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Research Article

Gastroprotective Potential of Hantap Leaves (*Sterculia coccinea* Jack) Extract in Stress-Induced Gastric Ulcers of Male White Rats

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ABSTRACT

Stomach ulcer is a prevalent digestive problem that can lead to serious complications such as bleeding in the digestive tract, perforation, recurrence, cancer, and even death. One of its potential remedies lies in the antioxidant compounds contained in hantap leaves. Accordingly, this study aimed to investigate the anti-gastric ulcer effects of hantap leaf extract in white male rats induced by water immersion and cold-resistant stress methods. Hantap leaf extract (EEDH) was obtained by maceration using 96% ethanol, resulting in a yield of 7.8%. The results of gastric macroscopic observations based on percentage of ulcer inhibition showed that EEDH doses of 50, 100, and 200 mg/kg BW did not have a significant difference (p<0.05) with ranitidine, exhibiting the same gastroprotective effects. An increase in the dose does not lead to a corresponding rise in the gastroprotective effect. Therefore, 50 mg/kg BW of EEDH was considered to be the optimum dose.

INTRODUCTION

Gastric ulcer is a wound in the mucosal layer (epithelial layer) of the stomach, characterized by mucosal irritation occurring with a diameter of 5 mm or more and a depth extending into the submucosa (Rau *et al.*, 2019). The pathogenesis is attributed to an imbalance between aggressive factors such as acids and pepsin, and defensive factors, including bicarbonate, mucus, prostaglandins, nitrogen monoxide (NO), and growth factors (Périco *et al.*, 2020). Several factors can contribute to the onset of gastric ulcers, including *Helicobacter pylori* infection, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), or stress (Lee *et al.*, 2017, Serafim *et al.*, 2021).

Stress-induced ulcers are mediated by histamine release, leading to increased acid secretion, decreased mucus production, reflux of pancreatic juices, and poor gastric blood flow. The formation process was favored by reactive oxygen species (ROS) and inhibition of prostaglandin synthesis (Bhattacharyya *et al.*, 2014). Peptic ulcer treatment was aimed at improving the patient's quality of life, eliminating complaints, healing ulcers, and preventing recurrence and complications (Abd El-Aziz Elsayad *et al.*, 2017). Some of the drugs used were cimetidine, ranitidine, omeprazole, and antacids. However, the use of synthetic medications had some side effects and limitations (Bi *et al.*, 2014). Therefore, there is a need to discover more effective drugs with low toxicity that possess potent gastric acid and ulcer inhibitory activity.

The interest in traditional medicine as a treatment option has been on the rise, driven by several advantages associated with the use of medicinal plants that appeal to people, including having low toxicity and being safe to apply (Yuan *et al.*, 2016). According to prediction, 80% of the world's population incorporates traditional medicine in their healthcare practices (Oyebode *et al.*, 2016).

Hantap (*Sterculia coccinea* Jack) is a type of tropical plant known for its potential in prevention and treatment, traditionally achieved by preparing the leaf extract through a process of cutting, squeezing, filtering, and direct consumption (Cahyani *et al.*, 2017). Among local communities, hantap leaves are commonly used as a remedy to prevent several kinds of diseases such as heartburn, and canker sores, promote bowel movements, promote childbirth, and treat flatulence (Saptarini and Mustarichie, 2020). The efficacy of this plant was related to the content of phytochemical substances, namely polyphenolic and phenolic compounds which have very strong antioxidant activity (Prastiwi *et al*., 2020). Based on the discovery, antioxidants play a crucial role in preventing gastric ulcers as oxidative stress is a significant factor in the development of this complication, since antioxidants are essential in protecting gastric mucosa from necrotic agents. Furthermore, gastric ulcers induce an inflammatory response associated with increased neutrophil infiltration, disrupting the oxidant/antioxidant and the inflammatory/anti-inflammatory cytokine balances (Almasaudi *et al*., 2016). The antioxidant activity involved scavenging ROS, metal ion chelation transitions, increasing enzymatic and non-enzymatic antioxidants, and reducing lipid peroxidation, hence, preventing gastric ulcers (Farzaei *et al*., 2015).

Based on the use of hantap leaves in the community and the pharmacological effects of the compounds they contained; no scientific study has been conducted to prove the gastroprotective activity. Therefore, this investigation aimed to test the gastroprotective potency of hantap leaf extract by water immersion method and restraint-induced stress ulcers.

METHODS

Materials and Chemicals

Fresh hantap leaves were collected from Salena Village, Ulujadi District, Palu City, Central Sulawesi, and identified at the Plant Biosystematics Laboratory, Department of Biology FMIPA Tadulako University (589/UN28.1.28/BIO/2022). These leaves are dark green with the characteristics of clearly visible leaf bones. Furthermore, the stem of the plant can be broken easily and the leaves are intact. Samples were processed into simplicia and then powdered for further experimentation. The chemical used were Ethanol 96% (Bratachem), aquadest, CMC Na (Bratachem), Ketamine HCl®, Ranitidine HCl (Hexpharm Jaya), NaCl 0.9% (Otsuka), Dragendorff reagent, Liebermann Burchard reagent, Mayer reagent, Wagner reagent, Steasny reagent, $FeCl_3$ (Merck), HCl (Merck), and Mg (Merck).

Extraction

Hantap leaves dry powder was macerated with 96% ethanol using a volume ratio of 1:10. This procedure was repeated to collect all the supernatants which were then evaporated and dried in a water bath to obtain the extract.

Phytochemical screening

Phytochemical screening of alkaloids, flavonoids, saponins, tannins, and steroids/triterpenoids was conducted according to the standard procedures with slight modifications (Abeysinghe *et al*., 2021).

Gastroprotective activity

Wistar male rats (150-250 g) were obtained from the Animal Laboratory at Tadulako University, Indonesia, and housed in standard cages at room temperature with 30-70% relative humidity and in 12 h dark-light cycle. Furthermore, a standard pellet diet and water were given *ad libitum*.

The use of the animals was approved (Number:8776 /UN 28.1.30/ KL/2022) by the Medical and Health Research and Ethics Committee of the Faculty of Medicine, Tadulako University. The animals were acclimatized for one week before the *in vivo* study which employed a combination of the water-immersion stress and the cold-resistant stress methods with modification (Zhao *et al*., 2020, Zhang *et al*., 2021). After acclimatization, the rats were divided into 6 groups each containing 4 animals: Group 1 which was the normal control was given 0.5% CMC Na suspension. Group 2, the negative control was given 0.5% CMC Na suspension. Meanwhile, in Group 3, the positive control was given ranitidine suspension of 27 mg/Kg BW. Groups 4, 5, and 6, which were the test groups were administered a suspension of hantap leaf extract at a dose of 50, 100, and 200 mg/kg body weight (BW), respectively. All treatments were conducted for 7 consecutive days, except for the normal control group. Before stress induction, the rats were fasted for 24 hours (on the 6th and 7th days of extract administration) but were still provided with drinking water and extracts. Furthermore, on the 7th day, the rats were treated with water-immersion and cold-resistant stress methods. During the stress water immersion, the animals were put into restrainers and immersed in cold water at 17°C for 8 hours. Afterward, it was continued by being treated using the cold-resistant stress method, where the rats remained in the restrainer and were placed in a cold room at a controlled temperature of 4°C for 2 hours. Following the stress induction, animals were euthanized with a ketamine HCl dose of 10 mg/200 g BW. Finally, the rats were dissected and their stomachs were excised for further analysis.

Macroscopic Observations

To assess ulcers macroscopically, several parameters were observed including the number of ulcers, ulcer score, ulcer area, ulcer index, and percentage ulcer inhibition (Sabiu *et al*., 2016, Abebaw *et al*., 2017). The number of ulcers was determined visually by investigating the formation in the rat's stomach. Scores were assigned based on the number of ulcers and the level of severity, namely 1, 2, 3, 4, 5, 10, and 25, indicated lesions <1.00 mm, 1.00-2.00 mm, 2.01-3.00 mm, 3.01-4.00 mm, 4.01-5.00 mm, >5.00 mm, and when there was a perforation, respectively. The ulcer diameter was measured using a digital caliper, while the index and % inhibition were calculated using the following formula:

$$\text{Ulcer index(IU)} = \frac{\textit{Ulcer score}}{\textit{Number of animals with ulcers}}$$

$$\text{\% Inhibition} = \frac{\text{IU(negative control)} - \text{IU(experiment group)}}{\text{IU(negative control)}} \times 100\%$$

Statistical analysis

The results were expressed as mean ± standard deviation (SD), and before selecting the appropriate analysis test, the normality and homogeneity of the data were assessed. After both were passed, a parametric test was conducted, specifically a one-way ANOVA, followed by a Duncan test to determine the average differences between treatments. However, when the data deviated from normality or were not homogeneous, a non-parametric test, such as the Kruskal-Wallis test, was performed, followed by the Mann-Whitney test. Finally, a value of p <0.05 was considered significant.

RESULTS AND DISCUSSION

Hantap leaf ethanol extract (EEDH) used in this study was obtained by maceration method using 96% ethanol and the yield was 7.8%. The components contained in the extract were subjected to qualitative phytochemical analysis using several reagents. The test showed that alkaloids had positive reactions with Dragendorff, Mayer, and Wagner reagents, as indicated by the formation of red, orange, white, and brown precipitates. The consistent foam formation confirmed the presence of saponins. Similarly, flavonoids, tannins, and steroids exhibited color changes to orange, green-black, and green, respectively, during the test. The phytochemical screening results of EEDH in Table 1 indicate the presence of significant constituents, including alkaloids, flavonoids, saponins, steroids, and tannins. These compounds may have contributed to the extract's antioxidant activity and potential benefits in treating gastric ulcers.

A previous study conducted by Saheed *et al*. (2018) demonstrated that alkaloids, flavonoids, saponins, tannins, and steroids play essential roles in protecting the gastric mucosa against oxidative insults from reactive metabolites and oxidative stress.

Table 1. Phytoconstituents of Hantap leaf ethanol extract (EEDH)

No	Phytoconstituents	EEDH
1	Alkaloids	+
2	Flavonoids	+
3	Saponins	+
4	Tannins	+
5	Steroids	+

+: indicates the presence.

Table 2. Results of gastric macroscopic observations

Group	Number of ulcers	Ulcer score	Ulcer Index
Normal control	0.00±0.00^{a}	0.00±0.00^{a}	0.00±0.00^{a}
Negative control	9.75±1.31^{c}	2.75±0.25^{c}	0.69±0.06^{c}
Positive control (ranitidine 27 mg/kg BB)	3.75±1.11^{b}	1.25±0.25^{b}	0.31±0.06^{b}
EEDH 50 mg/kg BW	5.00±2.12^{b}	1.25±0.48^{b}	0.42±0.16^{b}
EEDH 100 mg/kg BW	5.00±0.71^{b}	1.75±0.25^{b}	0.44±0.06^{b}
EEDH 200 mg/kg BW	4.00±0.91^{b}	1.25±0.25^{b}	0.31±0.06^{b}

Values are mean ± standard deviation (SD_; N = 4 in each group. Different letters indicate statistically significant differences ($p \leq 0.05$).

Additionally, phenolic compounds and alkaloids have been shown to regulate gastric acid secretion and safeguard the gastric mucosal epithelia from erosion and other aggressive factors.

In this study, the potential of EEDH as a gastroprotective agent was evaluated using male white rats induced by the stress method. This test was conducted using stress water immersion and cold-resistant methods, both of which were employed to induce stress ulcers. One of the most common stressors in experimental medicine has been restraint stress, which caused the strongest possible psychological frustration, followed by intense striving and physical activity. Water immersion and cold resistance stress methods drastically reduced body temperature, called hypothermia. This condition caused an increase in blood viscosity and narrowing of the vessels that supply blood to the gastric mucosa, hence, triggering damage to the stomach (Zhang *et al*., 2021, Khan *et al*., 2022). The test serves as an appropriate model to assess the anti-gastric ulcer effect and determine the optimum drug dose of EEDH.

Table 2 shows that ulcers did not occur in the normal group. The parameters of the number of ulcers in the ranitidine group and EEDH at 50, 100, and 200 mg/kg BW had a significant difference with the induction group ($p<0.05$). Ulcer score, area, and index in the ranitidine group and EEDH at 50, 100, and 200 mg/kg BW significantly differed from the negative control ($p<0.05$). The decrease in the number of ulcers, ulcer score, ulcer area, and ulcer index indicated that the administration of this extract could reduce the severity of ulcers in the stomach of rats. The inhibition percentage showed that the groups with doses of 50, 100, and 200 mg/kg BW were not significantly different from the ranitidine counterpart ($p>0.05$). This result implied that the extract had the same effect similar to ranitidine. Among the 3 doses, there was no significant difference ($p>0.05$), indicating that increasing the dose did not further enhance the gastroprotective effect. This finding could be attributed to the considerable variation in data between animals within each group. However, from the descriptive data, it was observed that the most effective and the optimal dose, were 200 mg/kg BW and 50 mg/kg BW, respectively.

The ulcer score test assesses the severity of the complication. As depicted in Figure 1 and described in Table 2, the negative control group had many superficial and deep ulcers. In this group, the mucosal injury was manifested by multiple hemorrhage red bands of varying diameters on the glandular stomach. The exposure of the animals to the frigid and cold restraint stresses caused a severe physiological imbalance, resulting in a stressful condition that led to ulceration. Furthermore, the image of the positive control and treatment groups in Figure 1 showed signs of recovery from stress and ulceration. The EEDH groups of 50, 100, and 200 mg/kg BW had several superficial and deep ulcers, while the ranitidine had superficial and deep ulcers but in smaller numbers.

The ulcer index value determined the percentage of ulcer inhibition in an inverse proportion. The percentage of ulcer inhibition was a numerical representation of the extent to which gastric ulcers have healed. According to Figure 2, the biggest inhibition percentage at 54.60% began from ranitidine positive control, followed by EEDH 50, 100, and 200 mg/Kg BW, at 47.25%, 37.34%, and 54.55%, respectively. The negative control treatment group had no

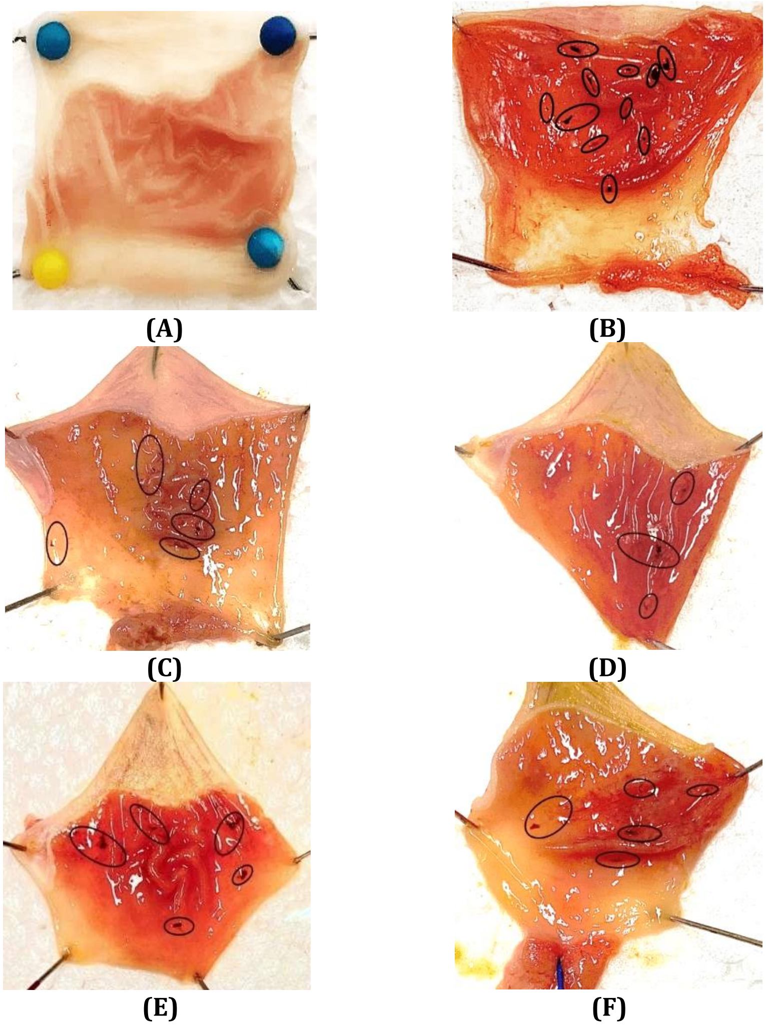

Figure 1. Effects of restraint water-immersion stress on gastric mucosal lesions in rats. (A=normal control); (B=negative control); (C=positive control); (D=EEDH 50 mg/kg BW); (E=EEDH 100 mg/kg BW); (F=EEDH 200 mg/kg BW).

Inhibition percentage because the index value was used as a control to compare with the group given the extract. The index value was directly proportional to the gastric damage experienced. Additionally, there was a direct proportionality between the percentage of ulcer inhibition and the ability of the sample to heal and reduce the level of gastric damage.

Figure 2 shows that the percentage of inhibition of EEDH at 50, 100, and 200 mg/kg BW was comparable to the ranitidine (positive control) and not significantly different (p>0.05). This finding implied that the leaf extract had a gastroprotective effect in healing ulcers, and the optimum dose was 50 mg/Kg BW. The healing effect of the ranitidine (positive control group) blocked the action of H_2 receptors on parietal cells, hence, it reduced acid and pepsin secretion and increased the healing speed (Kuna *et al.*, 2019).

Histamine release likely played a role in stress-induced ulcers, and acts as an aggressive factor, leading to aberrant motility and increased gastric output, while also inhibiting mucus formation, which is essential for the stomach's defensive mechanism. Furthermore, it disturbs the microcirculation of the stomach mucosa. Studies in animals have suggested that enhanced vagal activity was a primary contributor to stress-induced ulceration. However, vagotomy, a surgical procedure that involves cutting or removing a section of the vagus nerve, may partially or completely prevent stress-induced ulcers in such cases.

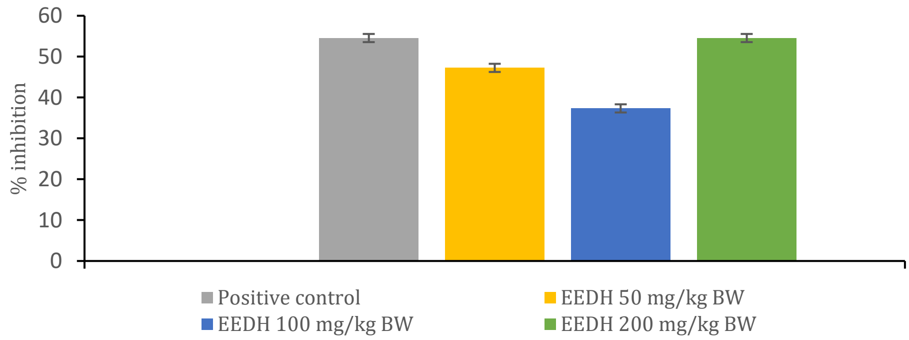

Figure 2. The percentage ulcer inhibition.
Values are mean ± standard deviation (SD); N = 4 in each group.
Different letters indicate statistically significant differences ($p \leq 0.05$)

Acetylcholine, a chemical mediator of the vagus nerve interacts with the muscarinic receptor to induce stomach acid secretion. This interaction sets off a series of events that ultimately increase the production of gastric acid. The parietal cells and histamine-secreting cell membranes had these receptors (Engevik *et al*., 2020). The vagus nerve stimulates gastric acid secretion by interacting with its chemical mediator (acetylcholine) and the muscarinic receptor. These receptors are located on the cell membranes of parietal and histamine-secreting cells. Therefore, acid secretion increased due to the action of acetylcholine on histamine cells and the activity of parietal cells. In addition to acid and pepsin-related factors, ROS also contribute to the harm caused by stress-induced ulcers.

The healing effect of gastric ulcers in the EEDH groups, administered at doses of 50 mg/Kg BW, 100 mg/Kg BW, and 200 mg/Kg BW, was attributed to the presence of flavonoids, saponins, and tannins, which played a role in the process. These secondary metabolites also functioned as antioxidants. Flavonoids, saponins, and tannins were active compounds in plants that protected against gastric ulcers by acting as a protective (protective) factor for the stomach. Previous studies reported that tannins and flavonoids were present in quite large amounts, at 72.16% and 28.66%, respectively, in hantap leaf extract. The antioxidant activity of the extract was classified as very strong using the DPPH method. Flavonoids acted as antioxidants that will counteract free radicals and inhibit the production of ROS in the pathogenesis of peptic ulcers (Mukheet *et al*., 2019; Zhang *et al*., 2020). Saponins provide gastroprotective activity by increasing fibronectin, leading to the formation of fibrin clumps that served as a basis for tissue re-epithelialization (Mukheet *et al*., 2019). Therefore, rapid fibrin clot formation facilitates fibroblast proliferation and accelerates tissue restoration at the ulcer site. The healing effect of tannins was attributed to the formation of microprotein deposits, creating a protective layer that enhanced resistant against biological and chemical irritants. Furthermore, tannins acted as antioxidants, effectively inhibiting the production of free radicals, and providing protection to the gastric mucosa from irritants by forming a protective layer (Demarque *et al*., 2018). In this study, it was observed that the extract of hantap leaves has a significant antiulcer effect against gastric ulcers in rodents. Finally, this finding supported the traditional use of these leaves' decoction.

CONCLUSIONS

In conclusion, the ethanol extract of hantap leaves had a gastroprotective effect with an optimum dose of 50 mg/kg BW.

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CONFLICT OF INTEREST

All authors declare no conflict of interest in this manuscript.

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