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THE EFFECT OF *MUNTINGIA CALABURA* ETHANOLIC LEAVES EXTRACT FOR ASPIRIN-INDUCED GASTRIC MUCOSAL DAMAGE

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ABSTRACT

Background: *Muntingia calabura* leaves have been claimed to relieve pain, fever, inflammation, and many others. Many studies has already prove the potential of these leaves as anti-inflammation, anti-nociceptive, and anti-proliferative. It might have capability to protect gaster from ulcer. **Objective:** This study aimed to know the effect of *Muntingia calabura* ethanolic leaves extract (MCELE) for aspirin-induced gastric mucosal damage on wistar rats. **Methods:** Twenty-five wistar rats is divided into 5 groups. K2 group (aspirin 300 mg/kg. K1, P1, P2, and P3 group received misoprostol 100 mcg/kg, MCELE 100 mg/kg, MCELE 250 mg/kg, and MCELE 500 mg/kg respectively 1 hour before the administration of aspirin 300 mg/kg. All treatments were administered orally once daily for 7 consecutives days. On day 8, all rats were sacrificed, and gastric tissues were collected for histopathological examination. The tissues were stained with hematoxylin and eosin (H&E) and evaluated under light microscopy to assess mucosal damage, including desqumasion, epithelial erosion, and ulceration. Statistical analysis was performed using the Kruskal-Wallis test, followed by the Mann-Whitney test for pairwise comparisons. Differences were considered statictically siginificant at $p<0.05$. **Results:** Histopathology test result showed a significant difference between K1 group and K2 group ($p=0.003$). Each treatment group also showed a significant difference when compared to K2 group ($p<0.05$). P3 group and K1 group showed a similar effect on rat's gastric mucosa ($p=1.000$). **Conclusion:** Administration of MCELE may lower gastric mucosal damage on wistar rats induced by aspirin, with 500 mg/kg dose is almost as effective as standard drugs (Misoprostol).

INTRODUCTION

Aspirin, one of *non-steroid anti-inflammatory drug* (NSAID) drugs, was often used as a treatment for pain, inflammation, and cardiovascular diseases. It's capability to effectively inhibit cyclooxygenase (COX), making it the drug of choice for analgetics and anti-inflammations. Aspirin could also act in the cardiovascular system as anti-platelet to prevent pathologic thrombosis and lower the risk of death on the patient of coronary heart disease and cerebrovascular disease.[1] But, the use of aspirin is associated with upper GI tract problems. There was a report of dyspepsia (31%), gastroduodenal erosion (60%), peptic ulcer (7%), and bleeding ulcer (0,6%), in which those risks raised up to 4 times on elderly.[2,3]

Muntingia calabura leaves, from the family *Elaeocarpaceae* is a traditional drugs that is believed could relieve headache, fever, inflammaton, diabetes, et cetera.[4] There were many studies that proven the potential of *Muntingia calabura* leaves as anti-inflammation, anti-nociceptive, anti-proliferative, anti-diabetic, anti-hypertension, and it's capability to protect gaster from ulcer.[5,6]

Muntingia calabura leaves contains mostly Flavone and Chalcone. Upadhye *et al.,* (2021) reported that the most active compounds in *Muntingia calabura* leaves are 2',4'-dihydroxychalcone

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(isoliquieitigenin); 5,7-dihydroxy-3,8-dimethoxyflavone; 5-hydroxy-3,8-dimethoxyflavone; 3,5,7-trihydroxy-8-methoxyflavone6]. These antioxidant were known to have effect on anti-inflammation, anti-diabetic, anti-microbial, and gastroprotective. According to a recent review by Narendra and Jyothi (2020), the ethyl acetate fraction of *Muntingia calabura* has been reported to increase PGE2 levels, enhance NO and non-protein sulfhydryl (SH) activity, and exhibit antioxidant properties.[7]

Aspirin inhibits COX through the acetylation of hydroxil on serin residue, which inhibits arachidonic acid reaction.[8] Aspirin on high-dose will inhibit both COX-1 and COX-2. If these 2 isoforms of COX is inhibited, it causes inhibition on prostanoid production such as PGE2. Low level of PGE2 will expose gastric wall mucosa to damage.[9]

MATERIALS AND METHODS

Research Methods

This study was conducted at Animal Testing Laboratory, Diponegoro University Faculty of Medicine. This research has received Ethical Clearance from Ethics Committee of Diponegoro University Faculty of Medicine. This study used true experimental method with post-test only group design.

Plant specimen and extract preparation

Muntingia calabura leaves were obtained from Faculty of Medicine, Diponegoro University, Indonesia, and only the green, not withered, and has complete parts were used. These leaves were left dry and then grounded, as much as 200 grams of grounded leaves were extracted by maceration method using 4 Liters of ethanol 70% for 48 hours. Extracted materials from maceration method is filtered using filter paper and evaporated using rotary evaporator with 500C temperature to obtain a thick extract that was considered free of solvent. The extract was then dissolved in aquadest to be given orally to the experimental rats.

Test subject

Subjects used in this study were 25 male wistar rats. Five healthy wistar rats was put in each group by random allocation sampling with around 12-weeks of age and weighed about 130-140 grams. Then it went through acclimatization for 7 days before treatment begun.

Intervention to animal model

K1 group (positive control group) were administered with misoprostol 100 mcg/kg 1 hour prior to aspirin 300 mg/kg, K2 group (negative control group) were only administered with aspirin 300 mg/kg, P1 group (treatment group) were administered with MCELE 100 mg/kg 1 hour prior to aspirin 300 mg/kg, P2 group (treatment group) were administered with MCELE 250 mg/kg 1 hour prior to aspirin 300 mg/kg , P3 group (treatment group) were administered with MCELE 500 mg/kg 1 hour prior to aspirin 300 mg/kg. These treatments would be given to the rats each day for 7 days. On day 8th, All wistar rats were given ether as sedative, terminated by cervical dislocation, and histopathology test is conducted on rat's gastric mucosa.

Response variables were severity classification of gastric mucosal damage, ranging from mucosa with no pathologic changes, epithelial desquamation, surface epithelial erosion, and epithelial ulceration under histopatholical examination of wistar rat's gaster organ to observe the effect of MCELE to the gaster's degree of injury. Scoring was done using modified Barthel-Manja Index.

Data analysis

Primary data collected was analyzed with SPSS IMB ver 20.0 using *Kruskall-Wallis* method followed by *Mann-Whitney* test. A value of $p<0,05$ was considered significant.

RESULTS

Descriptive analysis

Descriptive analysis on rat's gastric mucosal histopathology is shown in Table 1. Images of rat's gastric mucosa after treatment is shown in Fig. 1.

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Table 1. Frequency and percentage of rat's gastric mucosal histopatology

Group	NPC	ED	ESE	EU	Total
K1	100.00 % (25)	0.00%	0.00%	0.00%	100% (25)
K2	0.00%	0.00%	88% (22)	12% (3)	100% (25)
P1	20% (5)	68% (17)	12% (3)	0.00%	100% (25)
P2	48% (12)	52% (13)	0.00%	0.00%	100% (25)
P3	76% (19)	24% (6)	0.00%	0.00%	100% (25)

NPC: Non Pathologic Changes; ED : Epithelial Desquamation; ESE : Epithelial Surface Erosion; EU : Epithelial Ulceration

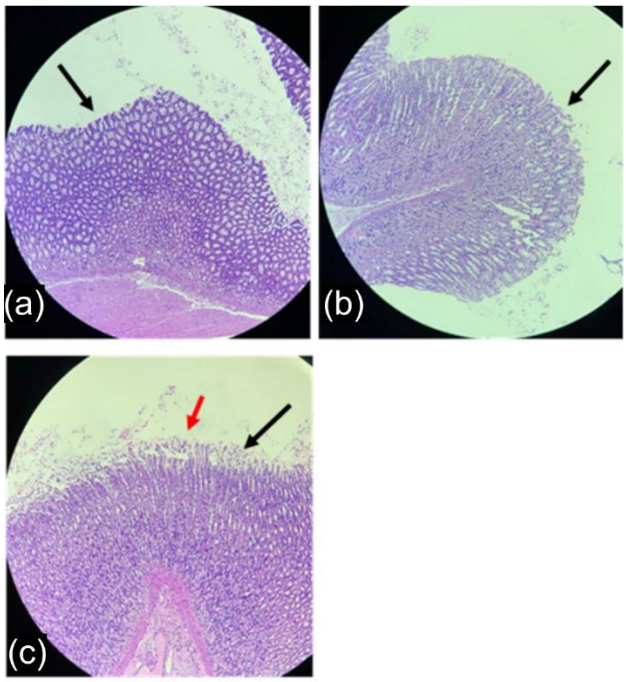

Figure 1. Histopathology test: (a) showed there was no pathologic changes (black arrow), photo taken from K1 group. Black arrow pointed on gastric mucosa with no pathologic changes. (b) showed epithelial desquamation (black arrow), photo taken from P3 group. (c) showed surface epithelial erosion (black arrow) and epithelial ulceration (red arrow)

Inferential analysis

Kruskall-Wallis test was conducted and showed significant difference between groups. Thus, Mann-Whitney test was conducted to analyze difference between each group. The result of *Kruskall-Wallis* test is shown in Table 2.

Table 2. *Kruskall-Walls* test on each group

Group	K2	P1	P2	P3
K1	**0.003**	**0.014**	0.134	1.000
K2		**0.004**	**0.005**	**0.003**
P1			0.221	**0.014**
P2				0.134

DISCUSSION

This study used aspirin as a negative control group. Administration of 300 mg/kg cause damage on gastric mucosa because of its capability to inhibit COX.[10,11] Inhibition of COX will cause arachidonic acid metabolism to decrease, lowering the level of PGE2. While PGE2 has a significant role in protecting gastric mucosa as a defense factor through activation of EP.[12] Low level of PGE2 causing a decrease in mucous production, mucosal perfusion, cell renewal, and increase mast cell activity. So that HCl acid and pepsin could directly damage gastric mucosa.

Administration of misoprostol 100 mcg/kg dose was effective in preventing gastric mucosal damage induced by aspirin.[11] Because this PGE1-analog drug, although its work is slightly different with PGE2, could stimulate EP receptors, which is EP2, EP3 and EP4. An increase in PGE1 level could hold back aggressive factor caused by the decrease in PGE2 level.[13] An increase in intracellular cAMP inhibit platelet inactivation and other mechanism induced by activation of EP2, EP3, and EP4 has proven to hold back mucosal damage induced by aspirin quite well.

MCELE, especially 500 mg/kg dose, significantly reduced gastric mucosal damage almost equal to standard drugs misoprostol 100 mcg/kg dose. A study conducted by Ivander *et al.* (2019) reported that the pharmacological effect of *Muntingia calabura* leaves extract is associated with its ability to enhance nitric oxide (NO) production through the modulation of nitric oxide synthase (NOS) and inhibition of reactive oxygen species (ROS), thereby supporting its protective biological activity.[14] The increase of NO level directly protects gastric mucosa by enhancing its microcirculation. Also, an increase in NO level might cause an increase in PGE2 level by enhancing inflammation reaction and COX interaction with cGMP-dependent mechanism. As pro-inflammatory cytokines level increases, gastric mucosal gene expression in producing COX would be enhanced, thus upregulating PGE2. NO also inhibited leukocytes attachment and platelet aggregation because cGMP inhibits phosphodiesterase, causing cAMP to keep

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activating protein kinase A which is known as platelet inhibitor. Furthermore, cGMP activates cGK which could inhibit platelet too.[15,16] Upregulation of PGE2 from NO pathway is on a dose-dependent basis, which means that the more NO modulated the more PGE2 produced.

Muntingia calabura extract could also increase in endogenous SH, which took a role as anti-oxidant and its existence inhibits ROS production. Its anti-oxidant capability could weakens TNF-α.[17,18]

There were a lot of *Muntingia calabura* leaves study conducted. Phytochemical studies have revealed that most compound found from its leave is Flavonoid and Chalcone.[19] Antioxidant activity of flavonoid is breaks free-radical chain reaction, lowering peroxide level, activating endogenous antioxidant protein in stress oxidative pathway.[20] This mechanism aligns with studies demonstrating flavonoids' capacity to mitigate inflammatory mediators such as TNF-α, reinforcing the anti-inflammatory effects observed in our study.[21]

In contrast, some studies present results that diverge form our findings, particularly concerning administration protocold and experimental conditions. For instances, research involving aspirin tipically emplys multiple daily doses (3-4 times per day) for analgesic purposes, whereas our study administered aspirin once daily. This difference in dosng frequency may significantly influence both therapeutic efficacy and gastric side effects, potentially explaining variations in stomach condition outcomes. Additionally, our study's rat model was not subjected to controlled feeding condition, unlike other studies that regulate diet strictly, introducing variability that can affect gastric and systemic responses. The relatively short 7-day administration period in your research also limits insight into long-term effects, whereas extended-duration studies often report cumulative or delayed adverse outcomes not captured within our timeframe.

These discrepancies can largely be attributed to differences in experimental design, including dosage regimen, treatment duration, and control of external variables such as diet. Such factors critically affect pharmacodynamics and physiological responses, underscoring the necessity for standardized protocols to facilitate accurate comparison and interpretation across studies.

CONCLUSION

Administration of MCELE may lower gastric mucosal damage on wistar rats induced by aspirin, with 500 mg/kg dose is almost equal to standard drugs (Misoprostol). MCELE gastric protection induced by aspirin works on a dose-dependent basis.

ETHICAL APPROVAL

Approved by the Ethics Committee of Diponegoro University Faculty of Medicine (No. 118/EC/H/KEPK/FK-UNDIP/IX/2019).

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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The authors did not receive support from any organization for the submitted work.

AUTHOR CONTRIBUTIONS

AFR conceptualized the study, conducting the experiment, and analyzed the data. AWU, EA, and NM validated and interpreted the data. AFR wrote the original draft manuscript. AWU, EA, and NM reviewed and revised the manuscript. AWU, EA, and NM were supervisors. All authors have read and approved the final version of the manuscript.

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