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The *In Vivo* Antiulcer Activities of the Combined Effect of Unripe *Musa Paradisica* Peel and *Carica Papaya* Leaf Extract

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Abstract

The study evaluated the antiulcer potential of the combined extracts of *Musa paradisiaca* peel and *Carica papaya* leaf in male Wistar rats. Twenty-four rats (110–160 g) were fasted for 18 hours and divided into six groups (n = 4) based on body weight. Groups A–F received distilled water (2.0 ml/kg), cimetidine (50.0 mg/kg), *Musa paradisiaca* extract (400.0 mg/kg), *Carica papaya* extract (400.0 mg/kg), and the combined extracts (400.0 mg/kg), respectively. Distilled water and cimetidine served as negative and positive controls. After one hour, all groups except group A received indomethacin (60.0 mg/kg, orally) to induce gastric ulceration. Eight hours later, the animals were sacrificed, and their stomachs were examined for ulcer index, gastric volume, pH, total and free acidity, Na^+/K^+ ATPase activity, and pepsin activity. These parameters provided a comprehensive assessment of gastroprotective efficacy. The extracts significantly mitigated indomethacin-induced ulceration by reducing ulcer index and gastric acidity, enhancing antioxidant enzyme activity, and suppressing inflammatory responses. Notably, the combined extract exhibited superior and synergistic gastroprotective effects compared to the individual extracts.

Keywords: *Musa parasidiaca*, *Carica papaya*, antiulcerogenic, peptic ulcer, indomethacin, ulcer index

Introduction

The gastrointestinal (GI) tract is one of the most essential organ systems responsible for food digestion, nutrient absorption, and maintaining physiological balance in the human body. Among the disorders that affect this system, *Peptic Ulcer Disease* (PUD) stands out as one of the most prevalent and debilitating conditions, particularly in developing nations where poverty, malnutrition, and inadequate healthcare infrastructure remain widespread (Sung *et al*., 2024). Peptic ulcer disease continues to be a global health concern, affecting about 10% of the world's population and posing a significant challenge to public health due to its impact on patients' quality of life (Havens *et al*., 2018). If left untreated, ulcers can penetrate the stomach's muscular layers, leading to severe mucosal damage; over time, these lesions may progress to chronic inflammation, bleeding, or even perforation (Tarnawski, 2005; Wang *et al*., 2018).

The precise pathogenesis of ulcers is multifactorial. It arises from an imbalance between some offensive and defensive factors within the stomach. Offensive factors encompass endogenous agents such as hydrochloric acid, pepsin, lipid peroxidation, and reactive oxygen species (ROS), as well as exogenous factors such as Helicobacter pylori infection, stress, smoking, excessive alcohol intake, and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) (Weltermann *et al*., 2021). Defensive factors comprise prostaglandins (PGs), mucin secretion, the mucus-bicarbonate

barrier, nitric oxide (NO), growth factors, mucosal blood flow, cellular regeneration, surface phospholipids, and endogenous antioxidants.

The primary therapeutic intervention for gastric ulcers is the inhibition of aggressive factors, combined with the stimulation of defensive factors (Wang *et al.*, 2018). The therapeutic goal in the management of ulcers is the control of gastric secretion using antacids, H_2 receptor blockers (ranitidine, cimetidine, famotidine, nizatidine, etc.), anticholinergics like pirezepin, telezipine, or proton pump inhibitors (lansoprazole, omeprazole, etc.), in addition to antibiotics used to eradicate H. pylori (Scally *et al.*, 2018). The prevention or cure of peptic ulcer is one of the most challenging problems in medicine because peptic ulcer therapy faces drawbacks, and most of the drugs currently available in the market show limited efficacy against peptic ulcer diseases and are often associated with severe side effects (Prabha *et al.*, 2011). The traditional treatment approaches for peptic ulcers primarily focus on suppressing acid secretion, eradicating *Helicobacter pylori*, and protecting the mucosa. However, these methods sometimes fall short, prompting a growing interest in complementary or alternative therapies, notably those involving plant-derived bioactive compounds (Boakye-Yiadom *et al*., 2021). Medicinal plants exert antiulcer effects through diverse, often synergistic mechanisms, including inhibition of gastric acid secretion, antimicrobial activity, and antioxidant activity.

Musa species, a tropical plant, has been consumed by humans for many years as nutritious and delicious fruits (Orhan *et al.*, 2021). Different species of Musaceae have been discovered. These include Musa paradisiaca (plantain), now called Musa acumintum (Banana), Musa ornate, Musa aurantiaca, etc (Ajoy *et al.*, 2011). Plantain is one of the oldest and best-known fruits of the world. It is a delicious, seedless fruit available year-round at an affordable price. It is a very hygienic fruit as it comes in a green-proof package. Its thick covering (peels) provides an excellent protection against bacteria and contamination (Raghu *et al.*, 2012). Generally, Musa species (including bananas and plantains) are herbaceous perennial plants (Okolle *et al.*, 2009). Musa paradisiaca (family: Musaceae), commonly known as plantain, is a perennial tree-like herb widely distributed in the tropics (Adinortey *et al.*, 2011). Their herbaceous nature results from the absence of a woody part after fruit ripening. All Musa species range between 2 to 9 meters in height (Okolle *et al.*, 2009).

Plantain (*Musa paradisciaca*) is used in herbal medicine to treat peptic ulcer disease. The usefulness of Musa paradisciaca in the gastric mucosa is due to the multiple active compounds. A natural flavonoid from the unripe plantain pulp, lecucoyanidin, protects the gastric mucosa from erosion (Mohammad *et al.*, 2011). Dried unripe plantains have been shown to possess antiulcerogenic activity and to be effective both as a prophylactic treatment and in healing aspirin-induced ulcers. In contrast, ripe plantain fruits were inactive (Orhan *et al.*, 2021).

*Carica papay*a (C. papaya), popularly known as pawpaw, is a typical example of a plant with beneficial characteristics as an alternative medicine. It belongs to the small family Caricaceae and is a significant fruit crop cultivated in tropical, sub-tropical, and temperate zones such as Australia, Brazil, China, Hawaii, Malaysia, Nigeria, and India (Nguyen *et al.*, 2013). Both ripe and unripe stages of papaya are edible and can be served in social gatherings as a salad or wine (Amin *et al.*, 2019). The use of *C. papaya* in folk medicine is made possible by the phytochemicals present in the plant, which include tannins, steroids, terpenoids, saponins, phenols, flavonoids, ferric reducing antioxidant properties (FRAP), pro-anthocyanidins, alkaloids, anthraquinones,

and cardiac glycosides (Ghaffarilaleh *et al.*, 2019). Preliminary phytochemical studies by Amazu *et al*. (2010) showed an abundance of alkaloids and average glycosides in the methanol extract of *C. papaya* seeds. The pulp contains three essential vitamins: A, C, and E, with potential antioxidant properties. Research has shown the presence of magnesium, potassium, copper, zinc, B-complex vitamins, such as pantothenic acid and folate, and dietary fiber (Amin *et al.*, 2019). Papaya also contains the enzyme papain, which increases gut transit time and is also used to ameliorate traumas, allergies, and skin lesions (Amin *et al.*, 2019). Studies have also shown the presence of proteolytic enzymes (chymopapain) with antiviral, antifungal, and antibacterial properties (Santana *et al.*, 2019).

C. papaya is a popular plant utilized in ethnomedicinal practices with diverse therapeutic applications across several nations. Decoctions from different parts of the plants have shown unique curative potency in traditional medicine (Nguyen *et al., 2016;* Nafiu and Rahman, 2015). Nafiu *et al*. (2016) reported that producers of herbal medicines use *C. papaya* as a principal constituent of their produce due to its significant potency in treating diseases. In Nigeria, *C. papaya* extracts are used to treat diabetes and malaria (Gbolade, 2022). Findings from various studies revealed that decoctions of *C. papaya* are used to ameliorate ulcers.

Methods

Chemicals, reagents, and equipment.

All chemicals and reagents used for this study were of analytical grade. The equipment included: a Magnetic stirrer, a weighing balance, metal cages, measuring cylinders and beakers, and syringes.

Plant collection and extraction

Fresh Unripe mature pulps of *Musa paradisiaca* (plantain) and *Carica papaya* (pawpaw) leaf were obtained from a farm in Abraka Town, Ethiope East Local Government Area, Delta State of Nigeria. The plants were identified and authenticated by a taxonomist at the Department of Botany, Delta State University, Abraka, Nigeria, with the voucher numbers DELSUH-068 and DELSUH-127 for Musa paradisiaca and Carica papaya, respectively. The unripe plantain was washed thoroughly with clean running water, peeled, sliced, and air-dried to constant weight. In a similar vein, the *Carica Papaya* leaf was washed thoroughly with clean running water and was air-dried to constant weight. The dried plant materials were ground into fine powder (flour). The powdered material, weighing 500 g, was separately soaked for 3 days using 2.5 L of solvent (methanol). Each extract was filtered, and the filtrate was concentrated in vacuo at 50 °C. The extract was stored in a refrigerator at 4 °C until needed.

Assessment of Antiulcer Effect of Plant Materials and Indomethacin

This was conducted on individual plant powders and their combinations to determine the combination of plant extracts with the best antiulcer effect. This study employed twenty-four (24) male albino rats that were randomly distributed into six (6) groups (A-F) of four animals per group.

In-vivo anti-ulcer study

Indomethacin-induced ulcer study

Twenty-four male Wistar rats (110 to 160 g) were starved for 18 h and grouped into six groups (n = 4) according to their weights. Groups A, B, C, D, E, and F were treated orally as follows:

Experimental Design:

Rats in each group specifically received (orally) the following treatment:

Group A (normal control): received 2.0 ml/kg body weight of distilled water

Group B (negative control): was given indomethacin 60mg/kg body weight

Group C (positive control): received 50 mg/kg body weight of cimetidine
Group D: received 200mg/kg of unripe Plantain (Pl) extract.
Group E: received 200mg/kg of unripe Pawpaw (Pw) extract.
Group F: received 200mg/kg of combined Pl +Pw extract.

Quantification of Ulceration:
Ulceration in indomethacin–treated rats was quantified using the procedure outlined by Szabo and Hollander (1985). Mean ulcer score for each animal was used to express ulcer index (U.I.), and the percentage inhibition against ulceration was determined using the expressions:
Ulcer Index (U.I) = [Ulcerated area/total stomach area] x 100.
% Ulcer inhibition = [(U.I. in control - U.I. in test) x 100] / U.I. in control.
Ulcer scores and descriptive remark (Szabo and Hollander, 1985).

Score	Remark
0	Almost normal mucosa
1	Vascular congestion (one or two lesions)
2	Severe lesions
3	Mucosa full of lesions

Acute Toxicity (LD50) Determination.
This was conducted using a combination of unripe Plantain peel and pawpaw leaf (Pl+Pw) extracts to establish the toxicity level. The method proposed by Lorke (1983) was employed.
This method has two phases: 1 and 2.
Phase 1
This phase requires nine animals. The nine animals were divided into three groups of three animals each. Each group of animals was administered different doses of the test substance (10, 100, and 1000 mg/kg). The animals were observed for 24 hours to monitor their behavior and assess the likelihood of mortality.
Phase 2
This phase involves using three animals, which were distributed into three groups of one animal each. The animals were administered higher doses (1600, 2900, and 5000 mg/kg) of the test substance and then observed for 24 hours for behavioral and mortality endpoints (Lorke, 1983).
The severity of behavioural changes was graded as mild, moderate, or severe based on standard OECD toxicity observation criteria. Mild changes were characterised by a slight reduction in activity and subtle behavioural alterations without functional impairment. Moderate changes were identified by lethargy, partial loss of coordination, and fatigue. In contrast, severe changes were defined by intense motor impairment, writhing responses, marked reduction in appetite, and significant neurologic disturbances.

Sample Collection:
At the end of the treatment period, the stomach contents of anesthetized animals were collected and analyzed for total acidity, free acidity, pepsin activity, and pH.
Determination of Total and Free Acidity
Free and total acidity were determined according to the method described by Reddy *et al*. (2012).
After centrifuging the gastric contents, 1 mL of the supernatant was transferred to a conical flask and diluted to 10 mL with distilled water. Topfer's reagent (2 drops) was added to it, and titrated with 0.01N NaOH to the yellow endpoint. Then, two drops of phenolphthalein were added, and the titration continued till the phenolphthalein endpoint was reached. The amount of 0.01N NaOH required to titrate to the methyl yellow endpoint was used to determine the amount of the free acid present. The amount of 0.01N NaOH required to titrate from the beginning to the phenolphthalein end point was used to determine the total acid present in the sample. Acidity was calculated using the following formula and expressed in mEq/L.

Acidity = [Volume of NaOH x Normality x 100 mEq/L] / 0.1

Determination of Pepsin Activity:

Pepsin activity was determined according to the methods proposed by Debanth *et al*. (1974). One milliliter (1ml) of diluted gastric juice was mixed with 0.5ml of 2% hemoglobin solution in 0.06 M Hydrochloric acid and incubated for 20 minutes at room temperature. Then, 0.6M ice-cold Trichloroacetic acid was added to the setup and centrifuged at 4000 rpm for 10 minutes. The supernatant (1.0 ml) was mixed with 1.0 ml of alkaline copper sulfate solution and 0.5ml of dilute Folin-Denis reagent, then incubated for 30 minutes at room temperature. The absorbance of the sample was measured by spectrophotometry at 610 nm. Pepsin activity was determined from a standard curve.

Evaluation of gastric pH

The gastric PH was determined by the method of Bigoniya and Singh (2014). The gastric content was collected, centrifuged at 1000 r/min for 10 min at 4°C, and the supernatant was used to measure pH with a digital pH meter, as suggested by Bigoniya and Singh (2014). The values obtained were recorded for statistical analysis.

Sodium potassium ATPase

The activity of Na^+/K^+-ATPase was determined using a modified colorimetric inorganic phosphate (Pi) liberation method, as described by Forbush et al. (1983) and Xie *et al*. (1989). Gastric mucosal tissues were rapidly excised, washed in ice-cold physiological saline to remove debris and blood, blotted dry, and weighed. The tissues were homogenized (10% w/v) in an ice-cold homogenization buffer consisting of 50 mM Tris–HCl (pH 7.4), 250 mM sucrose, and one mM EDTA using a Teflon-glass homogenizer. The homogenate was centrifuged at 1,000 × g for 10 min at 4 °C to remove nuclei and cell debris. The supernatant was collected and further centrifuged at 10,000 × g for 20 min at 4 °C to obtain the post-mitochondrial fraction used for enzyme assays. Protein concentration was determined using the Bradford method (Bradford, 1976).

Statistical Analysis

Obtained values were expressed as ± mean standard deviation (MSD) and analysed statistically using one-way analysis of variance (ANOVA) at a probability less than 0.05 (i.e, $p<0.05$), followed by Turkey's multiple comparison tests.

Results

Antiulcer potentials of methanol extracts of individual and binary combinations of unripe *Musa paradisiaca* peel and *Carica papaya* leaf (*in vivo* indomethacin model)

Ulcer indices, percentage ulcer inhibition, gastric juice variables, and pepsin activity are shown in Table 1. The principal finding was that indomethacin (Group 2) produced a marked increase in the mean ulcer index (20.25 ± 2.87) compared with the normal control (0.00 ± 0.00). Cimetidine (Group 3) and the combined *Musa paradisiaca* + *Carica papaya* extract (Group 6) produced substantial protection: ulcer index in Group 3 was 4.50 ± 3.42 and in Group 6 was 5.25 ± 3.40, both significantly lower than Group 2 ($p < 0.01$). *Musa paradisiaca* alone (Group 4) induced partial protection (ulcer index 11.50 ± 9.00) that did not reach conventional significance versus indomethacin ($p \approx 0.05$), while *Carica papaya* alone (Group 5) did not differ significantly from the indomethacin group (ulcer index 20.67 ± 11.37). Percent ulcer inhibition mirrored ulcer index: cimetidine ≈ 50% inhibition, combined extract ≈ 41.7% inhibition, *Musa paradisiaca* ≈ 16.7% and *Carica papaya* ≈ 11.1% (Table 1.0).

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Table 1. *In vivo* antiulcer parameters: ulcer index, % inhibition, free acidity, total acidity, pH, gastric juice volume, and pepsin.

Treatment Description	Ulcer Index Score	Percent Inhibition	Free Acidity (meq/L)	Total Acidity (meq/L)	pH	Pepsin (µg/ml)
Normal control (Water only)	0.00 ± 0.00^{d}	100.00 ± 0.00^{a}	92.38 ± 18.11^{c}	132.91 ± 26.05^{c}	3.73 ± 0.22^{a}	0.78 ± 0.10^{e}
Negative control (Indomethacin)	20.25 ± 2.87^{a}	0.00 ± 0.00^{e}	207.01 ± 87.70^{a}	297.81 ± 126.17^{a}	2.08 ± 0.22^{e}	6.01 ± 0.85^{a}
Standard drug (Cimetidine)	4.50 ± 3.42^{c}	50.00 ± 33.34^{b}	206.97 ± 49.61^{a}	234.54 ± 47.90^{b}	3.05 ± 0.13^{c}	2.34 ± 0.98^{c}
Plantain extract	11.50 ± 9.00^{b}	16.67 ± 19.24^{d}	133.44 ± 21.28^{b}	175.98 ± 20.68^{bc}	2.65 ± 0.13^{d}	2.60 ± 0.59^{c}
Pawpaw extract	20.67 ± 11.37^{a}	11.11 ± 19.24^{de}	103.35 ± 10.94^{c}	138.04 ± 10.16^{c}	2.97 ± 0.06^{c}	3.44 ± 0.25^{b}
Combined extract	5.25 ± 3.40^{c}	41.67 ± 16.67^{c}	106.20 ± 21.27^{c}	122.72 ± 5.80^{c}	2.90 ± 0.29^{c}	2.18 ± 1.19^{d}

Notes: *Values are presented as Mean ± SD, n = 4 per group. Superscripts (a, b, c, d, e) across each column indicate groups that are* ***significantly different (p < 0.05, LSD test).***

Acute oral toxicity

Results of the acute toxicity (Lorke) experiment should be presented in Table 2, including observed signs and behavioral changes, and mortality per dose.
The binary extract showed no mortality at any dose, up to the highest tested (5000 mg/kg). At lower doses (10–1000 mg/kg), no behavioral or physiological changes were observed, suggesting a wide margin of safety. Mild behavioral changes were only noticeable at 1600 mg/kg, whereas moderate to severe changes, including fatigue, writhing, and mild appetite loss, occurred at 2900–5000 mg/kg. Notably, despite these observable toxic signs at higher doses, no deaths were recorded.

Table 2. Acute oral toxicity observations and LD_{50} estimate.

Groups (Dose)	Number of rats	Death	Behavioral change	Fatigue	Writhing effect	Appetite effect
10 mg/kg	3	0	Nil	Nil	Nil	Nil
100 mg/kg	3	0	Nil	Nil	Nil	Nil
1000 mg/kg	3	0	Nil	Nil	Nil	Nil
1600 mg/kg	3	0	Mild change	Nil	Nil	Nil
2900 mg/kg	3	0	Moderate change	Yes	Nil	Nil
5000 mg/kg	3	0	Severe change	Yes	Yes	Mild loss

Based on these results, the lethal dose-50 (LD_{50}) of the combined extract is likely greater than 5000 mg/kg, placing it in the practically non-toxic category according to Lorke's classification. This implies that the combination of Musa *paradisiaca* peel and *Carica papaya* leaf extracts is relatively safe at therapeutic doses, with adverse effects observed only at extremely high concentrations.

Effect of extracts on Na^+/K^+-ATPase activity and Gastric Juice Volume: Table 3 presents the effects of different treatments on gastric Na^+/K^+-ATPase activity and gastric juice volume in experimental animals.

Table 3: Na^+/K^+-ATPase and Gastric Juice Volume

Group	Na^+/K^+ ATPase (U/mg protein)	Gastric Juice Volume (ml)
Group 1 Normal (Water)	12.04 ± 0.42^a	1.35 ± 0.26^c

Group 2 Negative (Indomethacin)	7.41 ± 0.71^{b}*	3.53 ± 0.63^{a}
Group 3 Standard (Cimetidine)	11.54 ± 1.09^{a}	1.27 ± 0.15^{c}
Group 4 (Musa paradisiaca)	9.56 ± 3.80^{ab}	1.95 ± 0.31^{b}
Group 5 (Carica papaya)	7.50 ± 1.48^{b}*	3.03 ± 1.28^{a}
Group 6 (Combined)	10.44 ± 1.68^{a}	1.15 ± 0.58^{c}

Different superscripts within a row indicate a significant difference at $p < 0.05$. Stars (*) denote a considerable reduction compared with the normal control (Group 1).

The principal findings were that indomethacin (Group 2) produced a significant decrease ($p < 0.05$) in Na^+/K^+-ATPase activity (7.41 ± 0.71 U/mg protein), compared with the highest mean value of 12.04 ± 0.42 U/mg protein in normal control. Treatment with cimetidine (Group 3, standard antiulcer drug) and the combined extract (Group 6) also produces high level of Na^+/K^+-ATPase activity when compared with the normal control, while *Carica papaya* (Group 5) alone did not differ significantly from the indomethacin group, although *Musa paradisiaca* extract alone (Group 4) produced a moderate improvement (9.56 ± 3.80 U/mg protein) in Na^+/K^+-ATPase activity. Regarding gastric juice volume, the indomethacin-treated group exhibited a marked increase (3.53 ± 0.63 ml) compared with the normal control (1.35 ± 0.26 ml), indicating excessive acid secretion and mucosal irritation. The administration of *Carica papaya* extract (Group 5) also maintained a relatively high gastric volume (3.03 ± 1.28 ml) while Musa paradisiaca (Group 4) and the combined extract (Group 6) significantly reduced gastric juice volume to 1.95 ± 0.31 ml and 1.15 ± 0.58 ml, respectively.

Discussion

In this study, the indomethacin model of gastric ulceration produced significant gastric mucosal damage in the negative control group. Indomethacin is well established to induce gastric lesions by inhibiting cyclooxygenase, depleting prostaglandins, and enhancing oxidative stress (Mohamed *et al*., 2022). In the present study, the ulcer index, gastric acidity, and pepsin concentration were all elevated in the indomethacin group, whereas the normal control exhibited no ulcerative damage. Treatment with cimetidine, the standard drug, significantly reduced ulcer indices and gastric secretion. Notably, groups treated with *Musa paradisiaca*, *Carica papaya*, or the combined extracts showed considerable gastroprotection, evidenced by reduced ulcer indices, reduced gastric acidity, and greater percentage inhibition of ulceration compared with the negative control. These results confirm earlier findings that papaya leaves and plantain peels possess potent antiulcerogenic properties (Pinto *et al*., 2015; Oladele and Adefegha, 2022).

The Na^+/K^+-ATPase enzyme plays a crucial role in maintaining gastric mucosal integrity by regulating ion balance across

cell membranes. The findings indicate that indomethacin administration significantly suppressed Na^+/K^+-ATPase activity and increased gastric juice volume, confirming its ulcerogenic effect on the gastric mucosa. In contrast, cimetidine restored enzyme activity and normalized gastric secretion, validating its protective role. Among the plant treatments, *Musa paradisiaca* showed a moderate increase in Na^+/K^+-ATPase activity and reduction in gastric acid secretion, while *Carica papaya* produced weaker effects. However, the combined extract of *Musa paradisiaca* and *Carica papaya* demonstrated the most pronounced restoration of enzyme activity and suppression of gastric juice volume, comparable to the standard drug. The results suggest that unripe *Musa paradisiaca* peel and *Carica papaya* leaf extracts, particularly when combined, exhibit significant antiulcer and gastroprotective effects, likely through enhancement of Na^+/K^+-ATPase activity and inhibition of gastric acid secretion.

Conclusion

The research demonstrates that unripe *Musa paradisiaca* peel and *Carica papaya* leaf extracts, individually and in combination, exert antiulcer activities. The study established that the extracts mitigated indomethacin-induced gastric ulceration by reducing ulcer index, lowering gastric acidity, preserving antioxidant enzymes, and limiting inflammatory responses. The combined extract demonstrated complementary and, in some cases, enhanced activity compared with the individual extracts. These findings support the conclusion that both plants, traditionally regarded as food and ethnomedicinal resources, have potential therapeutic relevance in the management of peptic ulceration.

Ethical Consideration and Approval

Ethical approval (REC/FOS/2025/24) for the study was sought from the Faculty of Science Ethics Committee of Delta State University, in line with the approved guidelines and the Declaration of Animal Research Ethics (ARE, 2009) on the use of animals for biochemical research.

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Abbreviations:

UI	Ulcer Index
MSD	Mean standard deviation
NSAID	Non-steroidal anti-inflammatory drugs
ROS	Reactive oxygen species
PGs	Prostaglandins

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