

Ameliorative Effect of Irish Potato Tuber, Unripe Plantain and Unripe Pawpaw Fruits Combination Beverage on Indomethacin-Induced Ulcer in Albino Rats

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Abstract- Peptic ulcer is one of the most common gastrointestinal disorders, which affects the world wide population. The present study was designed to assess the ameliorative effect of Iris potato tuber, unripe plantain and unripe pawpaw fruits combination beverage on indomethacin-induced ulcer in albino rats. Assessment of individual, binary and ternary combinations of the plant beverage extract was carried out by randomizing 40 male albino rats into ten groups (n=4), inducing ulcer in the rats with 30 mg/kg bw of indomethacin and treating with various beverages. Oral acute toxicity and histopathological tests were also conducted. Among the individual beverage extracts, irish potato beverage extract (Ir) produced the highest (94.59 ±2.36%) antiulcer activity, whereas binary combination of irish potato and unripe pawpaw (Ir+Pw) beverage extract was found to have the highest (94.27±2.00%) antiulcer effect when compared with the other combinations. Result of acute toxicity recorded no mortality up to the limit test dose of 5000 mg/kg bw. Results of histopathological examination showed indomethacin induced effect in the stomach were reversed by irish potato and unripe pawpaw (Ir+Pw) combination beverage extract. The observed healing potential of the beverage extract may be linked to presence of bioactive compounds in the plants. Therefore we recommend further studies to elucidate the bioactive principles responsible for antiulcer activity.

Keywords: Beverage; Bioactive; Indomethacin; Ulcer; Histopathological.

INTRODUCTION

Peptic ulcer is one of the most common gastrointestinal disorders, which affect the worldwide population. It is estimated that approximately 10% of the world population develops this condition, which represents a serious health problem with a large impact on the quality of life of millions of individuals[1]. Gastric ulcer can penetrate the muscular layers of the stomach, developing acute lesions in the gastric mucosa, hence, may leads to chronic inflammation when not properly treated, and to complications such as hemorrhages and perforations[2,3].

The development of gastric ulcer results from an imbalance between some offensive and defensive factors in the stomach. The offensive factors include endogenous agents and events that include hydrochloric acid, pepsin, lipid peroxidation, production of reactive oxygen species (ROS)] and exogenous factors. Here, exogenous factors are inclusive of *Helicobacter pylori* infections, stress, smoking, excessive alcohol consumption, and prolonged use of non-steroid anti-inflammatory drugs (NSAIDs)[4]. The defensive factors include prostaglandins (PGs), mucin secretion, mucus-bicarbonate barrier, nitric oxide (NO), growth factors, mucosal blood flow, cell regeneration, surface phospholipids, and endogenous antioxidants.

The main therapeutic intervention for gastric ulcers is the inhibition of aggressive factors combined with the stimulation of increased defensive factors[3]. The existing therapeutic drugs for the treatment of this pathology are proton pump inhibitors (PPIs—lansoprazole, omeprazole) and H₂-receptor antagonists (ranitidine, famotidine, nizatidine, etc.), in addition to antibiotics used to eradicate *H. pylori*[5].

However, prolonged use of anti-secretory drugs can cause many adverse effects[4,6]. For example, PPIs can cause abdominal pain, nausea, headache, diarrhea, osteoporosis, fractures, and in addition, pneumonia, insomnia, and kidney inflammation. These side effects are associated with an increase of gastric cancer risk[4]. The long-term use of H₂-receptor antagonists (H₂-RAs) can lead to the development of galactorrhea in women, gynecomastia in men, and alteration of the bacterial flora of the gastrointestinal tract[7].

The use of PPIs and H₂-RAs can lead to rapid tolerance during treatment, followed by a rebound effect of gastric hypersecretion after withdrawal of the drug, and ulcers may develop again[7]. Therefore, it is necessary to investigate new therapeutic alternatives with fewer adverse effects, which stimulate the ulcer healing process and prevent new relapses. In this context, the use of medicinal plants and derived phytochemicals has gained growing interest in the search for new drugs with less side effects[8] and to combat inflammation and oxidative stress in a more natural, drug-free fashion[9].

Irish Potato (*Solanum Tuberosum*), a starchy tuberous and perennial plant of family Solanaceae, commonly known as the night shades, is rich in phenols, flavonoid, saponin and has mild content of alkaloid[10].

Plantain fruit (*Musa Paradisaca*) belong to family, Musaceae, and order, Zingiberale, has been reported by many researchers to have hypoglycemic[11] and anti-ulcerogenic [12] activities.

Pawpaw, also known as *Carica papaya* belongs to family of Caricaceae and is cultivated in Tropical regions of the world for its edible melon like fruits[13]. It is one of the most popular and economically important fruit trees, and the fruit is consumed for its nutritional content[13]. The fruits and the seeds are highly rich in carbohydrate, natural vitamins and minerals particularly vitamin A, C and potassium. The bioactive constituent of the plant

include papain, chymopapain, alkaloid, flavonoids and phenolic[14].

MATERIALS AND METHODS

Drugs and Reagents

Drugs and reagents used in the present study include indomethacin (Jiangsu Ruinian Pharmaceutical), cimetidine (Saga Laboratory India), ethanol, hydrogen peroxide, hydrochloric acid, alkaline copper sulphate, eosin, haematoxylin, ammonium hydroxide, calcium chloride and alkaline picrate, Vanillin reagent (1% in 70% sulphuric acid). All the reagents used were of analytical grade.

Equipment:

The equipment include: Electronic Weighing Balance Mettler PT320 (Mettler Wagen, Switzerland), Hot-air Oven (LabTech India), Digital Spectrophotometer Model 390 VIS Spectrophotometer 21D, (Life Assistance Scientific Instrument Company China), Tissue Homogenizer-BLK397 (Kenwood Ltd Japan), Digital pH Meter (LabTech India), Bench Centrifuge (Clay Adams USA), Deep Freezer (Fresh Point FDF-196), Rotary Evaporator-RC-900 (KNF Neuberger USA),

Plant Collection:

Fresh Irish potato tubers, unripe plantain and unripe pawpaw fruits were purchased from Aba Grocery Market, Abia State, Nigeria. The plants were identified and authenticated in the Department of Crop Science, School of Agriculture Technology, Federal University of Technology, Owerri, Imo State, Nigeria, where they were assigned voucher specimen number as: Irish potato tuber (UIH22849), unripe pawpaw fruit (FHI106994) and unripe plantain (FHI10846).

Preparation Plant Powder:

Plants were peeled, washed thoroughly with clean running water, sliced and dried in the oven at 60°C to constant weight. The dried plant materials were grinded into fine powder (flour). A-3g of each of the plant powder was put into a conical flask and soaked in 100ml distilled water heated to 100°C for 5 minutes to prepare the beverage that was used in treating induced animals. Fresh beverage extract was prepared daily.

Animal Ethics Approval

This study was conducted under the animal ethics approval (Ref: FUTO/BCH/DEC/XXI/01/09), granted by Department of Biochemistry, School of Biological Sciences, Federal University of

Technology, Owerri, Imo State, Nigeria. The animals were handled according to guidelines for animal handling and care, specified by [15].

Assessment of Antiulcer Effect of Plants Material and Indomethacin

This was conducted on individual plant powder, binary (1:1 ratio) and tertiary (1:1:1 ratio) combinations of the plant powder to ascertain a combination of plant beverage with best antiulcer effect. This assessment employed forty male albino rats that were randomly distributed into 10 groups (A-J) of four animals per group.

Induction of Ulceration:

The rats were deprived of food for 24 hours but had free access to water until 2 hours prior to ulcer induction. Thereafter, ulcer was induced in the rats by administration single oral dose of 30 mg/kg bw of indomethacin, with exception rats in group A. Various degrees of ulceration that manifested 8 hours after indomethacin administration was determined using the fecal occult blood test for ulceration and further confirmed by extracting the stomach of animals from each group to check for ulceration.

Experimental Design

After confirmation of ulceration, feed and water were restored in all animal groups. Rats in each group specifically received (orally) the following treatment, once daily for 14 days.

Group A (normal control): received 3.0 ml/kg bw distilled water

Group B (negative control): received 3.0 ml/kg bw distilled water

Group C (positive control): received 200 mg/kg bw of cimetidine

Group D: received 3.0 ml/kg bw of Irish potato (Ir) beverage.

Group E: received 3.0 ml/kg bw of unripe Plantain (PI) beverage.

Group F: received 3.0 ml/kg bw of unripe Pawpaw (Pw) beverage.

Group G: received 3.0 ml/kg bw of combined Ir+PI beverage.

Group H: received 3.0 ml/kg bw of combined Ir+Pw beverage.

Group I: received 3.0 ml/kg bw of combined PI +Pw beverage.

Group J: received 3.0 ml/kg b.w of combined Ir+ PI +Pw beverage.

Quantification of Ulceration:

Degrees of ulceration in the indomethacin-treated rats were quantified using the procedure outlined by [16]. Rats were randomly selected from each group for quantification of ulceration. Each selected rat was mildly anaesthetized with dichloromethane, dissected and its stomach extracted and cleaned with distilled water. Then, cleaned stomach were pinned on a corkboard and ulcers were scored using microscope with square-grid eye piece based on a 0 - 4 scale (depicting the severity of vascular congestion and lesions/ hemorrhagic erosions) as described by [16]. Areas of mucosal damage were expressed as percentage of total surface area of the glandular stomach estimated in square millimeters. 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 [16]

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

Sample Collection:

At the end of 14 days treatment period, the stomach and duodenal contents of anaesthetized animals were extracted and used to determine total acidity, free acidity and pepsin activity.

Acute Toxicity (LD₅₀) Determination

This was conducted using Irish potato and unripe pawpaw (Ir+Pw) combination beverage extract to establish the toxicity level. Method proposed by [17] was employed.

Determination of Total and Free Acidity

Free and total acidity were determined according to the method described by [18]. After centrifuging the gastric contents, 1 ml of the supernatant was taken in a conical flask and diluted with distilled water to make a volume of 10 ml. Topfer's reagent (2 drops) was added to it, and titrated with 0.01N NaOH to yellow end point. Then 2 drops of phenolphthalein

was added and titration continued till phenolphthalein end point is reached.

The amount of 0.01N NaOH required to titrate to the methyl yellow end point was used to determine the measure 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. The acidity was calculated by the following formula and expressed in mEq/L[18].

$$\text{Acidity} = [\text{Volume of NaOH} \times \text{Normality} \times 100 \text{ mEq/L}] / 0.1$$

Determination of Pepsin Activity

Pepsin activity was determined according to the methods proposed by[19]. One milliliter (1ml) of diluted gastric juice was mixed with 0.5ml of 2% haemoglobin 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 1.0ml of alkaline copper sulphate solution and 0.5ml of dilute Folin-Denis reagent and incubated for 30 minutes at room temperature. The absorbance of the sample was determined by spectrophotometry at 610 nanometer (nm) wavelength. The activity of pepsin was determined from a standard curve.

Histopathology Study of Stomach Tissues:

The stomach tissues of the normal control, negative control, positive control groups and the group treated with irish potato and unripe pawpaw (Ir+Pw) combination beverage were examined for any evidence of histopathological changes. The tissues were fixed with 10% formal saline and dehydrated continuously with increasing concentrations of ethanol (30%, 50%, 70%, 90%, and 100% alcohol for 1hr, 2hrs, and 3hrs). The tissue samples were cleared by immersion in xylene for 3

hours; after which it was immersed in paraffin wax. Tissues were sectioned to about 3–6 micrometer (µm) thickness. Eosin and Hematoxylin (E & H) stains were applied and histopathological changes examined with light microscope fitted with digital camera (Nikon, ECLIPSE, TS100, Japan).

STATISTICAL ANALYSIS

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

RESULTS

Assessment of Antiulcer Effect

Irish Potato beverage extract has the highest anti-ulcer effect when compared to plantain and pawpaw beverages. Among the binary category, binary combination of Irish Potato and Pawpaw (i.e Ir+Pw) produces the highest (94.27±2.00%) antiulcer effect as shown in Table 1.

Acute Oral Toxicity.

Binary combination of Irish Potato and Pawpaw (i.e Ir+Pw) beverage extract recorded no mortality at all doses used in this study (Table 3)

Histopathological Study

Among the combination beverage extract, irish potato and unripe pawpaw combination (Ir+Pw) gave the highest ulcer protection (94.27 ± 2.00%) and was used for histological study. Figures 1-4 shows the photomicrograph of stomach of group A, group B, Group C, and group H rats. The irish potato and unripe pawpaw (Ir+Pw) combination beverage extract regenerated the indomethacin–induced distortion of stomach cells.

Table 1: Antiulcer Potentials of Aqueous Beverage Extracts of Individual, Binary and Tertiary Combinations Irish Potato Tuber, and unripe Fruits of Plantain and Pawpaw.

Treatment Groups	Ulcer index	% Ulcer protection	Total acidity	Free acidity	Pepsin activity
A (Normal control)	0.07 ± 0.05 ^a	98.85 ± 2.30 ^a	30.25 ± 5.26 ^{acde}	10.50 ± 1.00 ^a	27.67 ± 1.87 ^a
B (Negative control)	6.42 ± 0.19 ^b	-0.08 ± 2.99 ^b	108.00 ± 9.35 ^b	51.25 ± 2.87 ^b	49.23 ± 1.86 ^b
C (Positive control)	0.35 ± 0.11 ^{ac}	94.60 ± 1.67 ^{ac}	32.25 ± 4.03 ^{acde}	11.75 ± 2.22 ^{ac}	29.40 ± 1.36 ^a
D (Ir)	0.35 ± 0.15 ^{ad}	94.59 ± 2.36 ^{ad}	39.75 ± 5.56 ^{cde}	13.50 ± 1.29 ^{ad}	30.50 ± 0.75 ^{ac}
E (Pl)	0.36 ± 0.10 ^{ae}	94.51 ± 1.48 ^{ae}	25.75 ± 6.34 ^d	17.00 ± 2.83 ^{de}	35.35 ± 2.23 ^{cde}
F (Pw)	0.71 ± 0.10 ^{cde}	88.96 ± 1.64 ^{cde}	45.75 ± 11.47 ^{eg}	25.00 ± 1.63 ^f	36.86 ± 4.73 ^{de}
G (Ir+Pl)	0.62 ± 0.15 ^{cde}	90.31 ± 2.36 ^{cde}	16.75 ± 6.13 ^{ad}	14.00 ± 1.83 ^{ae}	32.70 ± 3.17 ^{ade}
H (Ir+Pw)	0.37 ± 0.13 ^{ad}	94.27 ± 2.00 ^{ad}	33.75 ± 11.30 ^{acde}	16.25 ± 0.96 ^{ce}	31.38 ± 2.34 ^{ad}

I (Pl+Pw)	3.55 ± 0.44 ^f	44.60 ± 6.84 ^f	79.25 ± 8.66 ^{fh}	26.75 ± 1.26 ^f	38.31 ± 2.69 ^e
J (Ir+Pl+ Pw)	0.55 ± 0.05 ^{cde}	91.40 ± 0.79 ^{cde}	61.75 ± 2.22 ^{gh}	15.00 ± 2.16 ^{ae}	28.89 ± 1.14 ^a

Ir = Irish Potato; Pl = Unripened Plantain; Pw = Unripened Pawpaw

Values are mean ± standard deviation of n=4. Values bearing different superscript letters are statistically significant (p<0.05).

Table 2: Decision Table

	Ir	Pl	Pw	Ir+Pl	Ir+Pw	Pl+Pw	Ir+Pl+Pw
Ulcer index	2	2	1	1	2	-1	1
% Ulcer protection	2	2	1	1	2	-1	1
Total acidity	2	2	2	2	2	-1	-1
Free acidity	2	-1	-1	2	1	-1	2
Pepsin activity	2	-1	-1	2	2	-1	2
TOTAL	10	4	2	8	9	-5	5

Basis of decision: 1. Statistically different from NC = -1 score
 2. Statistically different from PC = -2 score
 3. Statistically different from UC = +2 score

Table 3: Acute Toxicity Test Result of Binary Combination of Irish Potato and Pawpaw Beverage.

Groups	Ir + Pw (mg/kg)	No. of death recorded
Phase 1		
GP 1	10	0/3
GP 2	100	0/3
GP 3	1000	0/3
Phase 2		
GP 1	1000	0/3
GP 2	1600	0/3
GP 3	2900	0/3
GP 4	5000	0/3

LD₅₀<5000 mg/kg body weight



Fig. 1: Cross section of group 1 stomach showing the gastric gland in a normal shape, the gastric pits and gastric epithelium are in normal condition (x 400 mgfn stained in H & E).

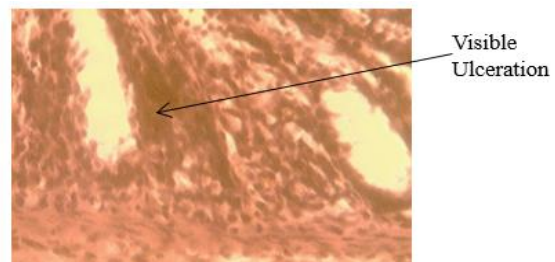


Fig. 2: Cross section of rat stomach and not treated showing the gastric gland and gastric pits compacted, there is visible ulceration seen, the parietal and chief cells are seen in multiples (ulceration seen) (x 400 mgfn stained in H & E).

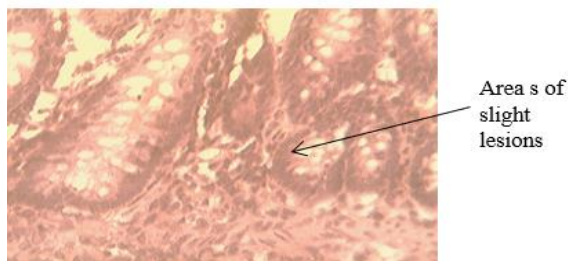


Fig. 3: Cross section of rat stomach treated with standard drug showing the gastric glands, gastric pits and muscularis mucosae slightly affected with lesions. The parietal cells and the chief cells also scanty (x 400 mgfn stained in H & E).

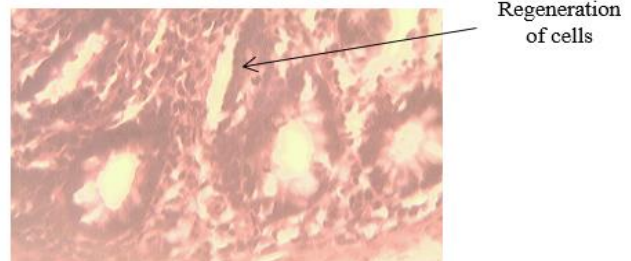


Fig. 4: Cross section of rat stomach treated with irish potato and unripe pawpaw (Ir+Pw) combination beverage extract showing stomach section partly distorted with regeneration of cells occurring (x 400

DISCUSSION

The ulcer index and percentage ulcer protection are critical parameters for assessing the anti-ulcer potential of treatments. The results showed that all treatment groups (C-J), significantly ($p < 0.05$) reduced the ulcer index and increased ulcer protection compared to negative control group. Notably, the combination of Irish Potato, unripe Plantain, and Pawpaw (i.e Ir+Pl+Pw; 1:1:1 ratio) exhibited a high percentage of ulcer protection ($91.40 \pm 0.79\%$) with a relatively low ulcer index (0.55 ± 0.05), demonstrating considerable efficacy.

Studies have shown that plant-based treatments can effectively reduce gastric ulcers. For example, a study has reported that plantain banana extracts possess anti-ulcerogenic properties, attributed to their ability to modulate gastric mucosal defense mechanisms[20]. Similarly, Pawpaw fruit extracts have been documented to exhibit significant anti-ulcer activities due to their rich phytochemical content, which includes flavonoids and vitamins[21]. The findings of the present study align with the reported literature, confirming the effectiveness of these plant extracts in ulcer treatment. However, the combination therapy used in this study appears to offer a synergistic effect, enhancing the overall protective potential compared to single plant treatments. This is consistent with the findings of[22], who demonstrated that a combination of plant extracts could provide superior therapeutic benefits due to the synergistic actions of various bioactive compounds.

When compared to standard treatment (Cimetidine), the aqueous extracts showed comparable efficacy in ulcer protection. Cimetidine is a well-known H_2 receptor antagonist used in ulcer treatment, and the fact that plant extracts provided similar protection underscores their potential as alternative or complementary therapies. This aligns with the growing body of research advocating for the use of natural products in managing gastric ulcers due to their minimal side effects and cost-effectiveness[23].

The ulcer index and percentage protection are primary indicators of the efficacy of antiulcer treatments. In this study, the normal control group exhibited a minimal ulcer index (0.07 ± 0.05) and high protection ($98.85 \pm 2.30\%$). Conversely, the negative control group showed a significantly higher ulcer index (6.42 ± 0.19) and negative protection ($-$

$0.098 \pm 2.99\%$), confirming successful ulcer induction.

The standard drug, cimetidine, demonstrates an ulcer index of 0.35 ± 0.11 and protection of $94.69 \pm 1.67\%$, aligning with known pharmacological efficacy. The Irish potato beverage at 3 ml/kg showed similar effectiveness (0.35 ± 0.15 ; $94.59 \pm 2.36\%$), indicating potent antiulcer activity comparable to cimetidine. Previous studies corroborate these findings, showing that potato juice has gastroprotective properties, likely due to its rich content of resistant starch and glycoalkaloids, which enhance mucosal defense and reduce gastric acidity[24,25].

Total acidity and free acidity are indicative of the stomach's acidic environment, which is a critical factor in ulcer formation and progression. The results indicate that the treatments significantly reduced total and free acidity compared to negative control group. The Potato/Plantain combination showed a particularly notable reduction in total acidity (16.75 ± 0.96), suggesting its effectiveness in neutralizing gastric acid.

Previous research supports the role of plantain and pawpaw in reducing gastric acidity. A study has found that unripe plantain could significantly lower gastric acid secretion, contributing to its antiulcer effects[26]. Pawpaw has also been reported to reduce gastric acidity due to its enzyme content, which aids in digestion and reduces acid production[27]. The current study's results are consistent with these findings, further highlighting the potential of these plant extracts in managing gastric acidity. The reduced acidity levels observed in the treatment groups suggest that these extracts can effectively create a less corrosive environment in the stomach, thereby promoting ulcer healing.

Total and free acidity are crucial in understanding the biochemical environment conducive to ulcer formation. The negative control group had significantly higher total (108.00 ± 9.35 mmol/L) and free acidity (51.25 ± 2.87 mmol/L). In contrast, the normal control group maintained low levels of total acidity (30.25 ± 5.26 mmol/L) and free acidity (10.50 ± 1.00 mmol/L). Treatments with Irish potato beverages significantly reduced acidity levels. For instance, the Irish potato beverage at 3 ml/kg resulted in total and free acidities of 39.75 ± 5.56 mmol/L and 13.50 ± 1.29 mmol/L, respectively. This reduction in acidity is consistent with findings from[28], which highlighted the alkaline nature of potato juice aiding in neutralizing stomach acid.

Pepsin activity is a crucial factor in ulcerogenesis, as pepsin can degrade the gastric mucosa, thereby exacerbating ulcer formation. The study shows that the treatments, particularly the Potato/Plantain/Pawpaw combination, significantly reduced pepsin activity compared to the negative group. The inhibitory effect on pepsin activity by plant extracts has been well-documented. It has been reported that various plant extracts could inhibit pepsin activity, thus providing a protective effect against gastric ulcers[29]. The reduction in pepsin activity observed in the present study is consistent with these findings, indicating that the aqueous extracts of Irish potato, unripe plantain, and pawpaw possess components that can inhibit pepsin activity. Pepsin activity, a marker for digestive enzyme activity, was elevated in the ulcer-induced negative control group ($49.23 \pm 1.86 \mu\text{mol/L}$) compared to the normal control ($27.67 \pm 1.87 \mu\text{mol/L}$). Treatments with Irish potato and its combination with pawpaw significantly reduced pepsin activity to 31.38 ± 2.34 , when compared to negative control. Notably, the Irish potato beverage at 3 ml/kg reduced pepsin levels to $29.40 \pm 1.36 \mu\text{mol/L}$, closely matching the normal control, reflecting effective inhibition of pepsin secretion or activity. The combination of Irish potato and pawpaw also showed significant efficacy with an ulcer index of 0.37 ± 0.13 and $94.27 \pm 2.00\%$ protection. This combination effectiveness suggests a synergistic effect, where bioactive compounds in pawpaw (e.g., papain, chymopapain) may complement the gastroprotective action of potato constituents[30]. The result of this present study is consistent with the findings of[31], who reported enhanced antiulcer effects when multiple plant extracts were combined. Previous studies have explored the anti-ulcerogenic effects of various natural products and formulations. For instance, studies on potato juice have demonstrated its ability to reduce gastric ulcers by neutralizing stomach acidity and reducing inflammation[32]. Similarly, pawpaw has been shown to possess significant antiulcer properties, attributed to its antioxidant and anti-inflammatory effects[33]. The results of the current study align with these findings, indicating that both Irish potato and pawpaw have significant anti-ulcerogenic potential.

CONCLUSION

The present study observed healing potential of the beverage extracts, which may be linked to presence

of bioactive compounds in the plants. Therefore we recommend further studies to elucidate the bioactive principles responsible for antiulcer activity.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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