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EVALUATION OF ANTI-ULCER ACTIVITY OF EXTRACT AND FRACTIONS OF *DIALUM GUINEENSE* ON INDOMETHACIN-INDUCED ULCER MODEL

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Keywords:

Anti-ulcer, *Dialium guineense*, Indomethacin, Peptic ulcer, Phytochemical

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ABSTRACT: Background: Peptic ulcer disease (PUD) is an injury of the duodenal mucous membrane that normally occurs due to an imbalance between the aggressive and the defensive factors. It accounts for an estimated lifetime prevalence of 5-10% globally. **Aim:** To evaluate the anti-ulcer effect and phytochemical constituents of extract and fractions of the leaves of *D. guineense* using an indomethacin-induced ulcer model. **Methods:** The powdered leaves were cold macerated in 95% v/v of methanol for 48 h. The extract was partitioned successively using ethyl acetate (EtOAc), and n-butanol to obtain their respective fractions. Phytochemical screening was conducted using validated methods. An acute toxicity study was carried out by modified Lorke's method. The anti-ulcer study was conducted using an indomethacin-induced rat model. **Results:** The yield of the extract was 4.1% w/w while EtOAc and *n*-butanolfractions yielded 0.36 and 0.93% w/w respectively. There was presence of tannin, flavonoids, saponins and terpenoids in the methanol extract. Acute toxicity study indicated no mortality or any behavioural changes even at an oral dose of 5000 mg/kg of a mouse. The extract (400 mg/kg) demonstrated the best anti-ulcer activity ($p < 0.05$), while the 200 mg/kg extract showed comparable anti-ulcer activity to the standard drug. The results further revealed that 400 mg/kg EtOAc fraction elicited the highest curative effect of 66.7%. **Conclusion:** The extract and fraction of *D. guineense* leaves displayed a significant anti-ulcer activity and may serve as a potential source of new lead compounds in the treatment and management of ulcers.

INTRODUCTION: Peptic ulcer disease (PUD)) is a recurring disease and has continued to be associated with high healthcare costs resulting from high morbidity and mortality rates despite the decrease in the incidence in recent years [1].

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The major risk-risk factors are the use of non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection. In most cases, it is presented with no symptoms.

However, complications such as perforation or stenos is, dyspepsia and upper stomach bleeding may occur [2, 3]. The incidence of peptic ulcer complications, especially in developed countries has decreased in recent decades according to epidemiological data. This decline has been attributed to a decrease in the prevalence

of *Helicobacter pylori* infection [4]. A rough assessment shows that about 5–10% of the population will have a PUD during their lifetime and a 0.3 to 1.9% yearly incidence [5, 6]. Also reported that 10% of the world's population is affected by chronic PUDs which predominantly affect both the stomach and the duodenum.

Herbal Medicine practice has been dated back to antiquity from generations in handling pathology. Naturally occurring compounds in their multiples exhibit synergistic actions as antiviral, antibacterial, anti-ulcer, antibacterial, antiprotozoal and antioxidant [7]. Traditional African medicine (TAM) has made a notable important contribution to the primary health care needs of Nigerians. More than 80% of Africans receive their healthcare needs from TAM [8]. It was also noted that certain medicinal plants are exceptional for their ethnobotanical and ethno-pharmacological relevance in healthcare [6]. About 360 plants have been reported as medicinal plants used traditionally for the management of gastric ulcers [9].

Dialium guineense, commonly known as Velvet tamarind, belonging to the family Fabaceae is reputed for its food and nutritional value throughout Africa. The medicinal properties of *D. guineense* are also well known in TAMs. Almost all the morphological parts of *D. guineense* is enriched with medicinal potential in management of diseases such as stomach disorders and hypertension [1, 10]. The stem and bark are also used as remedies for severe cough, toothache, bronchitis, ulcer, haemorrhoid, fever and jaundice. The Esan people of Edo State uses the stem bark as chewing stick for oral hygiene and stomach aches [11]. The saponins enriched extract from the fruit pulp was found to possess antimicrobial activities against methicillin-resistant *Staphylococcus aureus* [10].

Dalium guineense has been in use in folkloric medicine for the treatment of various diseases and they are well documented. The medicinal potentials discovered with this plant include anti-hypertensive, analgesic, anti-diarrheal, anti-hepatotoxic, antimicrobial, antioxidant and antipyretic [13, 14, 15, 16]. The pulp has been reported to have a protective effect against stomach ulcers [17]. In folk medicine, the fresh leaves can also be squeezed, and the squeeze applied to wounds [18]. Undocumented reports in many African populations suggest that the leaves are boiled, and the filtrate is used in the treatment of stomach ulcers. Therefore, this study was designed to evaluate the anti-ulcerogenic effect of extract and fractions of *D. guineense* leaves in an experimental rat model.

MATERIALS AND METHODS:

Experimental Rats: Healthy Albino rats (120 -170 g) of either sex, obtained from the Faculty of Veterinary Medicine, University of Nigeria Nsukka, were used in the study. They were acclimatized to animal house conditions, fed a standard laboratory diet and safe drinking water *ad libitum*. Each cage contained 5-7 rats with the cages having raised floors of wire mesh. All studies were conducted following the 8th edition guideline for the National Research Council [19] for the care and use of laboratory animals.

Collection and Identification of the Leaves: The leaf of the *D. guineense* was collected between 9 and 10am in November 2022 from the Enugu State University of Science and Technology staff quarter Agbani Nigeria. The plant was identified and authenticated by Mr. Patrick obi, a taxonomist at the Department of Pharmacognosy of the University and a voucher specimen (ID: FP/Cog/17038) was deposited in the herbarium of the department.

Extraction of *D. guineense* Leaves: The leaves were air-dried and reduced into a coarse powder using a mechanical grinder. About 835 g of the course leaf was macerated in 4.2 L of methanol for 48 h in a tightly stopped solvent bottle. The mixture was vigorously agitated at regular intervals. After 48 h, the mixture was filtered through a muslin cloth and then filtered through a separating funnel plugged with cotton wool. The filtrates were evaporated to dryness under vacuum using a rotary evaporator and water bath to obtain gummy concentration. The extract of the leaf of *D. guineense* (MED) was stored in the refrigerator at 4 °C.

Partition of MED: The dried MED (34.71 g) was dispersed in 200 ml of 10 % aqueous methanol and partitioned successively with equal volumes of ethyl acetate (EtOAc) and butanoyl (BuOH) using

a 1 litre separating funnel [20]. The partition obtained from each solvent was decanted and concentrated at reduced temperature and pressure using a vacuum rotary evaporator to furnish dried fractions of ethyl acetate and butanol.

Phytochemical Screening of Extract and Fractions: The MED, butanol and ethyl acetate fractions were qualitatively assessed for the presence of major phytochemical constituents such as alkaloids, tannins, glycosides, steroids, terpenoids, saponins, and flavonoids using standard analytical phytochemical screening procedures as described by Habourne [21].

Acute Toxicity Study: The acute toxicity was evaluated in compliance with Lorke's method [22]. The study was performed in two stages using 12 mice. The first stage involved nine mice fasting for 24 h with free access to water and divided into 3 groups (n = 3). Groups 1, 2 and 3 mice were treated with a single dose of 10, 100 and 1000 mg of MED/kg body weight of mice respectively, to possibly determine the range of doses of MED eliciting any toxic effect. Specific doses of1600, 2900 and 5000 mg of MED per kg of mouse were administered to one mice per dose respectively in the second stage of the test. The second phase was to further determine the exact LD_{50}. The mice were observed frequently for 24 h for signs of change in behaviour or death. The least lethal and highest safe doses were used to calculate the median lethal dose (LD_{50}) of MED.

Anti-ulcer Activity Evaluation: Fifty-six albino rats were randomly divided into eight groups of seven rats reaching different cages labelled groups 1 - 8. The rats were fasted for twenty-four hours with free access to water before the ulcer induction. To induce gastric ulcers, the rats were given 30 mg of indomethacin per kg body weight of ratorally. After six hours of treatment, two rats were randomly sacrificed from each group to confirm gastric ulceration [23]. The rats were administered with omeprazole (standard control) and MED (200 and 400 mg). The MED and omeprazole were administered once a day in all the experimental groups. On the 7th day, 7 hours after the last treatment, two rats from each group were randomly sacrificed by cervical dislocation. Their abdomen was opened through a midline incision using a dissecting kit and the stomachs were incised along the greater curvatures. The grouping of the rats and treatments were as follows:

Group 1 received 30 mg indomethacin per kg rat (negative control).

Group 2 received 30 mg indomethacin + 20 mgomeprazole per kg rat (positive control).

Group 3 received 30mg indomethacin + 200 mg MED per kg rat.

Group 4received 30 mg indomethacin + 400 mg MED per kg rat.

Group 5received 30 mg indomethacin + 200 mg BuOH fraction per kg rat.

Group 6received 30 mg indomethacin + 400 mg BuOH fraction per kg rat.

Group 7received 30 mg indomethacin + 200 mg EtOAc fraction per kg rat.

Group 8received 30 mg indomethacin + 400 mg EtOAc fraction per kg rat.

Determination of pH: The stomach fluid content of the ulcer-induced rat was washed with normal saline into a conical flask. An aliquot of gastric juice (1 mL) from the rat-induced ulcer was diluted with distilled water (1 mL) and the pH of the solution was measured using a pH meter [24].

Determination of Free Acidity: A 1 mL of gastric juice was mixed with phenolphthalein indicator (3 drops) in a 100 mL conical flask. The mixed solution was then titrated with 0.25 N NaOH to the equivalence point marked by colour change of pink to yellowish orange. The average volume of alkali added to achieve the end point was noted and the free acidity was calculated from the $N_a V_a = N_b V_b$ [24]

Determination of Total Gastric Acidity: Using the phenolphthalein indicator, 1 mL of gastric juice was titrated against NaOH (0.1 mol/L^{-1}) until the endpoint denoting colourless to light pink was attained. The average volume of NaOH used was noted and the total acidity was calculated from Equation 1 as follows:

Total gastric acidity = (Volume of NaOH x Normality of NaOH) / (0.1 x 100 mEq per L) …..1

Determination of Ulcer Score and Ulcer Index: The stomachs of the animals were incised as previously described and rinsed with water to eliminate blood clots and other gastric contents and then examined by a magnifier lens (10X magnification) to determine the formation of ulcers. The number of ulcers was counted; ulcer score of 0 to 5 representing severity of no lesions, mucosal oedema, 1-5 small lesions (1-2 mm in size), > 5 small or intermediate (3-4 mm in size) lesions, > 2 intermediate lesions or 1 gross (> 4 mm in size) lesions or perforated lesions respectively, ulcer index (UI) and percentage curative were calculated from equation 2 and 3 [25, 26, 27].

Ulcer index (UI) = (Total ulcer score) / (Number of ulcerated rats) ……2

Ulcer curative (%) = (UI of untreated-UI of treated) / (UI of untreated) × 100….3

Statistical Analysis: The experimental data (ulcer indices, free and total acidity) were expressed as SEM and processed using one-way analysis of variance (ANOVA), followed by a 2-sided Dunnett post hoc comparison test and a $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION: Indomethacin-induced ulcer model is one of the ulceration models used in anti-uler activity screening in experimental rats [23, 28, 29]. Nonsteriodal anti-inflammatory drugs (NSAIDs) such as indomethacin are known to cause gastric ulcers especially when abused or chronically used. They are known to induce ulcers through several mechanisms such as lipid peroxidation, prostaglandin synthesis inhibition, neutrophil infiltration, oxidative mucosal damage as a result of increased production of reactive oxygen species as well as disruption of surface-active phospholipids on the mucosal surface [30, 31, 32]. Therefore, the significantly observed high ulcer score and ulcer index after oral administration of indomethacin in the experimental rats may be attributed to the enumerated mechanisms and underlines the suitability of the model in this study.

Extraction of *D. guineense* Leaves: The coarse sample (835 g) of *D. guineense* yielded a gummy resin of 4.12%w/w (34.71g) of MED on exhaustive extraction, which on successive partitioning in ethyl acetate and *n*-butanolyielded 0.36% w/w (3.0 g) and 0.93% w/w (7.8 g) of EtOAc and *n*-butanol fractions respectively. All the yields (%) were calculated based on the 835 g coarse sample. There is relatively higher polar phytochemicals than the non-polar components in MED which resulted from the ability of different solvents or solvent systems to extract or partition plant phytochemicals based on their polarity differences [33].

Phytochemicals Constituents of MED and its Fractions: The phytochemical screening revealed that MED, ethylacetate and *n*-butanol fraction of *D. guineense* leaves contained terpenoids, tannins and flavonoids **Table 1**. There was absence of alkaloids, cardiac glycosides and steroids in all the extracts tested. The saponins were partitioned exclusively into *n*-butanol while flavonoids were partitioned into the ethyl acetate. Tannins and terpenoids were detected in both solvent fractions.

TABLE 1: PHYTOCHEMICAL CONSTITUENTS OF *D. GUINEENSE* LEAVE

Phytoconstituents	MED	EtOAc	*n*-Butanol
Alkaloids	-	-	-
Flavonoids	+	+	-
Tannins	+	+	+
Terpenoids	+	+	+
Cardiac glycoside	-	-	-
Steroids	-	-	-
Saponins	+	-	+

(-) = absent; (+) = present

Phytochemical analysis of MED, EtOAc and n-butanol fractions of *D. guineense* leaves revealed the presence of tannins, flavonoids, saponins and terpenoids and absence of alkaloids and steroids. These findings were comparable to a report by Akpan [34], where the methanol extract of the leaf of *Dialium guineense* showed the abundance of flavonoids, saponins, tannins, terpenoids, anthraquinone and carbohydrates. In another study, saponins, phenolics, alkaloids, glycosides, flavonoids, tannins, steroids, anthraquinone, reducing sugar, carbohydrates and terpenoids were detected in the stem bark [35].

The presence of these phytochemicals justifies the importance of the plant as nutraceutical. Several studies on phytochemical identification and eventual isolation of bioactive molecules from *D. guineense* has been reported. Some steroidal saponins such as diocin, aferoside B, aferoside C and paryphyllin C have been isolated from the

seed. Similarly, a flavonoid glycoside was charaterized from the aerial part of the plant [36]. Additionally, a feroside A, B and C have also been isolated from the seed of *D. guineense*. Flavonoids which were also detected in the EtOAc soluble are known to possess anti-ulcer effects due to their anti-secretory, cytoprotective, antioxidant and anti-inflammatory properties [17, 37]. Saponins and triterpenoid-related compounds increase mucus production while tannins directly protect the outermost layer of mucosa and change the mucosa structure that can resist chemicals and mechanical injury [38]. The significant anti-ulcer effect of MED and fractions of *D. guineense* leaves may be associated with the presence of some active secondary metabolites like flavonoids, tannins, saponins and terpenoids [39].

Acute Toxicity of MED: The acute toxicity test showed that MED was not toxic and there was no sign of behavioural changes and physiological alterations in the experimental mice even up to the dose of 5000 mg of MED per mouse kg body weight. Safety of plant extract plays significant role in traditional medicine. The acute toxicity of *D. guineense* leaf extract did not reveal any sign of MED treatment-related toxicity or death in the two phases, signifying that the extract was safe. This level of safety could justify why it is edible and can be used for different health purposes [40].

Curative Effect of MED and its Fractions: The ulcer curative effect of *D. guineense* was measured by the ulcer indices estimated from the ulcer scores of 0 to 5. The effect of MED and its fractions on indomethacin-induced ulcers revealed that the treatments significantly suppressed gastric lesions in comparison with the controls. A dose-dependent decrease in ulcer lesions was observed as all the groups treated with MED (400 mg/kg) dose showed higher curative effects than the 200 mg/kg dose **Table 2**. The 400 mg of ethyl acetate (66.67%) showed a higher effect than the n-butanol (60%)

The effect of extract and fractions of *D. guineense* leaf on indomethacin-induced ulcer model showed that the extract was capable of arresting gastric lesions induced by indomethacin. The results also showed that a dose-dependent decline in ulcer index for both the MED and the fractions was obtained in all the treated groups similar with the observation for the standard control group. It was further observed that MED (400 mg/kg) elicited the highest antiulcer activity as it had the least ulcer index (0.80±0.37) closely followed by 400 mg/kg ethyl acetate with 1.00±0.32. This anti-ulcer activity of MED, EtOAc and *n*-BuOH fractions was in agreement with previous works [27, 41]. Of all the treatments, 200 mg/kg of EtOAc fraction resulted in the highest ulcer index of 1.80±0.20 and the least antiulcer activity. However, a high ulcer index was continually observed in the untreated (negative control) group up to the end of the treatment suggesting that the induced gastric ulcer could not resolve. The MED had better activity compared to the fractions as the group treated with the 400 mg/kg crude extract fraction recorded the highest percentage curative of the gastric mucosa (73.3 %). Plant extract has shown to have better activities than the fractions in some previous reports, probably due to synergism in activity [26, 41].

TABLE 2: CURATIVE EFFECT OF MED AND ITS FRACTIONS

Group	Ulcer Index		Curative (%)
	Pre-induction	Post-treatment	
1	3.00±0.00	3.00±0.32	0.00
2	3.00±0.00	1.40±0.24*	53.33
3	3.00±0.00	1.40±0.24*	53.33
4	3.00±0.00	0.80±0.37*	73.33
5	3.00±0.00	1.80±0.20	40.00
6	3.00±0.00	1.00±0.32*	66.67
7	3.00±0.00	1.60±0.24	46.67
8	3.00±0.00	1.20±0.20*	60.00

Data expressed as mean ± SEM. Significant difference is set at *$p < 0.05$ is significant compared with group 1. One-way, ANOVA followed by Dunnett post hoc comparison

Effect of MED and its Fractions on pH: The gastric fluid content of the ulcer-induced rats was washed with normal saline, diluted with distilled water and the pH recorded with a pH meter. There was a significant rise in the pH of the gastric content in all the treated rats **Table 3**. The n-butanol fraction caused the highest upsurge from 2.23 at post-induction to 5.71 after treatment with a 200 mg/kg dose.

The effect MED and fractions of *D. guineense* on the pH of gastric content of indomethacin-induced ulcer in rats. The results showed that all the rats in all the treatment groups displayed comparatively low pH post ulcer induction denoting that the

stomach was pH acidic. However, it was observed that after the 14th day of MED, EtOAc and BuOH fractions treatment, a dose dependent rise in the gastric acidity was noticed in all the treated groups except for the groups that received the EtOAc fraction where the increase in pH was not dose-dependent.

TABLE 3: EFFECT OF *D. GUINEENSE* ON PH OF STOMACH FLUID CONTENT

Group	pH		ΔpH (%)
	Post-induction	Post-treatment	
1	2.88±0.34	2.55±0.24	-11.46
2	2.42±0.08	5.34±0.38*	120.66
3	2.68±0.05	5.60±0.37*	108.96
4	2.78±0.22	6.19±0.51*	122.66
5	2.93±0.29	6.50±0.26*	121.84
6	2.89±0.33	6.12±0.32*	111.76
7	2.23±0.09	5.71±0.38*	156.06
8	2.39±0.16	6.05±0.33*	153.14

Data expressed as mean ± SEM. Significant difference is set at *p < 0.05 is significant compared with group 1. One-way, ANOVA followed by Dunnett post hoc comparison

The results also further revealed that group that received 200 mg/kg ethyl acetate had the highest pH (6.50±0.26), than 400 mg/kg of the EtOAc fraction with mean pH of 6.19±0.51. There was a significant decline ($p < 0.05$) in the mean potential of hydrogen (pH) of all the rats treated with *D. guineense* and the standard control when compared to the untreated (negative control) group.

Effect of *D. guineense* on free and Total Gastric Acidity: The stomach fluid content of the ulcer-induced rats was washed with normal saline, the volume of NaOH added to neutralize the gastric fluid was noted and the free acidity was calculated.

All the treatments caused a significant decrease ($p < 0.05$) in the free acidity of the gastric fluid **Fig. 1**. The MED and ethyl acetate fraction caused a dose-dependent decline while the 200 mg/kg dose of *n*-butanol fraction elicited a higher decrease in free acidity than the 400 mg/kg dose. All the treatments caused a dose-dependent decrease in the total acidity of the gastric content. The ethyl acetate fraction elicited a decline compared with the MED and the standard **Fig. 2**.

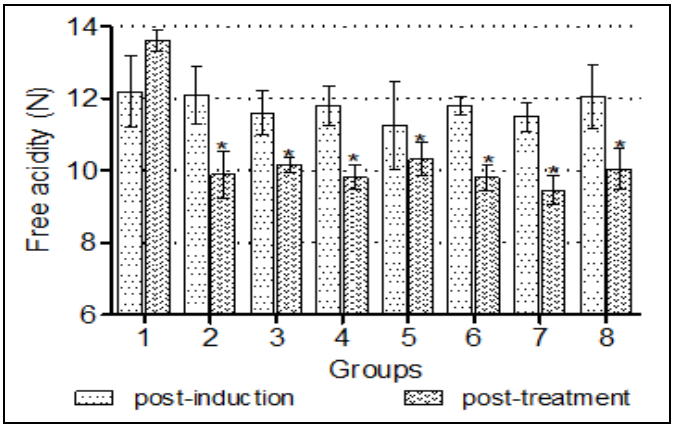

FIG. 1: EFFECT OF *D. GUINEENSE* ON THE FREE GASTRIC ACIDITY

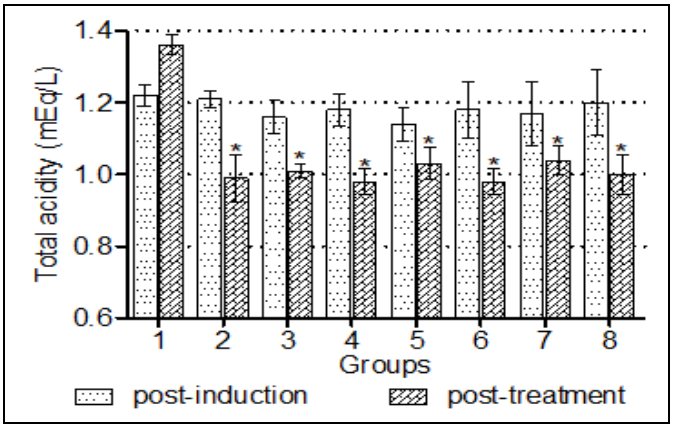

FIG. 2: EFFECT OF *D. GUINEENSE* ON THE TOTAL GASTRIC ACIDITY

CONCLUSION: The crude methanol extract and fractions of *D. guineense* leaf exhibited varying degrees of curative effect on indomethacin induced gastric ulcer in a dose dependent manner. It was seen to possess significantly greater anti-ulcer activity than the standard drug. Though the presence of phytochemicals in the extract and fractions of *D. guineense* leaf was confirmed, secondary metabolites responsible for these activities were not identified.

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