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PREVENTION OF GASTROPROTECTIVE ACTIVITY OF CHINESE BETEL EXTRACT (*PEPEROMIA PELLUCIDA* L.) ON THE HISTOPATHOLOGICAL FEATURES OF THE STOMACH IN A MOUSE MODEL OF GASTROENTERITIS

Aktivitas Gastroprotektif Ekstrak Sirih Cina (*PEPEROMIA PELLUCIDA* L.) terhadap Gambaran Histopatologi Gaster Mencit Model Gastroenteritis

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ABSTRACT

Gastroenteritis is a common gastrointestinal disorder characterized by inflammation of the stomach and small intestine, often leading to symptoms such as diarrhea, vomiting, and abdominal pain. This study investigates the gastroprotective effects of Peperomia pellucida (Chinese betel) extract on histopathological features of the stomach in a mouse model of gastroenteritis. Male Swiss strain mice, aged 2-3 months, were treated with different doses of P. pellucida extract (100, 300, and 500 mg/kg BW) for 7 days after inducing gastroenteritis with Escherichia coli infection. Histopathological examination showed that the extract significantly reduced cell degeneration, necrosis, and polymorphonuclear leukocyte infiltration in the stomach compared to the negative control group. The highest dose (500 mg/kg BW) exhibited the most prominent gastroprotective effect. These results suggest that P. pellucida possesses promising therapeutic potential for gastroenteritis, possibly due to its bioactive compounds such as flavonoids, tannins, and saponins. Further studies are needed to explore the underlying mechanisms and optimize its therapeutic application.

Keywords: *Bioactive compounds, Gastroprotective, Histopathology, Peperomia pelucida L*

ABSTRAK

Gastroenteritis adalah gangguan pencernaan yang umum ditandai dengan peradangan pada lambung dan usus halus, yang sering menyebabkan gejala seperti diare, muntah, dan nyeri perut. Penelitian ini menyelidiki efek gastroprotektif ekstrak Peperomia pellucida (sirih Cina) terhadap fitur histopatologis lambung pada model tikus gastroenteritis. Tikus jantan Swiss strain, usia 2-3 bulan, diberi perlakuan dengan dosis ekstrak P. pellucida (100, 300, dan 500 mg/kg BB) selama 7 hari setelah induksi gastroenteritis dengan infeksi Escherichia coli. Pemeriksaan histopatologi menunjukkan bahwa ekstrak tersebut secara signifikan mengurangi degenerasi sel, nekrosis, dan infiltrasi leukosit polimorfonuklear pada lambung dibandingkan dengan kelompok kontrol negatif. Dosis tertinggi (500 mg/kg BB) menunjukkan efek gastroprotektif yang paling mencolok. Hasil ini menunjukkan bahwa P. pellucida memiliki potensi terapeutik yang menjanjikan untuk gastroenteritis, mungkin karena senyawa bioaktifnya seperti flavonoid, tannin, dan sap-

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onin. Penelitian lebih lanjut diperlukan untuk mengeksplorasi mekanisme yang mendasari dan mengoptimalkan aplikasi terapeutiknya.

***Kata kunci**: Gastroprotektif, Histopatologi, Peperomia pellucida L., Senyawa bioaktif*

INTRODUCTION

Gastroenteritis is a type of diarrheal illness marked by an increased frequency of bowel movements, which may be accompanied by fever, vomiting, and abdominal pain. This activity focuses on the assessment and treatment of gastroenteritis, while also highlighting the contribution of the interprofessional team in enhancing care for patients affected by this condition. The term "gastroenteritis" comes from the Greek words "gastron," meaning "stomach," and "enteron," meaning "small intestine," so it refers to the inflammation of both the stomach and small intestine. Medically, gastroenteritis is recognized as a diarrheal disease, which involves an increase in the frequency of bowel movements, potentially accompanied by vomiting, fever, and abdominal pain. An increase in bowel movement frequency is defined as having three or more watery or loose stools within a 24-hour period or at least 200 grams of stool per day. Gastroenteritis can be categorized in several ways, with one classification based on the duration of symptoms, including acute, persistent, chronic, or recurrent forms (Hiyoshi et al., 2018).

Gastroenteritis can be caused by bacteria, viruses, fungi, and parasites, although this article will specifically focus on bacterial causes. The factors contributing to infectious diarrhea vary across different geographical regions, from urban to rural areas, and are influenced by co-morbidities and the immune status of the host. While viruses such as norovirus, rotavirus, and adenovirus are the most common causes of acute infectious diarrhea, as evidenced by stool cultures being positive in fewer than 5% of cases in most studies, other notable causes of watery diarrhea include Clostridium perfringens and enterotoxigenic *Escherichia coli* (ETEC). Bacterial infections tend to account for more severe cases of infectious diarrhea compared to other causes. For instance, one study showed that in otherwise healthy adults with severe diarrheal illness (defined as four or more watery stools per day for three or more days), a bacterial pathogen was identified in 87% of cases. Among these bacterial causes, nontyphoidal Salmonella and Campylobacter species are the most common in the United States (Kolsin et al., 2018).

Many people still do not take proper care of their stomach health. Gastritis often does not cause symptoms, but its hallmark is pain in the epigastrium. Other symptoms include vomiting, nausea, bloating, and loss of appetite (Saputra, 2017). Previous research indicates that most gastritis cases are caused by chronic bacterial infection of the gastric mucosa. Additionally, substances such as aspirin, alcohol, bile salts, and other agents can damage the gastric mucosa and alter the permeability of the epithelial barrier, which is crucial for the protection of the stomach and duodenum. Most gastritis cases (70-80%) result from functional gastritis, which is pain not caused by organic stomach disorders. If left untreated, gastritis can impair stomach function and increase the risk of gastric malignancy, leading to death (Muttaqin et al., 2011).

The choice of *Peperomia pellucida* (Chinese betel) in this research is based on its traditional use in herbal medicine and its potential pharmacological properties that could offer therapeutic benefits in treating gastrointestinal disorders. *P. pellucida* has been used in various cultures for its anti-inflammatory, antimicrobial, and antioxidant effects, which are believed to contribute to the overall health of the digestive system. Additionally, there is growing interest in exploring plant-based remedies as alternatives to synthetic drugs due to their lower toxicity and wide availability.

Research has suggested that *P. pellucida* may possess gastroprotective qualities that could help mitigate damage caused by gastrointestinal conditions such as gastroenteritis. By evaluating its impact on the histopathological features of the stomach in a mouse model, the study aims to further

understand how this plant extract might reduce inflammation, protect the stomach lining, and potentially improve gut health. The selection of *P. pellucida* is therefore driven by its promising biological activities and the need for alternative, natural therapies for gastroenteritis.

MATERIALS AND METHODS

Research Type

The population used in this study is mice. The sample used in this study is male Swiss strain mice aged 2-3 months, weighing 25-30 grams, obtained from the Veterinary Farma Center, Surabaya. The use of male Swiss strain mice aged 2-3 months and weighing 25-30 grams in this study is supported by several reasons commonly cited in scientific research for selecting this particular animal model.

1. Well-Established Model for Gastrointestinal Research: Swiss albino mice are a widely recognized and frequently used strain in gastrointestinal research due to their well-documented response to gastrointestinal disorders, including gastroenteritis. They are considered a reliable model for studying the effects of various treatments on the stomach and intestines, as they show similar pathological responses to human gastrointestinal conditions (Elvira et al., 2020; De Souza et al., 2019).
2. Standardization of Experimental Conditions: The use of male mice, particularly in the 2-3 months age range, helps control for hormonal variations that can influence gastrointestinal responses. The uniformity in weight (25-30 grams) also ensures that the mice are at a similar developmental stage, which minimizes variability in results (Koo et al., 2018). The age range corresponds to the young adult phase, where immune and digestive system functions are fully developed, making them ideal for studying disease models like gastroenteritis (Moulin et al., 2016).
3. Reproducibility and Comparability: Male Swiss mice are commonly used in studies of inflammation, infection, and pharmacology due to their consistent biological characteristics, which contribute to the reproducibility of research findings. This consistency allows for better comparison with other published studies (Sundar et al., 2020).
4. Ethical Considerations: Male Swiss mice are commonly preferred in preclinical studies due to ethical considerations regarding the use of animals. They are often selected for experimental work because of their ease of handling, relatively low cost, and availability (Hewitt et al., 2014).

Thus, the minimum number of samples in each treatment is 4 mice. Since there are 6 groups in this study, the minimum total is 24 mice. Using 4 mice per group in your study aligns with the general principles of Federer's formula, which helps ensure adequate statistical power while considering the variability of the data and ethical use of animals. This number provides a practical and statistically valid basis for your experiment while adhering to accepted guidelines for animal research. However, in this study, the number of samples per treatment was increased by 1, resulting in a total of 30 mice.

Research Procedure

1. Mice Acclimatization

Male mice were weighed and then placed in standard polypropylene cages with wood shavings as bedding for acclimatization for two weeks. The bedding was changed daily. The feed was softened with water, then shaped into an oval weighing approximately 90 grams per cage (containing 6 mice). Water was provided ad libitum. Feed and water were changed daily. After two weeks of acclimatization, the mice were divided into six treatment groups.

2. Treatment of Test Animals

The acclimatized mice were subjected to the following treatments: Group 1, as the normal control, where mice were not given gastric gavage, Group 2, as the negative control, where mice were given distilled water, Group 3, as the positive control, where mice were given *Yakult*, probiotic drink that originated in Japan in 1935. It is made from fermented milk, containing Lactobacillus casei Shirota with a volume of 0.26 mL, Group 4, where mice were given Chinese betel leaf

extract at a dose of 100 mg/kgBW with a volume of 0.5 mL, Group 5, where mice were given Chinese betel leaf extract at a dose of 300 mg/kgBW with a volume of 0.5 mL, dan Group 6, where mice were given Chinese betel leaf extract at a dose of 500 mg/kgBW with a volume of 0.5 mL.

To prepare an extract of *P. pellucida* (Chinese betel), fresh leaves are first collected and thoroughly washed to remove any dirt or contaminants. The leaves can then be either dried or used fresh, depending on the method of extraction. For an aqueous extract, the leaves are ground into a fine paste or powder using a mortar and pestle. The ground material is then mixed with distilled water in a ratio of 1:10 (plant material: solvent) and heated gently in a water bath at around 50-60°C for 30-60 minutes to facilitate the extraction of active compounds. After extraction, the mixture is filtered through filter paper or cheesecloth to separate the liquid extract from the plant residue. If a more concentrated extract is required, the solvent can be evaporated under reduced pressure or allowed to evaporate naturally. For an ethanol-based extract, the ground leaves are soaked in 95% ethanol (or a water-ethanol mixture) for 7-14 days at room temperature, with occasional shaking. After the extraction period, the mixture is filtered to obtain the liquid extract, which can be concentrated by evaporating the ethanol if necessary. The resulting extract, whether aqueous or ethanol-based, is then ready for use in experiments or further processing, ensuring that the concentration of the extract is carefully measured for consistent results in research.

3. Gastroenteritis (GE) Model Treatment in Mice

After 7 days of treatment, the mice were induced to develop a GE model by administering *E. coli* at a dose of $1x10^6$ CFU/mL per mouse per day for 7 days via gastric gavage.

4. Tissue Processing

The stomach tissues were fixed in formalin buffer to preserve cell morphology and prevent autolysis and bacterial or fungal growth. The next step involved creating paraffin blocks. Once the paraffin blocks were made, the tissues were sectioned using a rotary microtome or sliding microtome at a thickness of 4-6 microns. The obtained sections were picked up with a water-moistened brush and placed on the surface of a water bath. The expanded tissue sections were then transferred to glass slides coated with a tissue adhesive, dried at room temperature, and placed in an oven overnight.

5. Histopathological Observation of Mice Stomachs

Histopathological observation of the mice stomachs was conducted using hematoxylin and eosin (HE) staining. The tunica mucosa (epithelium, lamina propria, muscularis mucosa), submucosa, tunica muscularis, tunica serosa, and other parts potentially experiencing necrosis or apoptosis in the mice stomachs were examined.

6. Data Collection

The data obtained from this study include the number of cells showing anomalies in the tunica mucosa (epithelium, lamina propria, muscularis mucosa), submucosa, tunica muscularis, tunica serosa, and other parts potentially experiencing necrosis or apoptosis in the mice stomachs.

RESULTS AND DISCUSSION

Histopathological Description of Stomach

The testing of *P. pellucida* L. extract for its gastroprotective properties was conducted by observing the histopathological features of the stomach in a gastroenteritis model induced in mice. In this study, the researchers utilized 6 groups, with each group consisting of 4 mice. Observations of the histopathological features of the stomach in the gastroenteritis model (Figure 1-6) included cell degeneration, necrosis, and polymorphonuclear leukocytes (PMN) infiltration (Table 1).

Table 1. Histopathological Profile of the Stomach in Mice Model of Gastroenteritis

Group	Degeneration (%)		Necrosis (%)		PMN (%)	
Mean	SD	Mean	SD	Mean	SD	Mean
Normal	1.92%	0.01	1.85%	0.01	2.10%	0.01
Positive (+)	6.45%	0.03	4.32%	0.02	5.25%	0.02
Negative (-)	25.12%	0.05	20.37%	0.04	24.56%	0.03
PI (100mg/kgBW)	18.34%	0.03	15.78%	0.02	19.65%	0.03
PII (300mg/kgBW)	12.78%	0.02	10.12%	0.02	12.55%	0.02
PIII (500mg/kgBW)	7.68%	0.02	5.94%	0.01	8.14%	0.02

In Table 1, the research results show the histopathological profile of the stomach in terms of cell degeneration, necrosis, and PMN in a gastroenteritis model induced in mice. Normality tests resulted in p-values of 0.920 for the normal group (Figure 1), 0.512 for the negative control group (-) (Figure 2), 0.835 for the positive control group (+) (Figure 3), 0.704 for Group I (100mg/kgBW) (Figure 4), 0.698 for Group II (300mg/kgBW) (Figure 5), and 0.350 for Group III (500mg/kgBW) (Figure 6). All p-values were >0.05, indicating that the data were normally distributed and suitable for further testing. The comparison between Group I (100mg/kgBW) and Group II (300mg/kgBW) with a significance value of 0.195 (>0.05), suggesting similar gastroprotective effects in terms of cell degeneration between these two groups.

Cell Degeneration

The study found that the normal group had the smallest average percentage of cell degeneration, at 1.92%±0.01. The positive control group (+) had the second smallest average at 6.45%±0.03. The group treated with 500 mg/kgBW of *P. pellucida* L. (Group PIII) had the third smallest average at 7.68%±0.02. Group PIII (500mg/kgBW) also showed the smallest average compared to the other two groups treated with Chinese Betel extract.

Necrosis

The normal group had the smallest average percentage of necrosis, at 1.85%±0.01. The positive control group (+) had the second smallest average at 4.32%±0.02. The group treated with 500 mg/kgBW of *P. pellucida* (Group PIII) had the third smallest average at 5.94%±0.01. Similar to cell degeneration, Group PIII (500mg/kgBW) exhibited the smallest average compared to the other groups treated with *P. pellucida* extract.

Polymorphonuclear Leukocytes (PMN)

The normal group had the smallest average percentage of PMN, at 2.10%±0.01. The positive control group (+) had the second smallest average at 5.25%±0.02. The group treated with 500 mg/kgBW of *P. pellucida* extract (Group PIII) had the third smallest average at 8.14%±0.02. Similar to the other parameters, Group PIII (500mg/kgBW) showed the smallest average compared to the other groups treated with *P. pellucida* extract.

Gastroprotective refers to an effect produced by compounds that have the ability to shield the gastric mucosa. *P. pellucida* L. is believed to exhibit gastroprotective activity, as indicated by previous research conducted by Roslida and Aini (2009), which demonstrated that the ethanol extract of *P. pellucida*. can provide gastroprotective effects at an effective dose of 100 mg/KgBW. The gastroprotective action of this plant is attributed to different mechanisms produced by its various metabolite compounds (Yusuf et al., 2017). Phytochemical screening of *P. pellucida* L. revealed the presence of secondary metabolites such as flavonoids, tannins, saponins, triterpenoids, and steroids (Rachmawati and Rantelino, 2018; Pertiwi et al., 2022; Oloyede et al., 2011). A previous study identified dillapiole as the most active gastroprotective compound in *P. pellucida* L. However, further research is needed to fully understand the gastroprotective mechanism of dillapiole, as it does not seem to be linked to endogenous nitric oxide or prostaglandins (Rojas-Martínez et al., 2013).

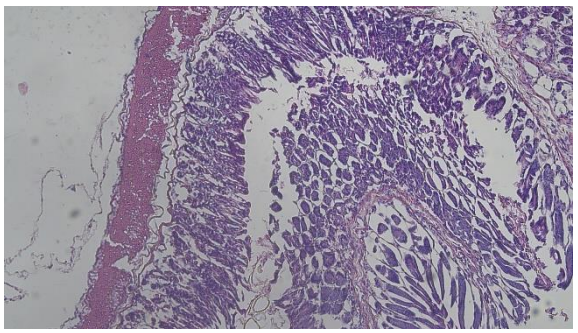

Figure 1. The Histopathological View of Mice Stomach Under Normal Treatment (N). (HE Stain, 100x Magnification)

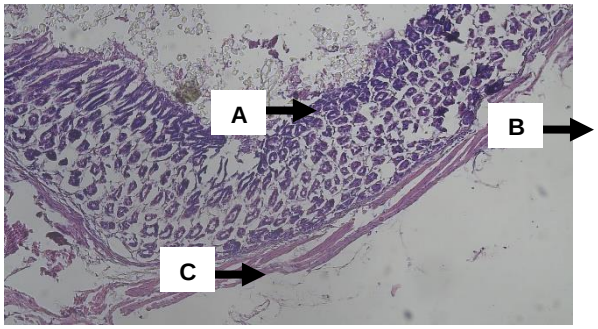

Figure 2. The Histopathological View of Mice Stomach Under Negative Control Treatment (K-) Reveals the Preence of (a) Karyorrhexis, (b) Karyolysis in the Epithelium, and (c) Deposition of Protein in The Lamina Propria (HE Stain, 100x Magnification)

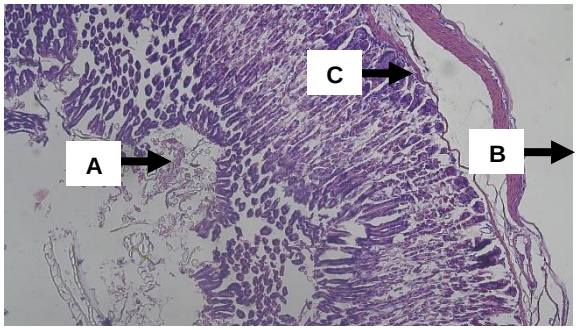

Figure 3. The Histopathological View of Mice Stomach Under Positive Control Treatment (K-) Reveals the Presence of (a) Karyorrhexis, (b) Karyolysis in the Epithelium, and (c) Deposition of Protein in The Lamina Propria (HE Stain, 100x Magnification)

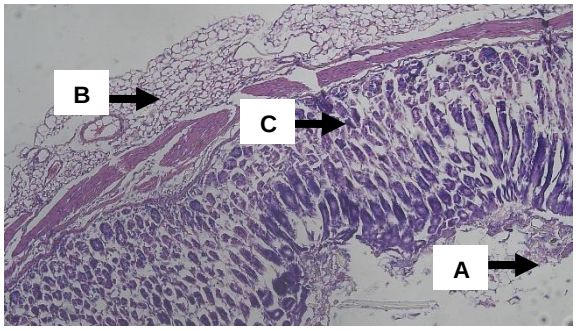

Figure 4. The Histopathological View of Mice Stomach Under Treatment 1 (P1) Reveals the Presence of (a) Karyo rhexis, (b) Karyolysis in the Epithelium, and (c) Deposition of Protein in The Lamina Propria (HE Stain, 100x Magnification)

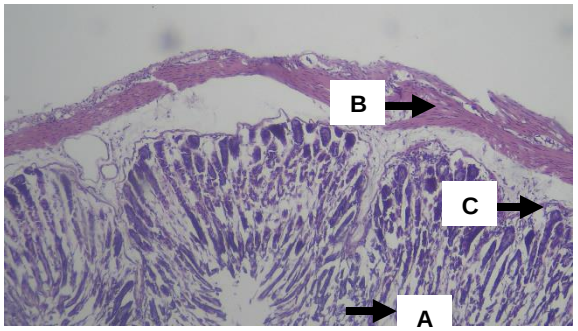

Figure 5. The Histopathological View of Mice Stomach Under Treatment 2 (P2) Reveals The Presence of (a) Karyo rhexis, (b) Karyolysis in the Epithelium, and (c) Deposition of Protein in The Lamina Propria (HE Stain, 100x Magnification)

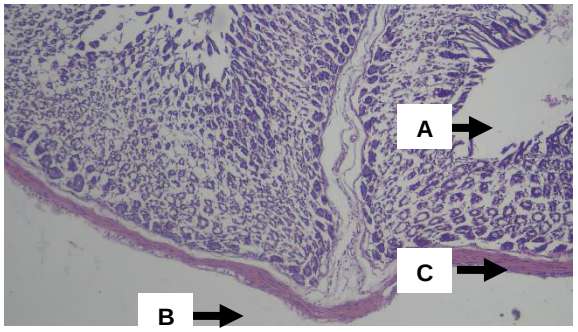

Figure 6. The Histopathological View of Mice Stomach Under Treatment 3 (P3) Reveals The Presence of (a) Karyo rhexis, (b) Karyolysis in the Epithelium, and (c) Deposition of Protein in The Lamina Propria (HE Stain, 100x Magnification)

Flavonoids exhibit anti-ulcer and anti-inflammatory effects through various mechanisms, including the inhibition of K+/H+ ATPase, reduction of HCl secretion, increased synthesis of PGE2 and COX-1, inhibition of bacterial growth, and antioxidant activity (Kalogeromitros et al., 2008). Alkaloids, as another type of gastroprotective agent, promote wound healing and enhance the production of gastric mucus following injury caused by harmful agents (Tan et al., 2002). Tannins are known for their astringent properties, which enable them to interact with proteins in the gastric mucosal layer. This interaction helps form a protective coating on the outermost layer of the mucosa, making it less permeable and more resistant to ulcers or irritation (Souza et al., 2012). Saponins contribute to gastroprotective activity by increasing fibronectin levels, leading to the formation of fibrin clots that serve as the foundation for tissue re-epithelialization. The faster these clots form, the quicker fibroblasts proliferate in the wound area, aiding in tissue repair (Indraswary, 2011).

CONCLUSION

Histopathological analysis revealed reduced cell degeneration, necrosis, and PMN infiltration, with the highest dose (500 mg/kg BW) demonstrating the most significant effects. The plant's bioactive compounds, such as flavonoids, tannins, and saponins, likely contribute to its anti-inflammatory and tissue-repairing properties. These findings support P. pellucida as a potential natural treatment for gastrointestinal disorders, warranting further research to understand its mechanisms and therapeutic benefits.

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