Pharmaciana
Vol.14, No.3, Nov 2024, Page. 309–323
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v14i3.27639

Gastroprotective activity of Banana peel (*Musa paradisiaca* var. sapientum) methanol extract purified on aspirin-induced gastric ulceration in Rats

Jastria Pusmarani[1]*, Risky Juliansyah Putri[2], Citra Dewi[2], Difa Fitriani[3], Setyo Purwono[4], Zullies Ikawati[5]

[1]Department of Pharmacology and Clinical Pharmacy of Universitas Mandala Waluya, Jl. A. H. Nasution no. G37 Kambu district, Kendari, South-East Sulawesi, Indonesia
[2]Department of Phytochemical of Universitas Mandala Waluya, Jl. A. H. Nasution no. G37 Kambu district, Kendari, South-East Sulawesi, Indonesia
[3]Department of Pharmacy of Universitas Mandala Waluya, Jl. A. H. Nasution no. G37 Kambu district, Kendari, South-East Sulawesi, Indonesia
[4]Department of Pharmacology and Therapy of Universitas Gadjah Mada, Jl. Farmako, Sekip Utara, Mlati, Kabupaten Sleman, Daerah Istimewa Yogyakarta, Indonesia
[5]Department of Pharmacology and Clinical Pharmacy of Universitas Gadjah Mada, Jl.Sekip Utara,. Mlati, Kabupaten Sleman, Daerah Istimewa Yogyakarta, Indonesia

Submitted: 23-01-2024 ***Reviewed: 21-02-2024*** ***Accepted: 10-09-2024***

ABSTRACT

Banana (*Musa paradisiaca* var. sapientum) is the world's most popular fruit-bearing crop, with rising consumption and waste. This study aimed to measure the metabolite compound and evaluate the gastroprotective properties of a banana peel-purified methanol extract. Animals test used in this study were divided into six groups: Group One received NaCMC 0.5%, Group Two received sucralfate, Group Three received aspirin 1000 mg/kg body weight, and groups four, five, and six received PBP at doses of 200 mg/kg body weight, 400 mg/kg body weight, and 600 mg/kg body weight, respectively, for seven days. Except for group 1, all groups were induced with aspirin at 1000 mg/kg body weight on the eighth day. The result of this study exhibited banana peel containing total phenolic, flavonoid, and tannin compounds with concentrations of 33.45 mg GAE/g, 19.92 mg QE/g, and 0.16 %, respectively. The results showed that pure extract of *Musa paradisiaca* var. sapientum fruit peel can reduce the incidence of gastric ulcers by decreasing the ulcer index ($p<0.05$). The results suggested that *Musa paradisiaca* var. sapientum peel has a gastroprotective effect against aspirin-induced gastric ulceration.

Keywords: *Musa paradisiaca* var. sapientum peel, Gastric ulcer, purified extract

.

Corresponding author:
Jastria Pusmarani
Universitas Mandala Waluya
Jl. A. H. Nasution no. G37 Kambu district, Kendari, South-East Sulawesi, Indonesia
Email: triapusmarani20@gmail.com

INTRODUCTION

Peptic ulcers are lesions that develop in the stomach or the nearby part of the small intestine known as the duodenum, and they are among the most prevalent ailments affecting the upper digestive system (Malik et al., 2018). The prevalence of peptic ulcer disease is estimated at 5–10% in the general population (Lanas & Chan, 2017). Peptic ulcers are caused by mucosal damage, which is mostly caused by platelet agglutination inhibitors such as long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori* (H. *pylori*) infection, alcohol consumption, and long-term use of tobacco (Wang and Wei, 2022; Jang et al., 2022). In addition, peptic ulcers may be induced by submucosal erosion, decreased cyclooxygenase, and deformation of the stomach mucosal layer (Ibrahim & Allam, 2022). Moreover, peptic ulcers result from disruptions in the body's defensive mechanisms, which include blood circulation, mucus level, mucosal membranes, cell renewal, and endogenous defense enzymes (Yaghoobi & Armstrong, 2022).

Aspirin is one of the NSAIDs that might cause gastric damage in the form of chronic inflammation produced by gastric acid stimulation because it breaks down the gastric mucosal barrier. Additionally, gastric acid can directly damage the mucosal epithelial cells, resulting in inflammation, bleeding, and gastric ulcers. Intestinal microorganisms, bile, and other stimulating factors have all been implicated in the process of aspirin-induced mucosal damage (Washio et al., 2016). Patients with a medical history of peptic ulcers or previous bleeding who are above 65 years old, who are taking anticoagulants or long-term steroids, and who consume high dosages of NSAIDs or combinations of NSAIDs are the most vulnerable to developing ulcers induced by NSAIDs (Narayanan et al., 2018).

Antacids, acid inhibitory agents, cytoprotective agents, histamine-2 (H_2) receptor antagonists, muscarinic receptor (M1) antagonists, *Helicobacter pylori* eradication drugs, and triple therapy regimens are the most often used pharmaceuticals to treat peptic ulcers (Dipiro et al., 2020). Typical adverse effects associated with these medications consist of joint discomfort, gynecomastia, erectile dysfunction, and systemic alkalosis (Handa et al., 2014). Nonetheless, prolonged use of proton pump inhibitors (PPIs) can lead to several adverse outcomes as they suppress gastric acid secretion, creating an environment conducive to the growth of ingested microbial pathogens and infections (Kuna et al., 2019). An earlier research study reported that the use of PPIs could increase the risk of acquiring enteric infections such as Campylobacter and Salmonella, as well as developing community-acquired pneumonia (Lambert et al., 2015).

Currently, numerous investigations are underway to explore the potential of natural substances in improving pharmaceuticals with minimal adverse effects. Bananas are widely consumed globally, with a production exceeding 100 million tons worldwide in 2013 (Vu et al., 2018). Some of the metabolite compounds identified in banana peel include tannins, flavonoids, polyphenols, terpenoids and phenolic (Thomas and Krishnakumar, 2017; Pusmarani et al., 2019; Kibria et al., 2019). When compared to other fruit peels like watermelon, melon, papaya, and pineapple, banana peel has a high phenolic concentration (Morais et al., 2015). Various metabolite compounds, such as terpenoids flavonoids, and phenolics, play important roles in human health as antioxidants and gastroprotective agents (Jabbar, 2022; Li et al., 2022; Al Amri and Hossain (2018) reported that the extract methanol from banana peel had higher antioxidant activity related to gastroprotective activity.

Kapadia et al. (2015) discovered that banana peels contained therapeutic compounds. Banana peels have various activities, such as antibacterial, antibiotic, and antioxidant (Rita et al., 2020). Furthermore, various pharmacological activities of banana peel include hepatoprotective, cholesterol-lowering, and anti-ulcerogenic activities (Berawi and Bimandama, 2018; Pusmarani et al., 2022; Aziakpono et al., 2021). The research that has been carried out has shown extracts of banana peel (*Musa sapientum*) protect the stomach mucosa against erosion and have ulcer-healing capabilities (Onasanwo et al., 2013). Therefore, based on these facts, this study aims to assess the gastroprotective activities of banana peel extract purified on aspirin-induced gastric ulceration in rats.

MATERIALS AND METHODS

Materials

Banana fruit peels (*Musa paradisiaca* var. sapientum) were obtained from the Poleang district, Bombana regency, Southeast Sulawesi. The plants were determined at the Biology Laboratory, Faculty of Teacher Training and Education, Halu Oleo University.

Methods

Extraction of Banana peel

A 5-kilogram dry peel of ripe banana was placed in a maceration vessel. The extraction of the sample was used through maceration and methanol as the solvent and left at room temperature for 24 hours. This method was repeated for 3x24 hours, or until the solvent was clear. The extract of banana peels was then filtered five times with filter paper. A rotary rotavapor was used to evaporate the macerate. After getting the extract, it was concentrated and weighed on an analytical balance. Then, the methanol extract of banana peel was calculated for its yield.

Purification extract of Banana peel

Liquid-liquid extraction was used to purify the banana peel extract through a separatory funnel. The viscous banana peel extract was dissolved in distilled water, mixed with *n*-hexane, transferred to a separating funnel, and shaken until the solution separated. This process was repeated until the solvent's yellow color was removed. Ethyl acetate was used to elute the n-hexane fraction until the solution was separated into two parts. The ethyl-acetate as an insoluble fraction was eluted by hot water and then concentrated as a viscous banana peel extract containing total phenolic, flavonoid, and tannin compounds using a rotary evaporator.

Determination of total phenolic content

Measurement of the overall phenolic content of the pure extract obtained from banana peels using the Folin-Ciocalteu method through spectrophotometry (Hossain et al., 2014). Gallic acid served as the standard for the experiment. The crude extract and the standard were mixed with the 7.5% sodium carbonate and Folin Ciocalteau reagent. The resulting mixture's absorbance was gauged at 775 nm. A standard curve is used to determine phenolic compounds and is reported as gallic acid equivalents (GAE) in milligrams per gram dry weight (mg/g extracted substance). The analysis of the sample was conducted three times to ensure accuracy.

Determination of total flavonoid content

The determination of flavonoid content in the purified extract obtained from banana peel was conducted through a colorimetric aluminum chloride test (Baba & Malik, 2015). In the experiment, quercetin served as the standard for the assay. The crude extract and the standard were combined with sodium nitrite, aluminum chloride, and distilled water. The mixture extract and standard were then incubated, followed by the addition of NaOH and thorough mixing. After cooling down, the absorbance of the mixtures was read at 415 nm. Using the calibration curve, the flavonoid compound was assessed and written as milligrams of quercetin equivalent per gram of dry weight (mg QE/g). Sample was analyzed three times to ensure accuracy.

Determination of tannin content

To determine the tannin content, an insoluble compound called polyvinylpolypyrrolidone (PVPP) was employed. PVPP is known for its ability to bind tannins (Pulipati et al., 2014). For the analysis of tannin content, a standard tannin solution was utilized. The crude extract was prepared by dissolving the extract with a content of 1 mg in methanol. Then, the extract of 1 ml was mixed with 100 mg PVPP. The mixture was vortexed and incubated at 40^{o}C for 15 minutes, followed by centrifugation at 3000 rpm for 10 minutes. The resulting mixture was read at 725 nm. The tannin compound was calculated using a

calibration curve and reported a percentage of weight per weight (% w/w). The experiment was performed in triplicate to ensure accuracy.

In vivo study: gastroprotective effect of banana peel methanol extract purified animals

A total of thirty male rats with Wistar species, that have a weight range of 150-200 g with the age 2-3 months were obtained from the animal enclosure of the integrated research and Testing Laboratory unit Preclinical and Experimental Animal Development of Universitas Gadjah Mada, Indonesia. The animals were then separated randomly into six groups with each group consisting of five rats. The group consisted of negative control (rats receiving 0.5% of Na-CMC), a sucralfate-treated (dose: 120 mg/5 ml), an induced control group (with 1000 mg/kg body weight of aspirin), and three groups received 200, 400, and 600 mg/kg body weight of purified banana peel methanol extract, respectively. All rats were adapted and acclimatized for 7 days. All animals were fed rodent pellets as a standard diet and water *ad libitum*. Before testing, all rats were not fed for 18 hours with still received water ad libitum. The animals were kept into a cage at a stable temperature (25 ± 2 °C) and relative humidity (50-70%) with controlled light (12 hours dark/12 hours light cycle). All studies were approved by the Animal Care Ethics Committee of the Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia (KE/FK/108/EC/2019), following the National Institute of Health (NIH) "Guidelines for the Care and Use of Laboratory Animals" (NIH Publications No. 85-23, Revised 1985).

Dose preparation and route of administration

The first group was given NaCMC 0.5%. The second group was treated with sucralfate 120 ml/5 ml. All animals were not fed for 18 hours and only given a drink before treatment. The third group was given aspirin at a dosage of 1000 mg/kg body weight, while groups 4, 5, and 6 were treated with purified banana peel methanol extract at doses of 200 mg/kg body weight, 400 mg/kg body weight, and 600 mg/kg body weight, respectively. All animals received oral treatment for 7 days. All animals except for group 1 were administered a dose of aspirin at 1000 mg/kg body weight to induce gastric ulcers on the eighth day. After six hours, all rats were euthanized with ketamine overdose by injected intraperitoneally. The abdomen were then dissected, eliminated, rinsed, and cut open along the larger curvature. The gastric juice was obtained for analysis, and the stomach was thoroughly washed with normal saline to eliminate blood clots and stomach contents. Macroscopic examination of the stomach by measuring the gastric pH, the volume of gastric fluid, and the extent of ulceration was calculated with a vernier caliper (Mahurkar and Sayeed, 2015; Kadhem et al., 2018).

The number of scorings was used to determine the ulcer score. (Table 1) (Pusmarani et al., 2019). The method described by Cho & Ogle (1979) was used to calculate the ulcer index (mm) for each group. The ulcer index and percentage inhibition were calculated using formula (1) and formula (2):

$$\text{Ulcer Index (UI)} = \frac{Total\ of\ Ulcer\ score}{Total\ of\ ulcerated\ rats} \quad \text{..... (1)}$$

$$\%\ \text{Inhibition} = \frac{IU\ (Induced\ Group) - IU\ (treated\ group)}{IU\ (Induced\ Group)} \text{ x } 100\% \quad \text{..... (2)}$$

The determination process of gastric juice and pH

The gastric juice were obtained and then subjected to centrifugation at 1000 rpm for 10 minutes. The volume of supernatant was measured in milliliters, and its pH was determined by a pH meter (Ulser, 2016).

Histopathological evaluation of gastric damage

The method for determining the histologic assessment of gastric tissue called gastric histopathologic examination follows the method of Carleton et al. (1980). Each stomach was placed in formalin 10% at

room temperature for 24 hours. The stomach was embedded in a paraffin block using an automated embedding machine. Gastric tissue samples were cut into 5 mm slices for sectioning and colored using hematoxylin-eosin for histopathological examination of the gastric mucosa (Sisay and Jemere, 2020). The histology of the stomach rats observed edema, inflammatory cell infiltration, and necrotic changes to define all rat stomachs (Kathirvelu et al., 2019; Zaghlool et al., 2019).

Table 1. Number of scoring lesions formed of gastric

Number of Scoring	Number of lesions (mm)
1	< 1
2	1.00 -2.00
3	2.01-3.00
4	3.01-4.00
5	4.01-5.00
10	>5.00
Perforation	>25

Data Analysis

The mean value and standard deviation of means are described with numerical data. All statistical analyses were calculated with SPSS 25.00 software. Kruskal-Wall test was used to analyze the data. The Mann-Whitney test was used to compare the groups with the control group with statistical significance at the $p < 0.05$ levels.

RESULT AND DISCUSSION

In extract of methanol from banana peel, it was found to yield an extract of 7.07%. The total phenolics level in *Musa paradiasiaca* var. sapientum peel purified extract was analyzed using a slightly modified Folin-Ciocalteu method with the standard (gallic acid), and the total phenolics level was 33.45 mg GAE/g (Table 2). The flavonoid content of *Musa paradiasiaca* var. sapientum peel purified extract was measured by aluminum chloride assay with quercetin as a standard and showed a flavonoid level of 19.92 mg GAE/g. The tannin level in banana peel purified extract was measured using an insoluble polyvinyl-polypyrrolidone with tannin as a standard, and it was found to be 0.16%. In this study, the banana peel had the highest level of flavonoid when compared to total phenolic and tannin.

The absorption measurements of standard gallic acid, quercetin, and tannin were entered into Microsoft Excel to create a graph of concentration versus absorption, which served as a calibration curve for standard gallic acid solution (Figure 1, Figure 2, and Figure 3).

Table 2. Determination of total phenolic, flavonoid and tannin levels of banana (*Musa paradisiaca* var. sapientum) peel methanol extract purified

Metabolite Compounds	Replication	Absorbance	Metabolite compound content	Metabolite compound levels average±SD
Total Phenolic (mg GAE/g)	1	0.132	33.86	33.45±0.3554
	2	0.144	33.23	
	3	0.139	33.26	
Flavonoids (mg QE/g)	1	0.031	19.55	19.92±0.4549
	2	0.032	19.79	
	3	0.032	20.43	
Tannins (%)	1	0.046	0.17	0.16±0.01
	2	0.043	0.15	
	3	0.044	0.16	

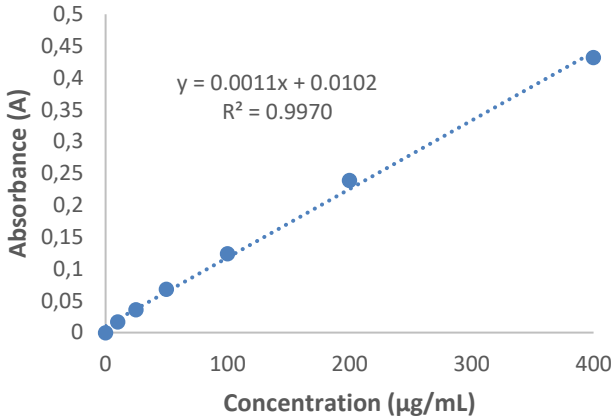

Figure. 1. Calibration curve of gallic acid at a maximum wavelength of 775 nm

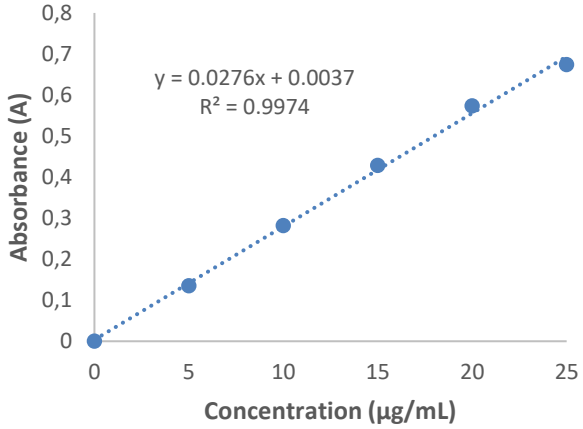

Figure 2. Calibration curve of quercetin at a maximum wavelength of 415 nm

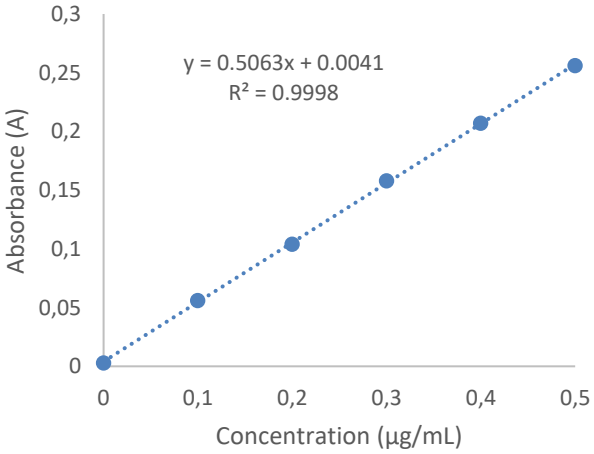

Figure 3. Calibration curve of tannin at a maximum wavelength of 725 nm

The gastroprotective effect of banana peel purified extract on gastric juice and pH is shown in Table 3. The findings of the research indicated that the purified methanol extract of *Musa paradisiaca* var. sapientum peel, administered with doses at 200 mg/kg and 400 mg/kg body weight (resulting in values of 2.63 ±0.727 and 1.61 ± 0.51, respectively), as well as sucralfate (with a value of 2.03 ±0.89), significantly decrease the volume of gastric juice when compared to the group that was induced with aspirin (1000 mg/kg body weight). The rising volume of gastric juice from the banana peel methanol extract purified was not statistically significantly different (Kruskal Wallis test, $p=0.475<0.05$) compared to the aspirin group. Based on some research results, one of the indicators that can be measured when a peptic ulcer occurs is a rise in gastric volume and the healing of gastric ulcers can be characterized by a decrease in the volume of stomach juice (Raish et al., 2021). Although the purification of banana peel extract raised the pH of the stomach, macroscopic and histopathologic observations showed that the extract was effective in promoting the healing of gastric ulcers.

The pH levels in the sucralfate group and banana peel methanol extract group were significantly increased compared to the other groups (Table 3). The pH value in the banana peel methanol extract group with doses of 200 mg/kg body weight (4.80±0.837), 400 mg/kg body weight (4.63± 2.663), and 600 mg/kg BW (4.87±0.641) was higher when compared to the induced group (4.20±0.837). Pre-treatment with purification banana peel extract 200 mg/kg BW, 400 mg/kg BW, and 600 mg/kg BW showed a significant increase in gastric fluid pH ($p=0.01<0.05$, $p=0.025<0.05$, and $p=0.01<0.05$, respectively) compared to group aspirin-induced ulcers. The increase in gastric fluid pH caused by the purified banana peel methanol extract showed no significant difference ($p < 0.05$) compared to the sucralfate group. The results agree with previous research that shows increasing the pH of gastric juices is associated with the healing process of gastric ulcers (Rahman et al., 2020).

Table 3 shows the effect of purified banana peel methanol extract at various doses on ulcers in rats before and six hours after receiving aspirin. The results indicate that oral aspirin administration causes damage to the gastric mucosa with an ulcer index of 7.6±3.362 (Figure 4). This damage is significantly different from the group receiving Na CMC ($p=0.005$, $p < 0.05$). These findings indicate that aspirin administration resulted in a marked ulcer index compared to the negative control group. Purified banana peel methanol extract with the dose of 200 mg/kg body weight substantially reduced ($p=0.018 < 0.05$) the ulcer index as compared to the induced group. Meanwhile, a purified banana peel methanol extract with a dose of 400 mg/kg BW significantly declined the ulcer index ($p=0.005<0.05$) compared to the induced group. Furthermore, purified banana peel methanol extract at a dose of 600 mg/kg body weight significantly reduced ($p=0.005<0.05$) the ulcer index as compared to the induced group. Moreover, purified banana peel methanol extract at a dose of 200, 400, and 600 mg/kg BW reduced the ulcer index 3.30±1.732, 0.00±0.000 and 0.00±0.000 giving 56.5%, 100%, and 100% protection, respectively.

Table 3. Gastroprotective activities of banana (*Musa paradisiaca* var. sapientum) peel extract purified

Animal group	Group	pH of gastric juice (Mean ± SD)	Volume of gastric juice (Mean ± SD)	Ulcer Index (Mean ± SD)	% inhibition
1	Na CMC 0.5%	5.20 ± 1.095	0.88 ± 0.565	0.00±0.000 [f]	0
2	Sucralfat (120 mg/5 ml)	4.40± 0.548	2.03 ±0.89	0.00±0.000 [f]	100
3	Aspirin (1000 mg/kg BW)	4.20±0.837	3.62 ± 1.31	7.60±3.362 [f]	0
4	Purified banana peel extract (200 mg/kg BW	4.80±0.837[e]	6.03 ±2.727[d]	3.30±1.732[a,f]	56.5
5	Purified banana peel extract (400 mg/kg BW)	4.63± 2.663[e]	2.63 ±0.727[d]	0.00±0.000[b,f]	100
6	Purified banana peel extract	4.87±0.641[e]	1.61 ± 0.51[d]	0.00±0.000[c,f]	100

(600 mg/kg BW)

[a,b,c] The aspirin, banana peel, and sucralfate groups demonstrated a significant reduction in ulcer index according to the Mann-Whitney test. [d,e] There was no significant difference in pH and gastric volume between the banana peel and sucralfate groups according to the Kruskal-Wallis test. There were significant differences in the ulcer index between the banana peel and the standard drug sucralfate, as indicated by the Kruskal-Wallis test.

According to our study, a purified banana peel extract significantly decreased the ulcer index after aspirin administration (Kruskal-Wallis test, $p = 0.000 < 0.05$), demonstrating that banana peel has gastroprotective activity against aspirin-induced gastric ulcers. Figure 4 shows the representation of the stomachs of rats after aspirin-induced gastric ulcers. Aspirin (1000 mg/kg body weight) induced superficial or deep erosions, inhibited prostaglandins, and decreased mucus.

Histopathological examination of the control group (Na CMC control group) demonstrated no significant damage to the stomach mucosa, such as necrosis in the tunica mucosa and submucosa, edema in the submucosa, plasma cell infiltration, and limfosit in the tunica mucosa and submucosa (Figure 5). The purified extract of the banana peel with doses of 200, 400, and 600 mg/kg BW, respectively were represented protects the gastric mucosa better, as evidenced by no specific pathological changes, no edema with infiltration in plasma cells or infiltration in the tunica mucosa and submucosa, and it has a comparable protective ulcer gastric effect with sucralfate groups (Figure 5). Aspirin 1000 mg/kg body weight as an inducer of necrosis ulcerative bleeding in the tunica mucosa-submucosa, edema in the tunica submucosa with neutrophil infiltration, lymphocyte and plasma cell tunica mucosa and submucosa (Figure 5).

An imbalance between pepsin, stomach acid, and the components of the gastrointestinal tract is responsible for maintaining the mucous membranes of the gastrointestinal tract, leading to peptic ulcers. The defense of gastric mucosal integrity involves balancing harmful factors such us hydrochloric acid (HCl) and pepsin with protective factors such as mucus and bicarbonate secretion, prostaglandins, mucosal blood flow, and nitric oxide (Yandrapu & Sarosiek, 2015). An agent exhibited a capacity to restore balance by reducing the secretion of gastric ulcers may play a role as an anti-ulcerative agent (Ezekwesili et al., 2014). Aspirin belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and works by inhibiting the activity of the cyclooxygenase (COX) enzyme, which leads to reduced synthesis of prostaglandins. This reduction in prostaglandins can increase gastric acid secretion, thereby increasing the risk of developing ulcers.
(Cryer & Mahaffey, 2014).

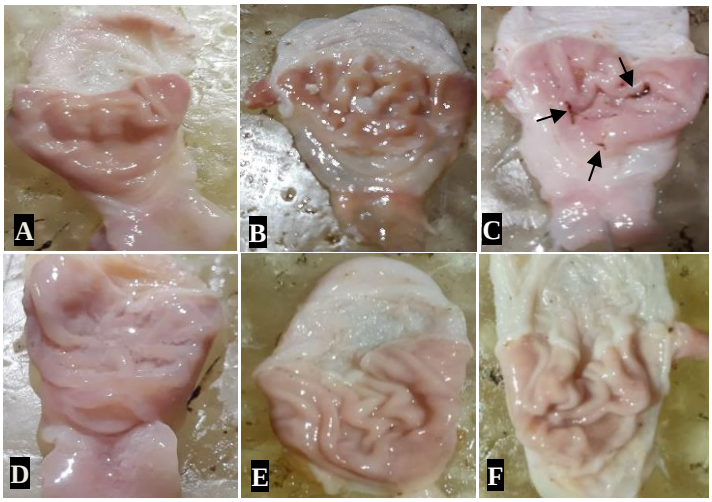

Figure 4. Macroscopic observation of stomach; (A) NaCMC group; (B) Sucralfate (120mg/5 mL) group; (C) Aspirin group (1000 mg/kg BW); (D) purified banana peel extract

200 mg/kg BW; (E) purified banana peel extract 400 mg/kg BW; (F) purified banana peel extract 600 mg/kg BW

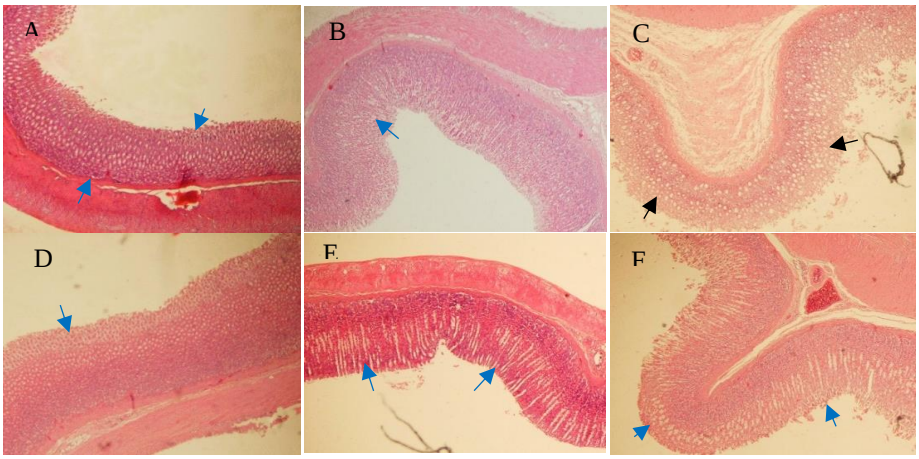

Figure 5. Microscopic of mucosa gastric: (A) Microscopic section of the control group Na CMC; (B) Microscopic section of group sucralfate (120mg/5 mL); (C) Microscopic section of aspirin (1000 mg/kg BW) group as the marker severe ulceration, necrosis, and hemorrhage; (D), (E), and (F) Microscopic section of received by *Musa paradisiaca* var. sapientum peel methanol extract purified with doses 200 mg/kg BW, 400 mg/kg BW, and 600 mg/kg BW, respectively and it was described normal gastric mucosa. The blue arrow indicates no change in gastric mucosal cell-specific pathology

The level of histologic damage to the stomach is microscopically classified into three categories: mild, moderate, and severe damage. In mild damage, there were changes in the gastric epithelium in one place where signs of inflammation were found, namely the spread of inflammatory cells in the lamina propria, and erosion was found, namely the release of some epithelial cells in the superficial part. In moderate damage, it was found that gastric epithelial changes occurred in several places (multifocal). In severe damage, changes in the gastric epithelium accompanied by signs of inflammation in the mucosa as in mild damage, but the changes that occur have been mild damage, but the changes that occur are evenly distributed (diffuse) throughout the epithelial (Sakura et al., 2017).

For many years, traditional medicine has employed natural products to treatment various ailments. The use of herbal drugs in complementary and alternative medicine (CAM) to address gastrointestinal issues is growing in both developed and developing nations. The use of medicinal plants as safe and effective therapies is supported by scientific evidence, as recommended by the World Health Organization (WHO) (Hervé et al., 2018). Medicinal/herbal plants and extracts are useful in the treatment of gastric ulcers with no noticeable side effects and at a low cost (Gohar & Zaki, 2014; Zheng et al., 2014; Saiah et al., 2018). Banana peel is a plant that has been shown to treat gastric ulcers. It contains various metabolite compounds that contribute to the healing of gastric ulcers (Mohammed et al., 2021).

The potential anti-ulcer capacity of purified methanol extract of banana peel (Musa paradisiaca var. sapientum) was investigated in this study using aspirin-induced ulceration models in rats. The study measured ulcer index, percent inhibition, pH, and volume of gastric juice. The ulcer index is a macroscopic marker to assess the extent of stomach ulceration or gastric damage in animal models. (Saheed et al., 2015).

Our results indicated no statistically significant differences in pH and gastric juice volume. It might be due to a reduced substance component or a higher dose is necessary. The volume of acid in gastric juice is a representation of gastric secretion, which includes various substances such as hydrochloric

acid (HCl), pepsinogen, bicarbonate, intrinsic factor, and protein. The decrease in the concentration of hydrogen ions in gastric juice indicated the high pH of gastric juice.

In this study, *Musa paradisiaca* var. sapientum peel showed gastroprotective activity (Kruskal Wallis test, $p=0.000<0.05$) against aspirin-induced gastric ulcer. This study's findings are comparable to those of prior research conducted by Fayyaz et al. (2021) and Pusmarani et al. (2019). Furthermore, similar to a result by Gogola (2020), the ethanolic extract of various banana peels, such as *Musa acuminata*, *Musa parasiaca* L., and *Musa acuminata Colla* cv. exhibits antioxidant and gastroprotective properties against aspirin-induced gastric ulcers. Moreover, Abdullah et al. (2014) revealed that banana peel (*Musa acuminata*) had antiulcerogenic properties, which were associated with metabolite components identified in the banana peel and pulp, such as saponins, flavonoids, and triterpenes.

This study presented that *Musa paradisiaca* var. sapientum peels contain phenolic, flavonoid, and tannin compounds. Additionally, flavonoids, polyphenols, terpenoids, saponins, and alkaloids were also found in banana peel (Pusmarani, Putri et al., 2019). Several phenolic compounds observed in banana peel include gallic acid, catechin, epicatechin, tannins, and anthocyanins (Singh et al., 2016). The medicinal plants and their chemical components identified by Kuna et al. (2019) exhibit preventive and therapeutic effects on peptic ulcers.

Plant metabolites known as phenolic compounds or polyphenols are molecules found in plants that are similar to the more well-known phenol groups (Harborne, 1989). Phenolic compounds were known to possess various physiological functions, including gastroprotective, vasodilator, antioxidant, antiplatelet aggregation, and cardioprotective properties (Sharifi-Rad et al., 2021; Shahidi and Ambigaipalan, 2015; Chiu et al., 2021). Polyphenols have been found to treat gastric ulcers through their antioxidant properties, which prevent tissue damage caused by free radicals (Ahmed et al., 2016).

Tannins possess astringent properties that can cause the precipitation of proteins in mucosal membranes and skin. These compounds have been shown to reduce gastric secretion, enhance the production of the mucus layer, and protect the gastric mucosa pH (Benchikh, 2018).

Saponins are metabolites that, through an anti-secretory mechanism, inhibit acid secretion and total acid production while decreasing the pH of gastric juice (Awaad et al., 2013). Another potential of saponin compounds' anti-ulcerogenic properties involves minimizing stomach mucosa's inflammatory responses and promoting mucin synthesis (M. Sharifi-Rad et al., 2018).

Flavonoids are the largest group of plant phenolic compounds, constituting more than 50% of the approximately 8,000 known polyphenols in the natural world (Puri & Hall, 1998). In addition, Flavonoids are the most widely distributed group of phenolic compounds, found in almost all parts of plants, particularly in photosynthesizing cells (Kumar & Pandey, 2013). Our investigation focused on *Musa paradisiaca* var. sapientum peel, which contains flavonoid compounds. Flavonoids in banana peel reduced mast cell histamine secretion, prevented lipid peroxidation, preserved the gastric mucosal glycoprotein moiety, and increased nitric oxide (NO) activity (Awaad et al., 2013).

Another study found that banana peel contains leucocyanidin as a natural flavonoid derived from unripe banana (*Musa sapientum*) that promotes cell proliferation, accelerates wound healing, strengthens the mucosal layer, and protects the gastric mucosa from erosion (Lewis et al., 1999; Lewis and Shaw, 2001). Furthermore, the antiulcer properties of bananas were attributed to the active component leucocyanidin, which could be responsible for promoting mucosal maintenance, cell proliferation, mucus secretion, and preventing the release of hydrochloric acid (HCl), ultimately leading to ulcer healing (Onasanwo et al., 2013). On the other hand, hydroxy ethylated leucocyanidin and tetra-allyl leucocyanidin, which are synthetic analogs of leucocyanidin, were found to have gastroprotective effects in rats with aspirin-induced erosions by increasing the thickness of the gastric mucus (Kumar et al., 2013). In a study by Obioma et al. (2018), unripe *Musa paradisiaca* ethanolic extract was found to have the potential to heal ulcers and may be suggested as part of the diet for individuals who are at a high risk of developing gastric ulcers due to aspirin treatment.

Natural antioxidants derived from herbs have been found to offer significant protection against a variety of diseases, including gastric ulcers (Palle et al., 2018). Purified banana peel extract demonstrated

free radical scavenging activities against DPPH with the highest antioxidant effect and the smallest IC_{50} values of 139.498 ppm (Jami'ah et al., 2018). Meanwhile, banana peel (*Musa paradisiaca*) was shown to have antioxidant activity by increasing OH radical scavenging ability, Fe^{2+} chelating ability, and MDA inhibition when the concentration of the extract was increased, paving the way for gastric ulcer treatments (IM et al., 2014).

These explanations for our findings, coupled with the histopathological data, revealed the purified banana peel extract's beneficial effects on treating aspirin-induced gastric ulcers. Therefore, gastroprotective benefits may be attributed to decreasing gastric acid production, protecting the gastric mucosal lining, or eradicating H. *pylori*. The gastroprotective activity of the purified extract from *Musa paradisiaca* var. sapientum peel is attributed to the presence of bioactive components with anti-ulcer activities, such as phenolics, flavonoids, tannins, leucocyanidin, and saponins (Farzaei et al., 2015; Pereira and Maraschin, 2015). Additionally, banana peel extract may enhance the protection of mucosal tissues and promote ulcer healing because of the presence of aqueous polysaccharides, which are major agents that coat the mucosa.

CONCLUSION

In conclusion, the banana peel purified extract contained total phenolic, flavonoid, and tannin compounds that are associated with banana peel's gastroprotective properties. In this study, it was demonstrated that purified banana peel extract exhibits a superior gastroprotective effect against aspirin-induced ulcers compared to standard medication (sucralfate).

ACKNOWLEDGEMENT

The financial support for this research was provided by the Indonesian Ministry of Education, Culture, Research, and Technology, and the authors gratefully acknowledge this support.

REFERENCES

Abdullah, F. C., Rahimi, L., Zakaria, Z. A., & Ibrahim, A. L. (2014). Hepatoprotective, antiulcerogenic, cytotoxic and antioxidant activities of Musa acuminata peel and pulp. Novel Plant Bioresources: Applications in Food, Medicine and Cosmetics, 371-382. https://doi.org/10.1002/9781118460566.ch26

Ahmed, O. E. I., Hashim, N. M., Yousif, M., Ibrahim, A. A. A., & Ismail Adam, H. A. (2016). Ahmed, O. E. I., Hashim, N. M., Yousif, M., Ibrahim, A. A. A., & Ismail Adam, H. A. (2016). Gastroprotective effects of (+)-catechin hydrate on ethanol-induced gastric ulcer in rats. Cienc Tec Vitivinic, 31. *Cienc Tec Vitivinic*, *31*.

Al Amri, F. S., & Hossain, M. A. (2018). Comparison of total phenols, flavonoids and antioxidant potential of local and imported ripe bananas. *Egyptian Journal of Basic and Applied Sciences*, *5*(4), 245–251. https://doi.org/ 10.1016/j.ejbas.2018.09.002

Awaad, A. S., El-meligy, R. M., & Soliman, G. A. (2013). Natural products in treatment of ulcerative colitis and peptic ulcer. *Journal of Saudi Chemical Society*, *17*(1), 101–124. https://doi.org/10.1016/j.jscs.2012.03.002

Aziakpono, O. M., Ofili, C. C., Chisom, M. U., Johnson, U. A., John, O. A., Sylvanus, M. C., Ogbonnaya, M., Chizoba, N. G., & Harrison, O. U. (2021). Anti-Ulcer Activities of Methanolic Extract of Musa Paradisiaca. *Journal of Advances in Medical and Pharmaceutical Sciences*, *23*(6), 10–17. https://doi.org. 10.9734/jamps/2021/v23i630240

Baba, S. A., & Malik, S. A. (2015). Determination of total phenolic and flavonoid content, antimicrobial and antioxidant activity of a root extract of Arisaema jacquemontii Blume. *Journal of Taibah University for Science*, *9*(4), 449–454. https://doi.org/10.1016/j.jtusci.2014.11.001

Benchikh, F. (2018). *Pharmacological effects of Myrtus communis L. on the gastrointestinal tract of rats and mice*.*Thesis*. Université Ferhat Abbas Sétif 1.

Berawi, K. N., & Bimandama, M. A. (2018). The effect of giving extract etanol of kepok banana peel (Musa Acuminata) toward total cholesterol level on male mice (Mus Musculus L.) strain

deutschland-denken-yoken (ddy) Obese. *Biomedical & Pharmacology Journal*, *11*(2). https://doi.org/10.13005/bpj/1431

Carleton, H. M., Drury, R. A. B., & Wallington, E. A. (1980). *Carleton's histological technique*. Oxford University Press, USA.

Chiu, H.-F., Venkatakrishnan, K.: K, Golovinskaia, O., & Wang, C.-K. (2021). In Vitro and In Vivo Study of Gastroprotective Effect of Purified Exract Andrographis Paniculata. *Molecules*, *26*(7), 2090. https://doi.org/10.3390/molecules26072090

Cho, C. H., & Ogle, C. W. (1979). Cholinergic-mediated gastric mast cell degranulation with subsequent histamine H1-and H2-receptor activation in stress ulceration in rats. *European Journal of Pharmacology*, *55*(1), 23–33. https://doi.org/10.1016/0014-2999(79)90144-4

Cryer, B., & Mahaffey, K. W. (2014). Gastrointestinal ulcers, role of aspirin, and clinical outcomes: pathobiology, diagnosis, and treatment. *Journal of Multidisciplinary Healthcare*, *7*, 137. https://doi.org/10.2147/JMDH.S54324

Dipiro, J., Yee, G., Haines, S., Nolin, T., & Ellingrod, V. (2020). *Pharmacotherapy: a pathophysiologic approach. 11th Editi*. New york: McGraw-Hill Companies.

Ezekwesili, C. N., Ghasi, S., Adindu, C. S., & Mefoh, N. C. (2014). Evaluation of the anti-ulcer property of aqueous extract of unripe Musa paradisiaca Linn. peel in Wistar rats. *African Journal of Pharmacy and Pharmacology*, *8*(39), 1006–1011.

Farzaei, M. H., Abdollahi, M., & Rahimi, R. (2015). Role of dietary polyphenols in the management of peptic ulcer. *World Journal of Gastroenterology: WJG*, *21*(21), 6499. https://doi.org/10.3748/wjg.v21.i21.6499

Fatimah, C, A., Rahimi, L., Zakaria, Z. A., & Ibrahim, A. L. (2014). Hepatoprotective, antiulcerogenic, cytotoxic and antioxidant activities of Musa acuminata peel and pulp. *Novel Plant Bioresources: Applications in Food, Medicine and Cosmetics*, 371–382. https://doi.org/10.1002/9781118460566.ch26

Fayyaz, A., Samad, A., Waseem, U., Shafique, S., Nasreen, S., & Hassan, S. (2021). Gastric mucosal damage with aspirin: results of experimental models in adult albino rats. *International Journal of Community Medicine and Public Health*, *8*(1), 50. https://doi.org/10.18203/2394-6040.ijcmph20205447

Gogola, D. (2020). Phytochemical screening, antioxidant and gastro-protective activity studies on the fruit peels of selected varieties of Banana. *Herbal Medicines Journal (Herb Med J)*, *5*(2), 45–59. https://doi.org/10.22087/hmj.v5i2.763

Gohar, A. A., & Zaki, A. A. (2014). Assessment of some herbal drugs for prophylaxis of peptic ulcer. *Iranian Journal of Pharmaceutical Research: IJPR*, *13*(3), 1081.

Handa, O., Naito, Y., Fukui, A., Omatsu, T., & Yoshikawa, T. (2014). The impact of non-steroidal anti-inflammatory drugs on the small intestinal epithelium. *Journal of Clinical Biochemistry and Nutrition*, *54*(1), 2–6. https://doi.org/10.3164/jcbn.13-84

Harborne, J. B. (1989). General procedures and measurement of total phenolics. *Methods in Plant Biochemistry*, *1*, 1–28. https://doi.org/10.1016/B978-0-12-461011-8.50007-X

Hervé, E. E., Bernard, G. N., Léandre, K. K., Paul, Y. A., & Etienne, E. E. (2018). Acute toxicity and gastric anti-ulcer activity of an aqueous extract of the leaves of Macaranga barteri Mll. Arg (Euphorbiaceae) on rat models. *Journal of Medicinal Plants Research*, *12*(9), 96–105. https:doi.org/10.5897/JMPR2017.6547

Hossain, M. D., Sarwar, M. S., Dewan, S. M. R., Hossain, M. S., Shahid-Ud-Daula, A. F. M., & Islam, M. S. (2014). Investigation of total phenolic content and antioxidant activities of Azadirachta indica roots. *Avicenna Journal of Phytomedicine*, *4*(2), 97.

Ibrahim, M. F. G., & Allam, F. A. F. A. (2022). Potential stem cell—Conditioned medium and their derived exosomes versus omeprazole in treatment of experimental model of gastric ulcer. *Acta Histochemica*, *124*(4), 151896. https://doi.org/10.1016/j.acthis.2022.151896

IM, F., Birnin-Yauri, A. U., & Jemaima, J. (2014). In vitro antioxidant properties of musa paradisiacal

peel aqueous extract. *Journal of Scientific and Innovative Research*, *3*(6), 563–568. https://doi.org/10.31254/jsir.2014.3603

Jabbar, A. A. (2022). Gastroprotective and Immuno-supportive Role of Alcea kurdica against Stress Induced Lesion in Japanese Quails. *Baghdad Science Journal*, 19 (4),716-724. https://doi.org/10.21123/bsj.2022.19.4.0716

Jami'ah, S. R., Ifaya, M., Pusmarani, J., & Nurhikma, E. (2018). Uji aktivitas antioksidan ekstrak metanol kulit pisang raja (Musa paradisiaca sapientum) dengan metode DPPH (2, 2-difenil-1-pikrilhidrazil). *Jurnal Mandala Pharmacon Indonesia*, *4*(1), 33–38. https://doi.org/10.35311/jmpi.v4i1.22

Jang, E., Park, M., Jeong, J. E., Lee, J. Y., & Kim, M. G. (2022). Frequently reported adverse events of rebamipide compared to other drugs for peptic ulcer and gastroesophageal reflux disease. *Scientific Reports*, *12*(1), 7839. https://doi.org/10.1038/s41598-022-11505-0

Kadhem, M. A., Abdul-Niby, A. A., & Khassaf, H. K. (2018). Study the effect of ethanolic extract of Anethum graveolens L. on aspirin induced Gastric Ulcer in Male Guinea Pigs. *Research Journal of Pharmacy and Technology*, *11*(9), 3793–3798. https://doi.org/10.5958/0974-360X.2018.00695.9

Kapadia, S. P., Pudakalkatti, P. S., & Shivanaikar, S. (2015). Detection of antimicrobial activity of banana peel (Musa paradisiaca L.) on Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans: An in vitro study. *Contemporary Clinical Dentistry*, *6*(4), 496. https://doi.org/10.4103/0976-237X.169864

Kathirvelu, P., Cheriyan, B. V., Jagan, N., Viswanathan, S., Kumar, S. V., & Kamalakannan, P. (2019). Gastroprotective and Antioxidant effect of Petroleum ether Extract of Eupatorium triplinerve Vahl. *Research Journal of Pharmacy and Technology*, *12*(11), 5163–5166. https://doi.org/10.5958/0974-360X.2019.00893.X

Kibria, A. A., Kamrunnessa, Rahman, M. M., & Kar, A. (2019). Extraction and Evaluation of Phytochemicals from Banana Peels (Musa sapientum) and Banana Plants (Musa paradisiaca) . *Malaysian Journal of Halal Research*, *2*(1), 22–26. https://doi.org/10.2478/mjhr-2019-0005

Kumar, M., Gautam, M. K., Singh, A., & Goel, R. K. (2013). Healing effects of Musa sapientum var. paradisiaca in diabetic rats with co-occurring gastric ulcer: cytokines and growth factor by PCR amplification. *BMC Complementary and Alternative Medicine*, *13*(1), 1–9. https://doi.org/10.1186/1472-6882-13-305

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: an overview. *The Scientific World Journal*, *2013*. https://doi.org/10.1155/2013/162750

Kuna, L., Jakab, J., Smolic, R., Raguz-Lucic, N., Vcev, A., & Smolic, M. (2019). Peptic ulcer disease: a brief review of conventional therapy and herbal treatment options. *Journal of Clinical Medicine*, *8*(2), 179. https://doi.org/10.3390/jcm8020179

Lambert, A. A., Lam, J. O., Paik, J. J., Ugarte-Gil, C., Drummond, M. B., & Crowell, T. A. (2015). Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. *PloS One*, *10*(6), e0128004. https://doi.org/10.1371/journal.pone.0128004

Lanas, A., & Chan, F. K. L. (2017). Peptic ulcer disease. *The Lancet*, *390*(10094), 613–624. https://doi.org/10.1016/S0140-6736(16)32404-7

Lewis, D. A., Fields, W. N., & Shaw, G. P. (1999). A natural flavonoid present in unripe plantain banana pulp (Musa sapientum L. var. paradisiaca) protects the gastric mucosa from aspirin-induced erosions. *Journal of Ethnopharmacology*, *65*(3), 283–288. https://doi.org/10.1016/S0378-8741(99)00005-7

Lewis, D. A., & Shaw, G. P. (2001). A natural flavonoid and synthetic analogues protect the gastric mucosa from aspirin-induced erosions. *The Journal of Nutritional Biochemistry*, *12*(2), 95–100. https://doi.org/10.1016/S0955-2863(00)00133-9

Li, C., Wang, L., Zhao, J., Wei, Y., Zhai, S., Tan, M., Guan, K., Huang, Z., & Chen, C. (2022). Lonicera rupicola Hook. f. et Thoms flavonoids ameliorated dysregulated inflammatory responses, intestinal barrier, and gut microbiome in ulcerative colitis via PI3K/AKT pathway. *Phytomedicine*, *104*, 154284. https://doi.org/10.1016/j.phymed.2022.154284

Mahurkar, N., & Sayeed Ul Hasan, S. M. (2015). Synergistic Antiulcer Effect of Melatonin and

Esomeprazole Combination in Pylorus Ligation, Ethanol, Aspirin induced Peptic Ulcers. *Asian Journal of Pharmaceutical Research*, *5*(1), 10–14. https://doi.org/10.5958/2231-5691.2015.00002.7

Malik, T. F., Gnanapandithan, K., & Singh, K. (2018). *Peptic ulcer disease*.

Mohammed, M. A., El-Hadi, A. E., Mohammed, E. A., Abbas, F. S., Musa, K. O., Al-Ameen, M. Y., Ahmed, A. M., Gassab, M. T. I., Hassan, H. M., & Abdelgadir, A. A. (2021). *Gastro-protective Effects of Green Banana (Musa cavendishii Lamb.) Pulp Powder on Aspirin-induced Gastric Ulcer in Albino Rats*.

Morais, D. R., Rotta, E. M., Sargi, S. C., Schmidt, E. M., Bonafe, E. G., Eberlin, M. N., Sawaya, A. C. H. F., & Visentainer, J. V. (2015). Antioxidant activity, phenolics and UPLC–ESI (–)–MS of extracts from different tropical fruits parts and processed peels. *Food Research International*, *77*, 392–399. https://doi.org/10.1016/j.foodres.2015.08.036

Narayanan, M., Reddy, K. M., & Marsicano, E. (2018). Peptic ulcer disease and Helicobacter pylori infection. *Missouri Medicine*, *115*(3), 219.

Obioma, N. E., Kelechi, O. J., Miracle, N. T., Ogbonnaya, E., & Offor, N. (2018). Ulcer healing effect of ethanolic extract of unripe musaparadisiaca on aspirin induced gastric ulceration in adult wistar rats. *European Journal of Pharmaceutical and Medical Research*, *5*(12), 58–62.

Onasanwo, S. A., Emikpe, B. O., Ajah, A. A., & Elufioye, T. O. (2013). Anti-ulcer and ulcer healing potentials of Musa sapientum peel extract in the laboratory rodents. *Pharmacognosy Research*, *5*(3), 173–178. https://doi.org/10.4103/0974-8490.112423

Palle, S., Kanakalatha, A., & Kavitha, C. N. (2018). Gastroprotective and antiulcer effects of Celastrus paniculatus seed oil against several gastric ulcer models in rats. *Journal of Dietary Supplements*, *15*(4), 373–385. https://doi.org/10.1080/19390211.2017.1349231

Pereira, A., & Maraschin, M. (2015). Banana (Musa spp) from peel to pulp: ethnopharmacology, source of bioactive compounds and its relevance for human health. *Journal of Ethnopharmacology*, *160*, 149–163. https://doi.org/10.1016/j.jep.2014.11.008

Pulipati, S., Babu, P. S., & Narasu, M. L. (2014). Quantitative determination of tannin content and evaluation of antibacterial activity of Amaranthus tricolor (L). *Int J Biol Pharm Res*, *5*, 623–626.

Puri, B., & Hall, A. (1998). *Phytochemical dictionary: a handbook of bioactive compounds from plants*. CRC press.

Pusmarani, J., Ifaya, M., Isrul, M., & Saleh, A. (2019). Gastroprotective effect of Lannea Coromandelica Stem Bark in Rat induced by aspirin. *Research Journal of Pharmacy and Technology*, *12*(4), 1646–1648. https://doi.org/10.5958/0974-360X.2019.00275.0

Pusmarani, J., Ifaya, M., & Putri, R. J. (2022). Hepatoprotector Effect of Banana Peel (Musa paradisiaca Sapientum) on Paracetamol Induced Rats. *Jurnal Farmasi Galenika (Galenika Journal of Pharmacy)(e-Journal)*, *8*(2), 109–116. https://doi.org/10.22487/j24428744.2022.v8.i2.15968

Pusmarani, J., Putri, R. J., Dewi, C., Purwono, S., & Ikawati, Z. (2019). Non Specific and Specific Parameter Standardization Of Banana Peel (Musa paradisciata Sapientum) and Andrographis Paniculata. *International Summit on Science Technology and Humanity*, 658–664.

Rahman, Z., Dwivedi, D. K., & Jena, G. B. (2020). Ethanol-induced gastric ulcer in rats and intervention of tert-butylhydroquinone: involvement of Nrf2/HO-1 signaling pathway. *Human & Experimental Toxicology*, *39*(4), 547–562. https://doi.org/10.1177/0960327119895559

Raish, M., Shahid, M., Bin Jardan, Y. A., Ansari, M. A., Alkharfy, K. M., Ahad, A., Abdelrahman, I. A., Ahmad, A., & Al-Jenoobi, F. I. (2021). Gastroprotective effect of sinapic acid on ethanol-induced gastric ulcers in rats: involvement of Nrf2/HO-1 and NF-κB signaling and antiapoptotic role. *Frontiers in Pharmacology*, *12*, 622815. https://doi.org/10.3389/fphar.2021.622815

Rita, S. W., Swantara, I. M. D., Asih, I., & Puspawati, N. M. (2020). Antibacterial activity and antioxidant capacity of selected local banana peel (Musa sp.) methanol extracts cultivated in Bali. *Int. J. Agric. Environ. Biores*, *5*, 242–251. https://doi.org/10.35410/IJAEB.2020.5519

Saheed, S., Olarewaju, S. A., Taofeeq, G., Olatunde, S. T., & Alanamu, A. A. (2015). Combined administration of Spondias mombin and Ficus exasperata leaf extracts stall Indomethacin-mediated

gastric mucosal onslaught in rats. *African Journal of Traditional, Complementary and Alternative Medicines*, *12*(1), 45–51. https://doi.org/10.4314/ajtcam.v12i1.7

Saiah, W., Halzoune, H., Djaziri, R., Tabani, K., Koceir, E. A., & Omari, N. (2018). Antioxidant and gastroprotective actions of butanol fraction of Zingiber officinale against diclofenac sodium-induced gastric damage in rats. *Journal of Food Biochemistry*, *42*(1), e12456. https://doi.org/10.1111/jfbc.12456

Sakura, Y. W., Jayawardhita, A. A. G., Kardena, I. M., & Sudimartini, L. M. (2017). Perbandingan gambaran histopatologi lambung tikus putih (Rattus norvegicus) jantan yang diberi amoxicillin dikombinasikan dengan asam mefenamat dan deksametason. *Indonesia Medicus Veterinus*, *6*(3), 246–253.

Shahidi, F., & Ambigaipalan, P. (2015). Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects–A review. *Journal of Functional Foods*, *18*, 820–897. https://doi.org/10.1016/j.jff.2015.06.018

Sharifi-Rad, J., Quispe, C., Zam, W., Kumar, M., Cardoso, S. M., Pereira, O. R., Ademiluyi, A. O., Adeleke, O., Moreira, A. C., & Živković, J. (2021). Phenolic bioactives as antiplatelet aggregation factors: the pivotal ingredients in maintaining cardiovascular health. *Oxidative Medicine and Cellular Longevity*, *2021*. https://doi.org/10.1155/2021/2195902

Singh, B., Singh, J. P., Kaur, A., & Singh, N. (2016). Bioactive compounds in banana and their associated health benefits–A review. *Food Chemistry*, *206*, 1–11. https://doi.org/10.1016/j.foodchem.2016.03.033

Sisay Zewdu, W., & Jemere Aragaw, T. (2020). Evaluation of the anti-ulcer activity of hydromethanolic crude extract and solvent fractions of the root of Rumex nepalensis in Rats. *Journal of Experimental Pharmacology*, 325–337. https://doi.org/10.2147/JEP.S258586

Thomas, A., & Krishnakumar, K. (2017). Banana peel: pharmacological activities: a Review. *International Journal of Innovative Research and Advanced Studies*, *4*(5), 62–64.

Ulser, T. (2016). Antiulcer activity of Musa paradisiaca [banana] tepal and skin extracts in ulcer induced albino mice. *Malaysian Journal of Analytical Sciences*, *20*(5), 1203–1216. https://doi.org/10.17576/mjas-2016-2005-27

Vu, H. T., Scarlett, C. J., & Vuong, Q. V. (2018). Phenolic compounds within banana peel and their potential uses: A review. *Journal of Functional Foods*, *40*, 238–248. https://doi.org/10.1016/j.jff.2017.11.006

Wang, Z., & Wei, Y. (2022). SEMA3D Plays a critical role in peptic ulcer disease-related Carcinogenesis Induced by H. pylori Infection. *International Journal of General Medicine*, *15*, 1239. https://doi.org/10.2147/IJGM.S343635

Washio, E., Esaki, M., Maehata, Y., Miyazaki, M., Kobayashi, H., Ishikawa, H., Kitazono, T., & Matsumoto, T. (2016). Proton pump inhibitors increase incidence of nonsteroidal anti-inflammatory drug–induced small bowel injury: a randomized, placebo-controlled trial. *Clinical Gastroenterology and Hepatology*, *14*(6), 809-815.e1. https://doi.org/10.1016/j.cgh.2015.10.022

Yaghoobi, M., & Armstrong, D. (2022). Peptic ulcer disease. In *Yamada's Textbook of Gastroenterology* (pp. 924–976). Wiley. https://doi.org/10.1002/9781119600206.ch49

Yandrapu, H., & Sarosiek, J. (2015). Protective factors of the gastric and duodenal mucosa: an overview. *Current Gastroenterology Reports*, *17*(6), 24. https://doi.org/10.1007/s11894-015-0452-2

Zaghlool, S. S., Abo-Seif, A. A., Rabeh, M. A., Abdelmohsen, U. R., & Messiha, B. A. S. (2019). Gastro-protective and anti-oxidant potential of Althaea officinalis and solanum nigrum on pyloric ligation/indomethacin-induced ulceration in rats. *Antioxidants*, *8*(11), 512. https://doi.org/10.3390/antiox8110512

Zheng, Y.-F., Xie, J.-H., Xu, Y.-F., Liang, Y.-Z., Mo, Z.-Z., Jiang, W.-W., Chen, X.-Y., Liu, Y.-H., Yu, X.-D., Huang, P., & Su, Z.-R. (2014). Gastroprotective effect and mechanism of patchouli alcohol against ethanol, indomethacin and stress-induced ulcer in rats. *Chemico-Biological Interactions*, *222*, 27–36. https://doi.org/https://doi.org/10.1016/j.cbi.2014.08.008