The colonic wall of controls shows normal morphological features with compact cells while colonic specimens from rats with damaged cells (2). The cells appear to be vacuolized and altered (arrows) and figure (3) showed vasoconstriction with minimal alteration because of reduction of mucosal damage at day 21.

Table 1: Effect of Hexane Leaf Extracts of *Leptadenia hastata* on indomethacin induced ulcer.

Group	Treatment Dose (mg/kg/bwt)	Ulcer indices	Rats Weights	% Protection
Group 1	-	-	-	-
Group 2 (-ve)	25	2.93±0.70	151.65 ± 8.49	-
Group 3 (+ve)	100	0.11±0.05[a]	154.05 ± 10.47	96.25%
Group 4	100	2.67±0.46[a]	154.92 ± 6.48	8.87%
Group 5	200	2.02±0.68[a]	161.89 ± 10.87[c]	31.06%
Group 6	300	1.53±0.28[a]	157.36 ± 8.06[c]	47.78%
Group 7	400	1.20±0.52[a]	161.89 ± 12.03[c]	59.04%
Group 8	500	0.75±0.21[ab]	154.37 ± 7.40	74.40%

Values are Mean ± SD (n = 5)
[a]Significantly (p> 0.05) decreased compared to negative control.
[ab]Significantly (p> 0.05) decreased compared to different extract concentration per group.
[c]Significantly (p> 0.05) increased compared to negative control.

Table: Effect of graded doses of hexane leave extracts of *Leptadenia hastata* on haematological parameters of rats (n=5).

Parameters	Control	-Ve control	+ve control	100mg/kg	200mg/kg	300mg/kg	400mg/kg	500mg/kg
PCV (%)	54.5±4.4	23.2±2.3	53.7±3.5	24.3±1.2	26.4±2.1	36.4±05	42.5±31	49.6±2.4
Hb (g/L)	13.7±4.3	9.12±0.2	13.4±1.2	10.11±0.3	10.23±0.1	12.3±02	12.8±23	14.1±0.1
RBC ($\times10^{12}$g/L)	8.6±0.2	5.3±1.2	8.7±1.0	3.8±1.2	4.5±0.4	6.0±2.3	6.3±0.3	7.5±1.3
MCV (fl)	65.3±2.8	52.2±1.0	64.62±2.1	38.2±2.6	42.4±0.3	50.6±01	53.7±0.3	59.8±2.3
MCHC (g/dl)	32.7±0.2	28.3±0.3	31.8±1.3	29.3±1.2	31.0±2.3	32.34±3.0	32.8±1.2	34.2±0.1
MHC(pg)	21.3±0.9	18.4±1.0	21.1±0.6	18.9±1.2	19.53±1.0	20.5±0.2	22.3±0.1[a]	22.4±2.4
WBC ($\times10^9$/L)	12.0±1.4	8.2±0.2	11.54±1.2	8.2±1.2	10.6±2.3	12.6±2.5	13.2±0.2	12.8±1.2
Lymphocytes($\times10^9$/L)	7.7±1.2	7.1±2.2	7.4±2.3	5.6±2.7	6.2±0.2	7.2±2.1	7.5±0.1	7.6±2.3
Neutrophils ($\times10^9$/L)	4.1±1.0	3.5±0.1	4.0±2.1	3.8±0.2	4.0±1.2	4.6±0.6	5.5±2.3	5.3±3.4
Monocytes ($\times10^9$/L)	0.2±0.1	0.15±2.1	0.3±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.3±0.1	0.3±0.1
Eosinophil's ($\times10^9$/L)	0	0	0	0	0.1±0.1	0.1±0.1	0.2±0.1	0.2±0.3

The value expressed as Mean±SD value with different alphabetical superscripts are significantly different at P<0.05 as compared to control.

Table: Effect of graded doses of hexane leave extracts of *Leptadenia hastata* on the serum biochemical parameters of rats (n=5).

Parameters	Control	-ve Control	+ve Control	100mg/kg	200mg/kg	300mg/kg	400mg/kg	500mg/kg
Total protein (g/L)	7.6±0.2	5.3±0.2	7.5±0.2	4.2±0.1[a]	7.4±0.1[b]	7.6±0.1	7.6±0.2	7.6±0.3
Albumin (g/L)	3.0±0.2	2.4±1.3	3.0±0.1	2.8±0.3	2.9±0.2	3.0±1.2	3.1±0.1[a]	3.0±0.3
Globulin (g/L)	4.2±0.2	3.4±2.0	4.1±2.3	4.0±0.1	3.9±3.4	4.1±1.0	4.2±0.3	4.3±0.1
ALT (U/L)	115.0±1.3	110±1.2	113.5±3.4	113.1±1.2	112.0±1.3	115.2±0.1	116±1.2	115.3±0.3
AST (U/L)	530.0±1.6	505±2.3	527.3±0.1	520.0±1.2	525.0±2.3	530.0±2.3	529±2.0	531.0±2.3
ALP (U/L)	240.0±1.4	225±0.1	238±1.5	240.0±0.2	239.5±0.1	239.6±2.4	240.1±0.3	240.3±0.1
Total bilirubin (µmol)	0.4±0.1	0.1±2.1a	0.4±2.3	0.3±0.2	0.3±0.3	0.4±2.3	0.4±0.3	0.4± 0.1
Conj. bilirubin (µmol)	0.2±0.1	0.1±2.1	0.2±0.3	0.17±0.1	0.2±0.2	0.2±0.1	0.3±2.0	0.3±3.2
Unconj.Bilirubin (µmol)	0.3±0.02	0.2±0.2	0.19±2.1	0.28±0.02	0.3±0.05	0.3±0.07	0.3±0.07	0.4±2.0[d]

The value expressed as Mean ± SD value with different alphabetical superscripts a b c and d are significantly different at P<0.05 as compared to control.

DISCUSSION

The inhibitory action of indomethacin on prostaglandin synthesis coupled with free radicals' formation has been critical biochemical events in the pathogenesis of gastric ulceration.[24,26] The understanding of these events might be of utmost relevance in designing new antiulcer drugs. With the inherent adverse side effects and considerably high cost of synthetic drugs, exploiting natural products of plant source which are believed to be non-toxic, efficacious and affordable will be most appropriate in the treatment of gastric ulcer. Ethanopharmacolgy is rapidly gaining grounds in sustaining human health and in the prevention of certain diseases like gastric ulcer resulting from drug toxicity.[26,27] This has been ascribed to possession of phytonutrients with excellent antioxidant properties that play significant roles in managing toxicity related disorders. Interestingly, studies have revealed the presence of some of these bioactive principles in *Leptadenia hastata* as well as reported them to promote good health.[18,19,20,21,3] In this study, we have also specifically quantified the heamatological and biochemical effects of the leaf extracts on indomethacin-induced ulceration rats. The measurement of aspartate transferase (AST) and alanine amino transferase (ALT) are two of the most common tests used in investigating hepatic integrity. They are widely distributed throughout the body and participate in body metabolism. They are found in the body organs, most commonly in the liver and kidney. The result in table 2 has shown little or no negative effects on the level of the heamatological and biochemical parameter when compared with the control.

The pH gives an idea of the level of acidity and volume of gastric secretions. Low pH value is a manifestation of decreased hydrogen ion concentration in gastric juice. This has been linked to pathogenesis of ulcer and gastric damage in experimental animals,[29,25] and has also attributed gastrointestinal injury to eroded mucin content. The erosion is facilitated by onslaughts of both internal (pepsin and oxidants produced in the gastric lumen) and external (drugs and chemicals) aggressive agents on mucosal epithelia. In the present study, the significant increase in ulcer index and gastric volume following oral administration of indomethacin in the ulcerated rats may be attributed to either free radicals' formation or inhibition of prostaglandin synthesis. Decreased prostaglandin level has been attributed to impaired gastro protection and increased gastric acid secretion which are important events in the etiology of mucosal ulceration. This agrees with the reports of Bech[30,28] and Muhammed[31] where indomethacin was reported to have caused alterations in gastric secretions of rats. Conversely, pretreatments with *Leptadenia hastata* n-hexane extracts significantly reduced these parameters. A combination of events was noticed after various extract administration including release of preformed mucus, wound retraction and re-epithelialization is observed on the histopathology (slide number 1,2,3) in ulcer-healing process after indomethacin injury which agrees with the report of.[22,32] Besides the extracts provide significant buffering capacity for the neutralization of luminal acid, and enhances the mucus which offers protection against both endogenous aggressors and exogenous gastro toxic agents such as indomethacin, thereby enhancing the rate of local healing process as reported by Alanko.[4]

In this study, the increased pepsin activity coupled with decrease in mucin secretion in the indomethacin-ulcerated rats indicated altered hydrophobicity and reduced protective ability of the mucosal membrane against hemorrhagic erosion, thus, resulting in tissue damage. This implied decreased ability of the gastric mucosa to withstand the offensive onslaught of indomethacin. Besides presence of extract antioxidant action that protects the mucus layer and arrests ulcer pro-aggression, drugs that increase the synthesis and secretion of gastric mucus would accelerate gastric ulcer healing. Pretreatment with *Leptadenia hastata* extracts however, facilitated ulcer healing process, which is associated increase in weight as was reported by Abubakar *et al.*,[1] that the plant was used as vegetable by many African populations and medicine due to its nutritive and therapeutic properties, this was confirmed by Umaru *et al.*,[35] in their studies that the plant contained substantial amount of linoleic and α-linoleic acids whereas the leaves are rich sources of protein, calcium and zinc This in turn can increases the weight and encouraged speedy wound healing of the ulcerated areas of the mucosal epithelia and shielded the gastrointestinal membrane, thus putting an end to the

effects of the influence of indomethacin in the ulcerated rats as reported by Naito.[32] The ulcer indices of mucosa epithelia cells was prominently displayed from 100mg/kg to 500mg/kg in a chronological order. However, extracts at 300 and 500mg/kg/bwt per dose, depicts a better ulcer healing capacity and is compared favorably well with omeprazole.

It was also reported that indomethacin decreases antioxidant enzymes (SOD, CAT and GST) activity in rat stomach thereby inducing gastric ulceration.[33] The protection observed by the aqueous leaf extracts of *Leptadenia hastata* against indomethacin induced ulcer rats may be linked to their beneficial medicinal attributes. These include ability to scavenge free radicals and regulate mucosal membrane permeability thereby countering the effect of indomethacin on gastric acid secretion as reported by Inas,[25] Muhammed,[31] and Gege-Adebayo.[34] This shows that *Leptadenia hastata* extracts has gastro protective potentials against indomethacin ulcerated rats.

CONCLUSION

This study clearly demonstrated that oral administration of the crude extracts of *Leptadenia hastata* has positive effects on ulcer and potential Inhibitory action of indomethacin on prostaglandin synthesis coupled with free radicals' formation which has been a critical biochemical event in the pathogenesis of gastric ulceration. It's also nontoxic potential on the biochemical and haematological parameters at dose 100 - 500mg/kg/bwt. Thus, it's safe to conclude that the n-hexane extracts of the leaves possess antiulcer properties. Hence the plant is safe to be used as antiulcer since there was no abnormality in both the biochemical and haematological parameters.

SIGNIFICANT STATEMENT

The result of the study indicate that the extract was effective in ulcerogenic control in all the ulcer induced groups at 100-500mg/kg/bwt which was claimed by herbal practitioners that the plant contains some bioactive compounds effective for wound healing.[40]

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