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# Fermented *Carica papaya* Improved Behavioural, Biochemical and Morphological Deficits in Ibuprofen-Induced Duodenal Ulceration in Wistar Rats: Protective and Therapeutic effects

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## ABSTRACT

Ulcers particularly duodenal ulcers have remained a nagging problem despite the availability of drugs. This implies an uncertainty about a permanent treatment as ulcers are currently being managed. This study investigated the protective and therapeutic effects of unripe and ripe fermented *Carica papaya* (*C.papaya*) juice compared to omeprazole on ibuprofen-induced duodenal ulcer using adult Wistar rat model. Thirty-five adult Wistar rats were placed into seven groups (N=5). Group-A, the control was given distilled water (1ml). Group-B (ibuprofen treatment only) was induced with duodenal ulcer using ibuprofen (400mg/Kg BW) Group-C and Group-D were administered fermented unripe and ripe *C.papaya* respectively (0.75ml extract+0.25ml distilled water) six hours after administration of the ibuprofen; the administration of the fermented extract continued for a period of 14 days. Group-E and Group-F (pre-treated fermented ripe and unripe *C.papaya* extract respectively) received fermented unripe and ripe *C.papaya* respectively at first for 12 days. Additionally, on days 12 to 14, a single daily dose of ibuprofen (400mg/kg BW) was administered to the same groups of rats. Group-G (omeprazole) were induced with duodenal ulcer [ibuprofen (400mg/kg BW)] and after six hours, omeprazole was administered to the rats; the drug was administered daily (single dose) and continued for a period of 14 days. All administration was done orally. Phytochemical screening identified alkaloids, terpenoids, saponins, flavonoids, tannins, glycosides and phenols in *C.papaya* juice. Pre-treatment with fermented *C.papaya* juice showed significant antagonistic improvement in body weight, behavioural activities, antioxidant and oxidative stress markers, and histological demonstration. These findings suggest that the extracts have both ameliorative and protective effects and may prove useful in the management of duodenal ulcers.

***Keywords:*** *Carica papaya* extract, Duodenal ulcers, ameliorate deficit, *in vivo*, Ibuprofen-induced

## INTRODUCTION

Gastrointestinal disorders (GIDs) are among the most prevalent diseases that plague individuals worldwide. Studies shows that GIDs are common in both the male and female populations but some types are more predominant than others [1]. Ulcerative colitis, gastroesophageal reflux disease (GERD) and peptic ulcer diseases (PUD) are common examples of structural gastrointestinal (GI) disorders that alter the typical morphology of the digestive tract, resulting in reduced functionality of the affected GI organ and may require surgical intervention [2].

Annually affecting approximately 10 to 15 percent of the world population is a type of peptic ulcer known as duodenal ulcers [3]. Duodenal ulcer is an acid-induced injury usually found within the proximal duodenum, and is characterized by inflammation in addition to denuded mucosa that may extend into the submucosa or muscularis propria of the organ [4]. There are two major risk factors for duodenal ulcers- *Helicobacter pylori (H. pylori)* and non-steroidal anti-inflammatory drugs (NSAIDs). The general use of NSAIDs for its analgesic and anti-inflammatory properties are well known in pain management therapies. However, its mechanism of action has proven to result in ulcerogenic lesions [5,6].

The use of medications such as $H_2$ blockers and proton pump inhibitor have been shown to drastically reduce the effects of NSAIDs and most of the lesions caused by NSAIDs [7]. In spite of the fact that synthetic drugs use has been on the increase for the management and treatment of ulcers, their security and efficacy has continuously remained flawed due to the reality that most drugs designed have shown some negative side effects [8].

Scientific quest to develop a permanent treatment for duodenal ulcers with little or no adverse effects has led to researchers delving into the world of herbal medicine. Most plants in recent times are being explored to confirm if these medicinal plants have pharmacological mechanism of actions that could prove useful as believed by old wives' tale and books about herbal medicine [9].

Amongst the numerous plants being researched on includes *Carica papaya (C. papaya)* popularly known as *papaya* or pawpaw. The uses of pawpaw plant (seeds, ripe fruits, unripe fruits, latex, root, leaves, flowers and stem bark) and its therapeutic correlation with human wellbeing have been well documented [10]. Extracts from different parts of *C. papaya* plant have shown protective effects against many diseases, especially when used as antiparasitic, antiseptic, antimicrobial, anti-inflammatory, antihyperlipidemic, antihypertensive and antioxidants [10,11]. Hence, the present study investigated the protective and therapeutic effects of unripe and ripe fermented *C. papaya* juice compare to omeprazole on ibuprofen-induced duodenal ulcer using adult Wistar rat model.

**Materials and Methods:** All protocols on animal handling strictly followed the guidelines of the Institutional Animal Care and Use Committee (IACUC) as approved by the PUMS Ethics Review Committee, Pamo University of Medical Sciences (PUMS), Port Harcourt, Rivers State, Nigeria. Adult Wistar rats (weight = 1

50±10g) were acquired from the animal house, PUMS (Pamo University of Medical Sciences) animal holdings, Port Harcourt, Rivers State. Wistar rats were kept in standard polypropylene cages, allowed to acclimatize to their new environment for 2 weeks, under standard laboratory conditions at PUMS animal holdings facility where they had liberal access to rat chow and water *ad libitum.*

Ibuprofen and Omeprazole were purchased from Tree of Life pharmacy, Oyigbo LGA of Rivers State, Nigeria, in July 2021. Freshly prepared ibuprofen (400mg/kg) and omeprazole (20mg/kg) were dissolved in 1ml of distilled water. Wistar rats were fasted for 24 hours prior to oral administration of ibuprofen (400mg/kg), and allowed for 6 hours. Fresh unripe and ripe *C. Papaya* fruit were obtained from the local Oyigbo market at Oyibgo, LGA of River State, and were used for the identified and authenticated *C. Papaya* in the Department of Plant Science and Biotechnology, University of Port Harcourt, Rivers State, with authentication number; UPH/PSB/2021/A15a and UPH/PSB/2021/A15b allocated to the ripe and unripe *Carica papaya* fruit respectively.

This method was proposed by Owoyele *et al.,* with slight modification [12]. Briefly, *C. papaya* fruits were washed thoroughly with running tap water. The unripe and ripe *C. papaya* fruits were separately weighed (ripe; 10kg while unripe; 11kg), peeled, cut into cubes and then grated into a pulp. 200ml of tap water was added to 1kg of the fruits (thus, 2litres of water and 2.2 litres of water for ripe and unripe C. *papaya* respectively), sealed in fermenting jars securely to prevent air interference. The jars were left at room temperature and allowed to ferment for four days. The juice extract was decanted to collect the sediments, which was subjected to phytochemical analysis and stored in a refrigerator.

Further, a pilot study was introduced to determine the toxicity and effective dosage of the fermented extract. In each group, Wistar rats were administered various doses (25%, 50%, 75%, and 100%). General observations were made on the fecal matter, eating habits, social activity and agility, as well as histological analysis and biochemical assays were carried out in order to select the most effective dose. Rats (n=35) were randomly placed into seven groups (n=5) and treated orally as follows: Group-A which was the control was given 1ml of distilled water. Group B (ibuprofen treatment only) was induced with duodenal ulcer using ibuprofen (400mg/Kg BW) Groups C and D were administered fermented unripe and ripe *C. papaya* (0.75ml extract+0.25ml distilled water) six hours after administration of the ibuprofen; the administration of the fermented extract continued for a period of 14 days. Groups E and F (pre-treated fermented ripe and unripe *C. papaya* extract respectively) received fermented unripe and ripe *C. papaya* respectively at first for 12 days. Additionally, on the days 12 to 14, a single daily dose of ibuprofen (400mg/kg BW) was administered to the same groups of rats. Group G (omeprazole) were induced with duodenal ulcer [ibuprofen (400mg/kg BW)] and after six hours, omeprazole was administered to the rats; the drug was administered daily (single dose) and continued for a period of 14 days.

The animals were weighed before the experiment began and after the experiment was concluded using a weighing scale

(Atom electronic compact scale), to determine if the treatment affected the body weight of the adult Wistar rats. Behavioural study was done 24 hours after the last administration, to check for duodenal ulcer associated dysphoric feelings in rats using open field test (OFT) behavioural paradigms. In brief, each rat was separately placed in the middle of the box and its explorative movements were recorded. At the end of the experiment, the video capturing each rat movement was analysed [13]. Immediately after all behavioral study, rats for histology were euthanized using chloroform vapor and then subjected to trans-cardial perfusion in which a flush of 50 ml of 0.1 M PBS (pH 7.4) was followed by 500 ml of 10% buffered formalin. Rats anterior abdominal wall were incised using surgical blade, scissor and scalpel. The small intestine was dissected out with an incision made from the pylorus to the duodenojejunal flexure. Observation of duodenal mucosa for the presence of duodenal ulceration was done immediately. The duodenum was then rinsed in 0.1 M PBS (pH 7.4) three times, for 5 mins each, and then post-fixed in 10% buffered formalin solution for 24 hours after which they were taken for histological (H&E) tissue processing. Rats processed for biochemical study were not subjected to trans-cardial perfusion. The duodenum was excised, rinsed in 0.1 M PBS (pH 7.4) for 5 mins each, and then placed in PBS in which they were stored at 4°C. after which sections of the duodenum were homogenized for biochemical assay. Results obtained were analysed using GraphPad Prism® software (Version 8.1) and tested for analysis of variance (ANOVA) with Tukey's multiple comparisons test. Significance was set at $p<0.05$.

**RESULTS:** ***Table 1*** shows the phytochemical constituents of *C. papaya* juice. The results of phytochemical screening carried out in order to identify major metabolites in ripe and unrip *C. papaya* juice revealed that, the juice contains alkaloids, terpenoids, saponins, flavonoids, tannins, glycosides and phenols. Examining body weight changes can be a defining factor in knowing the state of different condition, of which significant body weight loss is a key pointer in assessing the severity of different disease state. ***Fig. 1*** below shows a significant negative reduction in body weight following ibuprofen treatment. However, ibuprofen and then protective and therapeutic treatment using *C. papaya* was able to ameliorate ibuprofen menace. As shown in ***Fig. 2,*** oral administration of ibuprofen (400 mg/kg Bw) to rats greatly affected their locomotory and social behaviour. This study establishes a statistically significant depletion in line crossing frequency and rearing frequency performance **(*fig. 2a-b*)** of rats exposed to ibuprofen treatment. A notable depletion was seen in the number of faecal matters, grooming duration and grooming frequency performance of rats exposed to ibuprofen treatment **(*fig. 2c-e*)**. However, the various intervention using fermented *C. papaya* juice (unripe and ripe) progressively restored these behavioural defects associated with experimental ibuprofen exposure. Catalase (CAT) and Superoxide dismutase (SOD) serves a key antioxidant role in biological systems. Their expression is vital in maintaining normalcy and supressing oxidative stress. This study establishes a statistically significant decline in CAT and SOD expression resulting from ibuprofen assault. Furthermore, it justifies the high level of malondialdehyde (MDA) expression in this study following IBU-

induced duodenal ulceration. However, the various intervention using fermented *C. papaya* extract (unripe and ripe) significantly restored this enzymatic alteration. This positive effect is significantly suggestive as a comprehensive remedy for duodenal ulcer, when compared to standard medicinal drugs like omeprazole (see ***fig. 3a-c***).

The general cytoarchitecture of the duodenum of control (CON) rats showed that, the mucosa (M) of the duodenum has the characteristics villous with glandular crypts between the villi (V), extending down to the muscularis mucosae (MM). Ibuprofen treated rats exhibited Villi necrosis (yellow arrow), which was also demonstrated in (IBU+FUP and IBU+FRP respectively). At higher magnification, gaps in the mucosae (black arrow), resulting from mucosa cell necrosis at various stages (red circles). However, there were substantial antagonistic improvement following fermented rip and unripe *C. papaya* treatment.

**Table 1: showing C. papaya juice phytochemical screening**

| S/N | Phytochemical | Ripe | Unripe |
|---|---|---|---|
| **1** | **Alkaloids** | + | + |
| **2** | **Terpenoids** | + | + + |
| **3** | **Saponins** | + | + + |
| **4** | **Flavonoids** | + | + + + |
| **5** | **Tannins** | + | + + + |
| **6** | **Glycosides** | + + + | + |
| **7** | **Phenols** | + + | + + + |

**Key:** += minimal, + += medium and + + += large amounts

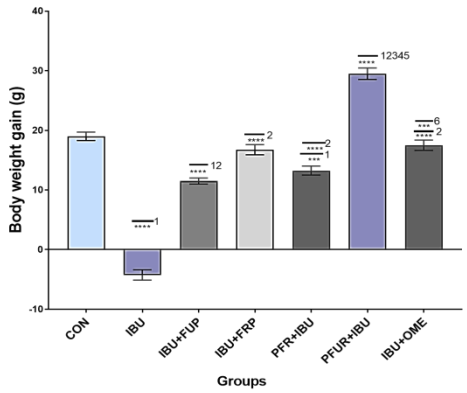


**Figure 1: Wistar rats body weight changes.** Note: CON (control), IBU (Ibuprofen), FUP (fermented unripe *C. papaya*), FRP (fermented ripe *C. papaya*) and OME (Omeprazole).

*, **, *** represents $p<0.05$, $p<0.01$ and $p<0.001$ when compared with CON and IBU respectively.

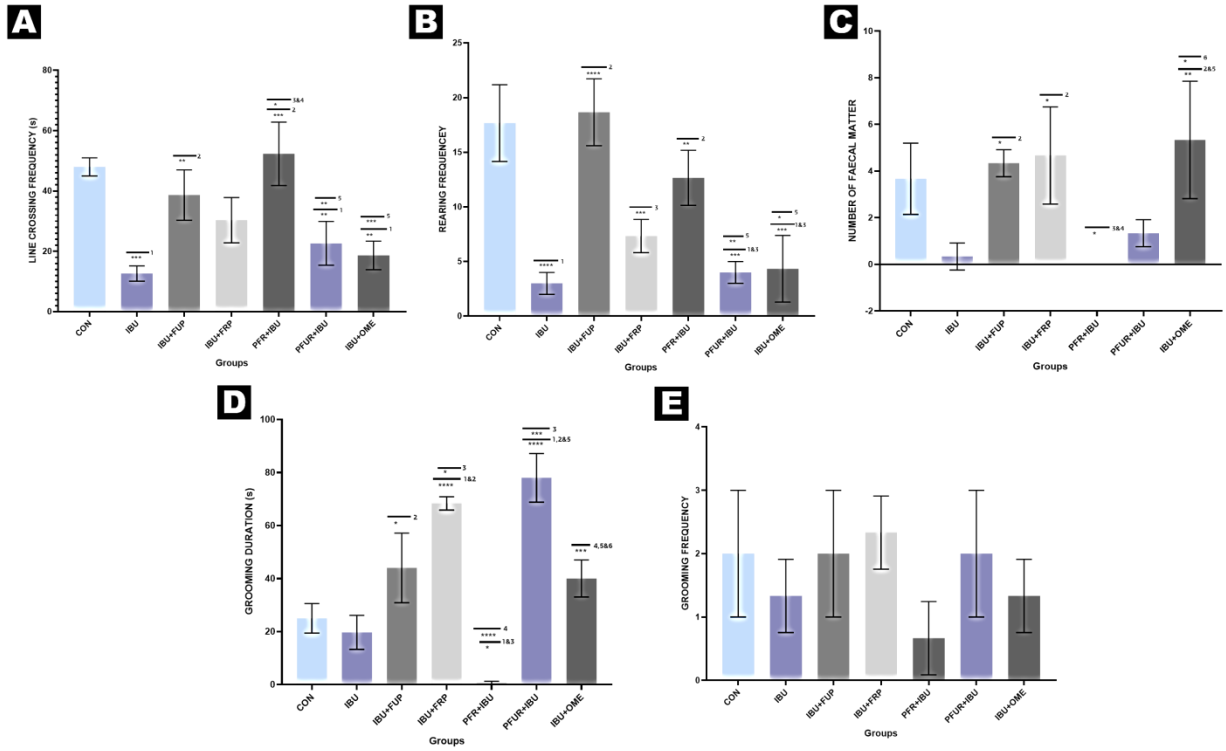


**Figure 2: (A-E): Wistar Rats Behaviour. (a) Line Crossing Frequency; (b) Rearing Frequency; (c) Number of Faecal Matter; (d) Grooming Duration; (e) Grooming Frequency.**

Note: CON (control), IBU (Ibuprofen), FUP (fermented unripe *C. papaya*), FRP (fermented ripe *C. papaya*) and OME (Omeprazole).

*, **, *** represents $p<0.05$, $p<0.01$ and $p<0.001$ when compared with CON and IBU respectively.

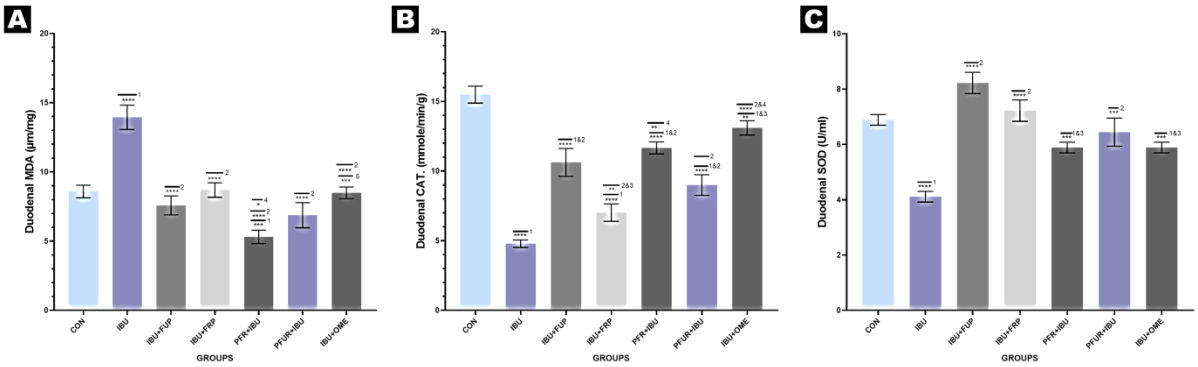


**Figure 3: (A-C): Wistar rats Duodenal Biochemical changes. (a) MDA; (b) CAT; (c) SOD.**

Note: CON (control), IBU (Ibuprofen), FUP (fermented unripe *C. papaya*), FRP (fermented ripe *C. papaya*) and OME (Omeprazole).

*, **, *** represents $p<0.05$, $p<0.01$ and $p<0.001$ when compared with CON and IBU respectively.

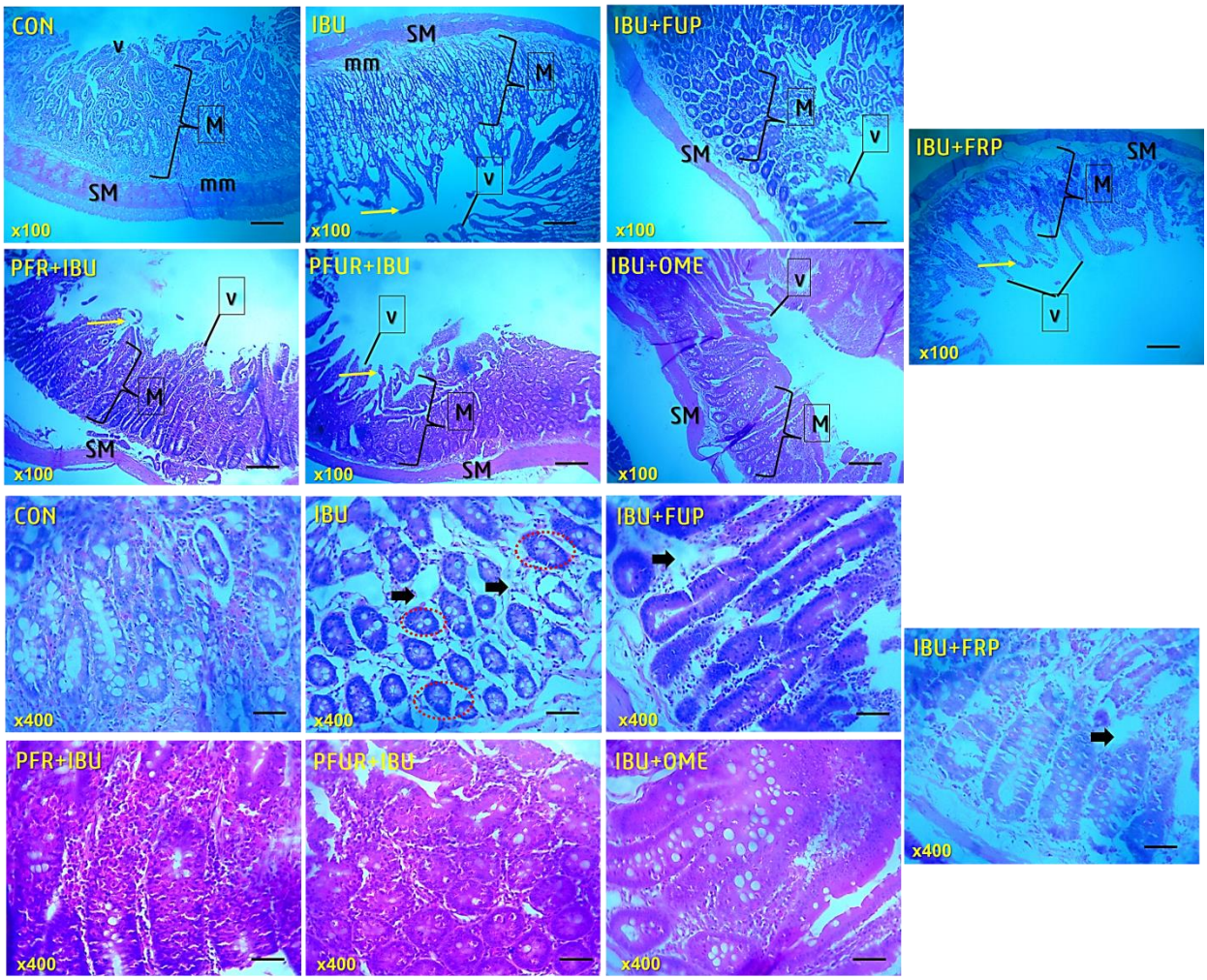


**Figure 1: Sections of the duodenum of Wistar rats (H&E x100; x400).**

Note: CON (control), IBU (Ibuprofen), FUP (fermented unripe *C. papaya*), FRP (fermented ripe *C. papaya*) and OME (Omeprazole).

**DISCUSSION AND CONCLUSION:** This study looked at the protective and therapeutic effects of unripe and ripe fermented *Carica papaya* (*C. papaya*) juice on an ibuprofen-induced duodenal ulcer. The duodenum plays a very important role in the digestion and absorption of food in the biological system. Reports from Awaad *et al.*, showed that, phytoconstituents derived from medicinal plants have antiulcerogenic action and work in a variety of ways [14]. The two extract contain alkaloids, terpenoids, saponins, flavonoids, tannins, glycosides, and phenols, according to the results of phytochemical screening conducted out to identify key metabolites in ripe and unripe *C. papaya* juice. Though *C. papaya* juice were fermented, the phytonutrient results obtained in this study were comparable to those reported previously by other authors who studied *C. papaya* extract in their unfermented state [15, 16, 17]. Phenol compounds protect the mucosa of the gastrointestinal tract against lesions caused by several experimental ulcer chemical and necrotic agents. Phenols are antihistaminic, which means they lower

histamine levels, and they prevent acid gastric output by preventing histamine release from gastric mast cells and inhibiting the gastric H+ /K+ proton pump. Also, phenol have cytoprotective properties that improve mucosal blood flow, induce mucobicarbonate formation in the gastrointestinal mucosa, and raise the level of prostaglandin [18]. Saponins cause the development of mucus, which protects the gastric mucosal barrier from acid effects and inhibits the production of PGF2 specifically [19]. Flavonoids are known to have antisecretory and cytoprotective effects. Prostaglandin, bicarbonate, and mucus secretion are stimulated by flavonoid activity. As well, the mucosal integrity reactive oxidants in the gastro-intestinal system are prevented from deteriorating [20]. Tannins are known to protect the mucosa outer layer, making it less permeable and more resistant to chemicals, mechanical harm, and irritation, and therefore preventing ulcer formation [20].

The acute toxicity investigation results, which used the two fermented extracts (C. papaya extract-unripe and ripe), revealed that there were no indicators of toxicity or mortality at 75% administration dose during the pilot experimentation. Further, the animals given the two fermented extracts in this study, gained weight normally. The stimulating impact of *C. papaya* extract (unripe and ripe) on the central nervous system areas that control appetite could explain the rats' weight gain. As a result, animals' daily food consumption increased, according to observations. This agrees with the work of Unigwe *et al.* whose research showed an increase in bodyweight and performance of broilers fed with *papaya* leaf meal. Thus, *C. papaya* efficiency can be linked to it phenol, flavonoid and tannin phytoconstituent [21].

Oral administration of ibuprofen (400 mg/kg Bw) to rats greatly affected their locomotory and social behaviour. We found in this study that, the locomotory and exploratory activities of rat exposed to ibuprofen were significantly altered. Rearing and grooming activities which correlate anxiety and depressive-like states were also highly compromised following ibuprofen exposure. This is suggestive of the inflammatory damages associated with ibuprofen ulceration can hamper the exposed rats cognitive and working memory performance of the central nervous system areas that control cognitive and executive function such as learning, anxiety and depression etc, and these could explain the rats' poor social behaviour, linked to the reduced exploratory/locomotory as well as rearing and grooming performance on the behavioural apparatus. Thus, it is important to examine the neurological intricacies, which could possibly contribute in defining the aetiology of ibuprofen induced ulceration models. However, the various intervention using fermented *C. papaya* juice (unripe and ripe) progressively restored these behavioural defects associated with experimental ibuprofen exposure.

The production of reactive oxygen species (ROS) is thought to be a major source of lipid oxidation, which results in alterations in membrane fluidity and permeability [22]. In this study, the primary phospholipids in the duodenal cell membrane were oxidized, the membrane structure was compromised, and membrane fluidity and permeability increased, resulting in a breakdown of the equilibrium inside and outside of cells and,

ultimately, cell destruction. Thus, a high level of malondialdehyde (MDA) expression following ibuprofen-induced duodenal ulceration was seen. As a result, we deduced that ROS played a key role in ibuprofen-induced stomach lesions. This report agrees with the work of Colucci, *et al.,* [23]; Boyacioglu, *et al.,* [24] and Hafez, *et al.,* [25]. Catalase (CAT) and Superoxide dismutase (SOD) serve a key antioxidant role in a biological system. Their expression is vital in maintaining normalcy and scavenging ROS. To combat ROS, cells have defence systems such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). These defence systems protect the mucosa of the duodenum from the toxicity of oxygen-derived free radicals [22]. In agreement with published literatures [22], this study establishes a statistically significant decline in CAT and SOD expression resulting from ibuprofen assault. Maisarah *et al.,* studied the antioxidant properties of *C. papaya* and discovered that *C. papaya* has remarkable antioxidant properties, proving that it has a positive correlation with free radical scavenging activity thus attesting to the higher SOD and CAT levels attained in this study [26].

Histological investigation showed high dose Ibuprofen administration to induce duodenal morphological damages. It is possible for ibuprofen to induce apoptosis in gastric mucosal cells, since it appears to increase leukocyte infiltration into the gastric mucosa, which is followed by ROS production [22, 27]. Recently, cell damage caused by ROS was considered as the main reason for NSAID induced gastric damage. In consistence with the published reports [22, 27], we observed duodenal lesions characterized by gaps in the mucosae, resulting from mucosa cell necrosis at various stages, edema, hemorrhage, inflammatory infiltration, and loss of epithelial cells in ibuprofen treated rats, through microscopic examination at a higher magnification, which was consistent with the behavioral results, markers of oxidative stress and antioxidant parameters results reported in this study. However, there were substantial antagonistic improvement following fermented ripe and unripe *C. papaya* therapies. *C. papaya* was capable of causing notable ameliorating impact on the morphology of the duodenum, by providing antioxidant and anti-inflammatory herbal supplement that enhanced the antioxidant and anti-inflammatory biological system against ibuprofen toxicity.

Conclusively we can say that *C. papaya* juice proves useful in managing of duodenal ulcers experimentally. *C. papaya* juice caused no toxic or adverse alterations to the duodenum in this study. However, *C. papaya* juice effectively lessened duodenal ibuprofen insults, suggesting its excellent antioxidative and anti-inflammatory abilities that enhanced the antioxidant and anti-inflammatory system against ibuprofen toxicity. Thus, we recommend that outreaches and awareness programs should be done to elucidate the extent of damaging effects these NSAIDs have on the gastrointestinal tract, and the possible protective and therapeutic effects of *C. papaya* juice.

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