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Protective effect of juwet fruit extract (*Syzygium cumini* L.) on duodenum histomorphometry and histopathology of male mice exposed to pyrantel pamoate

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ABSTRACT. Pyrantel pamoate, known as an anthelmintic under the brand name Combantrin®, is effectively used to kill worms in the intestines. However, long-term use of it has been associated with side effects and risk of drug resistance. *Syzygium cumini* L.is known for its antioxidant and anti-inflammatory which may support antiparasitic effects and tissue healing. This study aims to examine the effect of juwet (*S. cumini* L.) fruit water extract (JFWE) on the duodenum structure of mice suspected to be infected with worm, through histomorphometric analysis and histopathological examination. The pyrantel pamoate was only administered once after the acclimatization period, while the JFWE was administered for 3 weeks. A total of 30 male mice were divided into six groups: negative control (aquadest), positive control (pyrantel pamoate, Combantrin® 20 mg/mL), and JFWE at doses of 5 mg/mL, 10 mg/mL, 20 mg/mL, and 40 mg/mL, administered for 3 weeks. Histomorphometric and histopathological evaluations were conducted by microscopically observing the duodenum structures, including intestinal villi, and the thickness of the mucosa, submucosa, and muscularis layers. The results showed a significant difference for the decrease in intestinal villi height and thickness of the mucosa, submucosa, and muscularis layers in JWFE doses of 5 mg/mL and 10 mg/mL administration group, compared to the negative control group (aquadest), the treatment groups of pyrantel pamoate, and JFWE doses of 20 mg/mL and 40 mg/mL ($p<0.05$). The conclusion is that the administration of juwet fruit water extract doses of 20 mg/mL and 40 mg/mL can improve the histomorphometry structure and also the histopathology of the duodenum of male mice.

Keywords: duodenum; histomorphometry; histopathology; juwet fruit; pyrantel pamoate

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INTRODUCTION

In developing countries such as Indonesia, where many communities have low socioeconomic levels, helminth infections remain a prevalent issue. The most commonly encountered helminth infections are caused by Soil-Transmitted Helminths (STH) (Annisa *et al*., 2018). The causative species include *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms), *Trichuris trichiura* (whipworm), and *Strongyloides stercoralis* (Aryadnyani *et al*., 2021). Anthelmintic are agents of drugs used to expel or destroy parasitic worms from the body by paralyzing of killing them. Commonly used anthelmintics for animals include pyrantel pamoate (Jacob *et al*., 2022), ivermectin (Lehne, 2013), albendazole (Anwar *et al*., 2020), and abamectin (Putri *et al*., 2021). Continuous use of commercial anthelmintics without considering their half-life can leave residues. If these residues accumulate in large amounts, they can lead to resistance against anthelmintic treatments (Putri et al., 2021).

Although commercial anthelmintic drugs are effective in killing worms, they still have side effects. Besides being expensive, some parasitic worms may develop resistance to these drugs. An alternative approach is to explore herbal medicines that are also effective in eliminating parasitic worms but with fewer side effects, lower costs, greater accessibility, and protective effect of the tissue, especially for the intestinal structure (Rajeswari, 2014). Several studies have shown that secondary metabolites in plant extracts possess anthelmintic properties (Hamzah *et al*., 2016; Sunita

et al., 2017), but no studies have shown its effect as an agent that protects the gut, where worms thrive.

One plant species that has been increasingly studied is *Syzygium cumini* L. (Gupta *et al*., 2024). *S. cumini* in Java Indonesia, known as juwet, is a medicinal plant belonging to the Myrtaceae family, which has been widely used as a therapeutic drug, including being used for antidiabetes, anti-inflammatory, antibacterial, and for indigestion. Phytochemical screening of juwet revealed the presence of various bioactive compounds such as flavonoids, alkaloids, tannins, phenolic acids, and essential oils. In addition, juwet also has beneficial antioxidant potential for various diseases attributed to its free radical scavenging properties, and growth inhibition of pathogenic microorganisms (Gupta *et al*., 2024; Katiyar *et al*., 2016). In addition, juwet is known for its medicinal properties, including its anthelmintic activity, which can paralyze and kill worms (Azam *et al*., 2020).

The use of juwet fruit water extract (JFWE) as an anthelmintic in mice has not been explored before, nor has its potential in improving the structure of digestive system tissues, particularly the duodenum infected by worms. Therefore, this study aims to investigate the protective effect of JFWE at graded doses using histomorphometry and histopathological approaches to assess its impact on the duodenum of infected mice. JFWE has the potential to serve as a natural therapeutic agent in supporting intestinal structural integrity and mitigating pathological impacts caused by parasitic infection, thereby offering a treatment alternative based on natural compounds.

MATERIALS AND METHODS

The preparation of juwet (*Syzygium cumini* L.) fruit water extract was conducted at the Research Laboratory, while the treatment of mice was carried out at the Animal Laboratory, Faculty of Medicine and Health Sciences, Universitas Kristen Krida Wacana, from September 2024 to December 2024. The preparation of histological slides of the duodenum was performed at the Histology Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya.

This research has passed the ethical review issued by the Medical and Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Krida Wacana Christian University Jakarta with No. SLKE: 1794/SLKE/IM/UKKW/FKIK/KEPK/VIII/2024.

Preparation of juwet fruit water extract (JFWE). Fresh *S. cumini* fruits were washed and sorted, then the skin and pulp were separated from the seeds. The skin and pulp were extracted using a juicer method with the addition of HCl to adjust the pH to 1. The juiced extract was filtered, and the obtained filtrate was concentrated using a thermostatic water bath.

Preparation of experimental animal. A total of 30 male BALB/C mice (8 weeks old, 20-25 g) were obtained based on the sample size calculation using the Federer formula for completely randomized design: $(t–1)(n–1)\geq 15$, with $t = 6$ treatment groups and $n = 5$ replications per group. All mice were acclimatized for 7 days under standard laboratory conditions (temperature: 22 ± 2°C, 12-hour light/dark cycle) in clean cages with wood shavings. Mice were provided ad libitum access to food and water. Health and behavior were monitored daily. The mice were randomly divided into six groups: negative control (aquadest), positive control (pyrantel pamoate, Combantrin® 20 mg/mL), and treatment groups receiving JFWE at graded doses of 5 mg/mL, 10 mg/mL, 20 mg/mL, and 40 mg/mL. Pyrantel pamoate (Combantrin® 20 mg/mL) was given orally on day 8 and day 18 to all groups except the negative control. The JFWE was administered orally daily for 21 days. On the final day of the study (day 21), all mice were fasted for 12 hours before termination (anesthesized using ether 1,9%, followed by cervical dislocation) and dissection.

Histomorphology and histopathology processing. Histological slides were prepared (Khasanah & Husen, 2024; Kiernan, 2015). The obtained duodenum samples were fixed in 10% Neutral Buffered Formalin for 24 hours at room temperature (22–25°C), following the 10:1 volume ratio (formalin:tissue). After fixation, tissues were trimmed using a scalpel and placed in labeled tissue cassettes. Then, the trimmed tissues were dehydrated in graded alcohol series from low to high concentrations (70%, 80%, 90%, and 95%). The samples then underwent clearing in xylene for 2x30

minutes. Tissues were then infiltrated and embedded in paraffin wax at 60°C for 2 hours. The paraffin blocks were then colled and stored at room temperature until sectioning. Afterward, the tissue blocks were sectioned using a rotary microtome at a thickness of 5 µm. The ribbons were floated in water bath at 40–45°C, then mounted on glass slides pre-coated with Vectabond. Slides were dried at 37°C for 2-3 hours. Slides were then deparaffinized in xylene (2x5 min), followed by rehydration in descending alcohol concentrations (95%, 90%, and 70%) and rinsed in distilled water. Then each slides were immersed in hematoxylin for 5-8 mins, followed by dipping in aquadest for 5 mins. Next, the slides were dipped in 0.1% acid alcohol (1% HCl in absolute ethanol) for 1 min, and dipped in aquadest for another 5 mins. Then, the slides were dipped in 1.5% lithium carbonate for 30 sec, followed by eosin Y for 3 mins, then briefly in aquadest. Following that, slides were dehydrated by dipping in ascending alcohol (95% and 100%), then cleared in xylene. Lastly, the slides were mounted and covered with coverslips and observed under a microscope with integrated digital camera (Olympus MCCH20, microscope CH20). Four fields of view per sample were analyzed (Harijati *et al*., 2017; Khasanah & Husen, 2024).

Data analysis. The data for intestinal villi height and the thickness of the mucosa, submucosa, and muscularis layers were analyzed using one-way Anova (α = 95%), followed by an LSD test at a 95% confidence level using SPSS software version 26.00.

RESULTS AND DISCUSSION

The histomorphometric measurements of the duodenum in cestode-infected mice are presented in Table 1.

Table 1. Average of intestinal villus height and thickness of layer in mice duodenum treated for 21 Days

Group	n	Intestinal Villus Height (µm)	Mucosal Layer Thickness (µm)	Submucosal Layer Thickness (µm)	Muscular Layer Thickness (µm)
Negative control	5	357.50 ± 6.59[a]	425.04 ± 12.67[a]	260.59 ± 5.04[a]	65.39 ± 1.88[a]
Positive control	5	364.73 ± 16.47[a]	422.18 ± 15.08[a]	261.22 ± 4.55[a]	64.94 ± 0.50[a]
JFWE 5 mg/mL	5	387.66 ± 13.77[b]	460.30 ± 23.99[b]	274.65 ± 7.65[b]	72.13 ± 1.32[b]
JFWE 10 mg/mL	5	381.70 ± 12.89[b]	456.05 ± 10.62[b]	270.69 ± 6.83[b]	71.01 ± 1.38[b]
JFWE 20 mg/mL	5	358.78 ± 6.85[a]	417.38 ± 8.19[a]	259.64 ± 4.65[a]	65.04 ± 1.57[a]
JFWE 40 mg/mL	5	354.33 ± 12.80[a]	413.13 ± 9.36[a]	254.47 ± 9.55[a]	63.73 ± 0.39[a]
Sig		**0.001**	**0.000**	**0.001**	**0.000**

[a,b] Different letters indicate significant differences ($p<0.05$)
[*] Negative control (aquadest); positive control (pyrantel pamoate, Combantrin® 20 mg/mL)
[*] Treatment with JFWE (Juwet Fruit Water Extract)
[*] Data are presented as mean ± SE from one-way Anova at a significance level of 0.05, with superscript letters indicating LSD test results at a 95% confidence interval

Based on the one-way Anova and LSD post-ho test results shown in Table 1, there was no significant difference ($p>0.05$) in the villi height between the negative control group (aquadest), pyrantel pamoate (Combantrin®) 20 mg/mL, and the JFWE groups at concentrations of 20 mg/mL and 40 mg/mL. However, these groups showed significant differences ($p<0.05$) compared to the 5 mg/mL and 10 mg/mL juwet extract groups.

The intestinal villi of the duodenum are composed of a single layer of columnar epithelial cells with nuclei positioned at the basal part of the cells (McKay *et al*., 2017; Williams *et al*., 2014). The normal morphology of epithelial cells, without signs of degeneration or necrosis, indicates that the nutrient absorption process remains functional in the intestinal villi. Kiela & Ghishan (2016) explained that almost all nutrient absorption and other compounds occur in the epithelial cells of the intestinal villi and mucosal layer, with absorbed nutrients being transported through blood vessels. McKay *et al*. (2017) and Tincati *et al*. (2016) state that the intestinal epithelial layer is the link between the interior of the body, namely the lamina propria and mucosal layer, and the intestinal lumen which is exposed to various antigens, a vast microbiota, various protozoa, and helminth parasites. The intestine is a favored site for helminth parasites, as it provides a sheltered environment,

a soft mucosal lining surface that is easily sloughed off to gain access to the food-rich microvasculature in the blood, and a flow of nutrients digested by the host.

Furthermore, McKay *et al*. (2017) state that nematodes can cause significant damage to the small or large intestine of mammalian hosts. Physical damage caused by these nematodes, which have tissue- or blood-feeding activity, can increase epithelial cell permeability, and cause an increase in intestinal villi height. The increased villi height in the 5 mg/mL and 10 mg/mL juwet extract groups was a result of small intestine inflammation caused by cestode infection. A characteristic of intestinal inflammation is the elongation of intestinal villi (Wiadnyana *et al*., 2015). This is further supported by Table 1, which shows that the average villi height in the 5 mg/mL and 10 mg/mL juwet extract groups exceeded the normal range. The normal villi height in the small intestine of mice is 333.25 ± 42.25 µm (Hidayat *et al*., 2021) and 288.95 ± 7.73 µm (Zou & Zheng, 2013). The normal villi height in the duodenum is 356.58 ± 21.21 µm (Aboregela *et al*., 2020).

The villi height in the pyrantel pamoate (Combantrin®) 20 mg/mL, juwet extract 20 mg/mL, and juwet extract 40 mg/mL groups effectively reduced small intestine inflammation (resulting in villi height lower than the normal value), leading to wound healing and structural improvement of the duodenal villi in mice. JFWE contains flavonoid compounds that can stimulate epithelial formation (Devi *et al*., 2021). In addition to affecting the villi height of the duodenum, cestode infection also influences the thickness of the duodenal mucosal layer.

The thickness of the duodenal mucosal layer in mice, based on the results of one-way Anova and LSD tests (Table 1), showed that the JFWE groups at concentrations of 5 mg/mL and 10 mg/mL were significantly different from the aquadest group, the Combantrin® 20 mg/mL group, and the JFWE groups at concentrations of 20 mg/mL and 40 mg/mL ($p<0.05$). Thickening of the duodenal mucosal layer may indicate both inflammation and tissue repair. Signs of inflammation in the duodenum include thickening of the mucosal, submucosal, and muscular layers due to the localization of macrophages, eosinophils, and other lymphocytes (Jatsa *et al*., 2018). Epithelial tissue repair in the intestinal villi of the duodenal mucosal layer occurs as part of the healing process initiated by lymphocytes (Sunarno *et al*., 2016).

Thickening of the intestinal muscular layer is associated with increased contractility of smooth muscle cells lining the intestinal wall. This increased contractility is an important mechanism for expelling parasites from the gastrointestinal tract (Else *et al*., 2020; Klementowicz *et al*., 2012). Additionally, worm infections can manipulate the host's immune response, making helminthiasis a chronic infection that is often asymptomatic (Figueiredo *et al*., 2010; Vanhooren *et al*., 2023). The elimination mechanism for expelling worms involves increased epithelial cell turnover, mucin production by goblet cells, and smooth muscle contraction, which can lead to structural changes in the intestines, particularly in the muscular layer (Anto *et al*., 2020; Klementowicz *et al*., 2012).

The JFWE groups at 20 mg/mL and 40 mg/mL showed a reduction in inflammation due to the anti-inflammatory effects of the extract. The reduction in inflammation indicates that the muscular layer thickness is returning to normal levels, and the healing process is progressing. Furthermore, the decrease in muscular layer thickness is attributed to the expulsion of parasitic worms from the duodenum, preventing further stimulation of smooth muscle contractility in the intestinal wall. This study shows that JFWE at 20 mg/mL and 40 mg/mL reduces intestinal villi height, mucosal layer thickness, submucosal layer thickness, and muscular layer thickness in male mice. This finding is supported by the histopathological images of the duodenum, where necrosis of the simple columnar epithelial cells forming the intestinal villi was observed in the control and pyrantel pamoate (Combantrin® 20 mg/mL) groups due to worm metabolism adhering to the duodenal wall. In contrast, the JFWE treatment groups up to 40 mg/mL showed no significant histopathological changes in the

duodenum of male mice during the 3 weeks study period. Changes in duodenal histopathology of mice after treatment for 3 weeks can be seen in Figure 1.

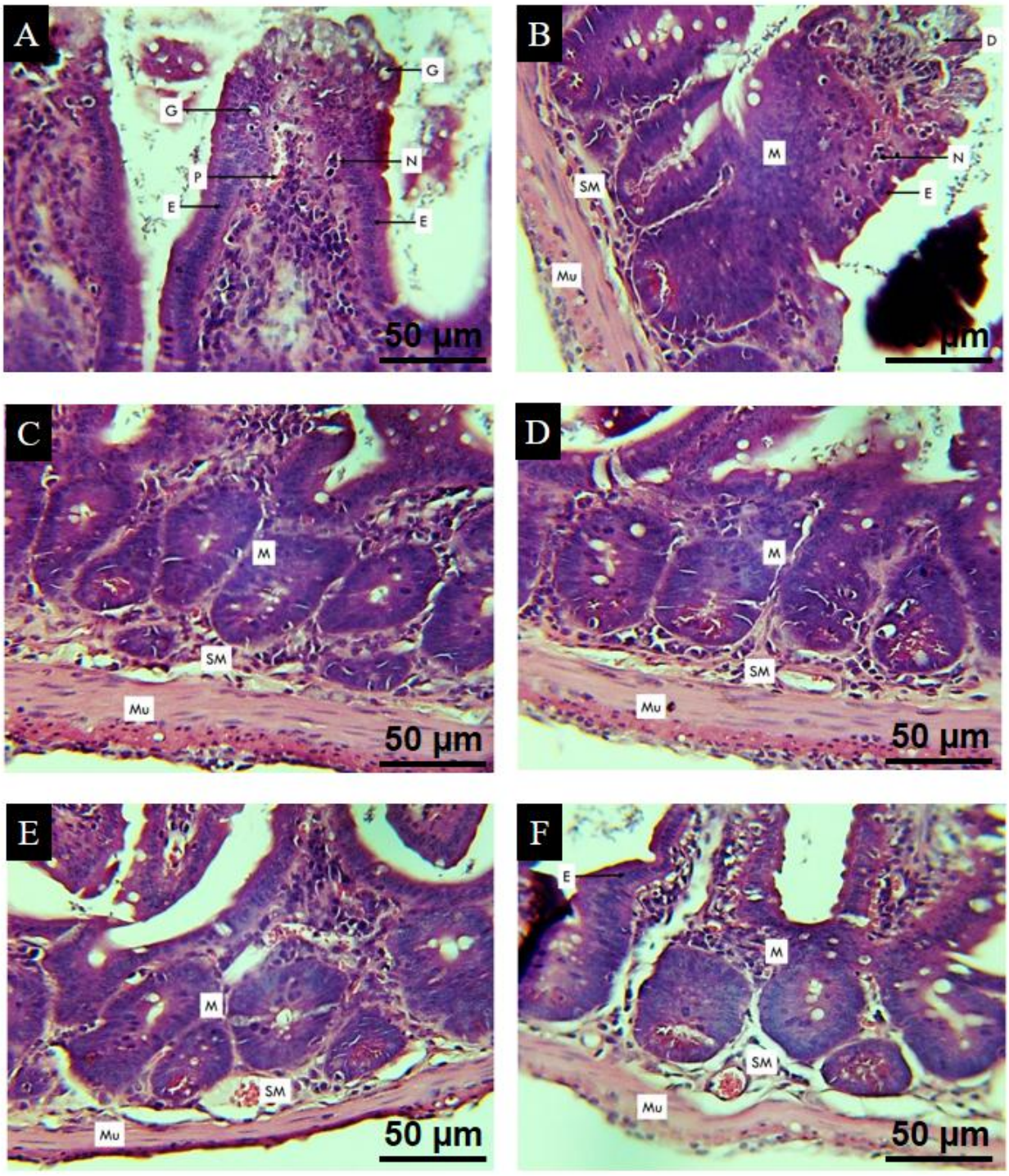

Figure 1. Photomicrograph of a transverse section of the duodenum (HE, 400x). Note: 1. Negative control group (aquadest), 2. Positive control group Pyrantel Pamoate, Combantrin® 20 mg/mL, 3. Treatment group with JFWE 5 mg/mL, 4. Treatment group with JFWE 10 mg/mL, 5. Treatment group with JFWE 20 mg/mL, 6. Treatment group with JFWE 40 mg/mL, inflammation (P), necrosis (N), goblet cells (G), simple columnar epithelial cells (E), mucosal layer (M), submucosal layer (SM), muscularis layer (Mu), degeneration (D)

Based on previous studies, juwet fruit was known to contain secondary metabolites such as flavonoids, saponins, alkaloids, and tannins. In particular, alkaloids plays a role as an anthelmintic (Gupta *et al*., 2024; Katiyar *et al*., 2016; Azam *et al*., 2020). The anthelmintic activity of alkaloid

compounds involves the inhibition of acetylcholinesterase enzyme activity, leading to muscle paralysis in worms, ultimately causing their death (Pratama, 2021).

The improvement in duodenal histopathology of mice given JFWE may also be due to its high antioxidant activity. It is also possible that the antioxidant activity in JFWE in the intestine serves to protect intestinal cells from damage caused by free radicals. Ahmed *et al*. (2020) reported that juwet pulp and seeds are a source of natural antioxidants that can be used efficiently, where the phenolic compounds contained therein can repair histopathological changes in organs damaged by free radical exposure (El-Anany & Ali, 2013). Unlike pyrantel pamoate, which acts purely as an anthelmintic but cannot fully help repair the damage to the duodenal structure, JFWE showed not only as an anthelmintic but can also repair damage to the duodenal structure due to its antioxidant activity.

CONCLUSION

The histomorphometric analysis of the duodenal structure in the treatment groups receiving 20 mg/mL and 40 mg/mL of JFWE demonstrated significant improvements in the height of intestinal villi, as well as the thickness of the mucosa, submucosa, and muscularis layers. These findings suggest that the extract plays a role in the recovery process from helminth-induced damage in the duodenum. The reduction in inflammation, as indicated by the normalization of tissue thickness, supports the potential anti-inflammatory and healing properties of the JFWE. Additionally, the histopathological analysis of the duodenum further confirmed these findings, as no structural abnormalities or degenerative changes were observed in the treatment groups receiving 20 mg/mL and 40 mg/mL of the extract. However, thile conventional H&E staining revealed structural improvements, it may not fully capture molecular or cellular-level changes involved in tissue repair and immune modulation. Therefore, future studies incorporating immunohistochemistry (IHC) are recommended to assess the expression of relevant biomarkers which would give insight into the mechanisms underlying the protective effects of JFWE. In conclusion, JFWE at concentrations of 20 mg/mL and 40 mg/mL may effectively aid in intestinal tissue repair and recovery, providing a potential natural alternative for combating helminth infections while minimizing tissue damage.

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