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Antidiarrheal and The Mechanism Of Action Of Combination *P. guajava, C. papaya, A. hybridus, M. oleifera, S. polyanthum*

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ABSTRACT

Diarrhea is a major global health concern, and current drug treatments face limitations regarding effectiveness and safety, with perceived scores of effectiveness and safety being only 6.3/10 and 6.6/10, respectively. This study aimed to investigate the antidiarrheal potential of a combined ethanolic extract derived from five leaves: Psidium guajava, Carica papaya, Amaranthus hybridus, Moringa oleifera, and Syzygium polyanthum, utilizing castor oil-induced diarrhea and intestinal transit time models in mice (five groups, n=5 per group: negative control, positive control (Diapet® 3.12 mg/20 g BW), and three dose levels: 1.56, 3.12, and 6.24 mg/20 g BW). The results demonstrated a significant antidiarrheal effect ($p<0.05$) across all tested doses compared to the negative control for all parameters (frequency, consistency, fecal weight, duration, appearance, and intestinal transit), with the highest dose (Dose III: 6.24 mg/20 g BW) showing the superior activity overall. Furthermore, the decrease observed in the intestinal transit time suggests that the combination extract's mechanism of action is likely achieved through the inhibition of intestinal peristaltic movement.

Keywords: *Antidiarrheal, Amaranthus Hybridus, Carica Papaya, Moringa Oleifera, Psidium Guajava, Syzygium Polyanthum*

INTRODUCTION

Diarrhea is a condition characterized by passing soft or liquid stool consistency more frequently, often three to four times a day (Nemeth & Pfleghaar, 2024). Clinically, the etiology of diarrhea can be caused by various factors such as infections (bacteria, viruses, parasites), malabsorption, allergies, poisoning, immunodeficiency, and many more (Ditri, 2017; Li et al., 2016). In developing countries, the death rate due to diarrhea is one of the serious public health problems, especially for pediatric and geriatric populations (Ugboko et al., 2020). Diarrhea is a leading killer among children under age 5, in which 1,200 children dying each day (UNICEF, 2019). Moreover, the death rate of diarrhea in elderly people reached 18.4 per 100,000 population (Srivastava et al., 2022). The available drugs to treat diarrhea cause intolerable side effects such as vomiting, nausea, abdominal pain, dry mouth, heart rate problems, and intestinal paralysis (Akel & Bekheit, 2018; Habib et al., 2023; Osugi et al., 2021). Meanwhile, the scores of the impression of the effectiveness and safety of the available drugs are 6.3/10 and 6.6/10, respectively (Taylor et al., 2023). In addition, there are still other problems, the challenging treatment for chronic diarrhea condition (Ditri, 2017). Therefore, a natural origin novel drug development to treat diarrhea that more effective, safe, and able to be used in geriatrics, pediatrics, and also in chronic diarrheal conditions is necessary.

The leaves of *Psidium guajava*, *Carica papaya*, *Amaranthus hybridus*, *Moringa oleifera*, and *Syzygium polyanthum* have been proven empirically and preclinically as antidiarrheal (Rahman et al, 2023). However, single therapy of these plants were not superior than positive control (loperamide) (Fauzi et al., 2020; Hussain et al., 2009; Mazumdar et al., 2015; Mulyati, 2022). Moreover, the popular available herbal drugs “Diapet” to treat diarrhea in Indonesia also not superior than loperamide (Sheila, 2015). The safety study of each of these

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plants showed good safety or nontoxic (Atchou et al., 2021; Harun et al., 2021; Lim et al., 2021; Manekeng et al., 2019). The combination antidiarrheal activity of these plants is still unknown. Therefore, the study's purpose was to determine the antidiarrheal activity of the combination ethanolic extract of *Psidium guajava* leaves, *Carica papaya* leaves, *Amaranthus hybridus* leaves, *Moringa oleifera* leaves, and *Syzygium polyanthum* leaves.

MATERIALS AND METHODS

Equipment and Materials

The materials used on this study including rotary evaporator (RV 10 Werke GmbH & Co. KG, Germany), waterbath memmert (WNE 14, Memmert GmbH & Co. KG, Germany), dissecting set (GEA, Germany), syringe 1 mL (B Braun Melsunge AG, Germany), sonde oral for mice (Surya Agung, Indonesia). All the plants used in this study involving *Psidium guajava* leaves, *Carica papaya* leaves, *Amaranthus hybridus* leaves, *Moringa oleifera* leaves and *Syzygium polyanthum* leaves were obtained from Pager Ageng Village, Tasikmalaya, West Java, Indonesia

METHODS

Plant and extract preparations

The leaves of plants were conducted wet sortation, washing, dry sortation, and pollination. The simplicia leaf powders were extracted using 96% ethanol with the maceration method. Soaking is carried out for a period of 1 x 24 hours while occasionally stirring. This extraction was repeated three times with a new solvent every 24 hours. The macerate was then evaporated using a rotary evaporator to make a separate ethanol solvent with the extract. After that, further extract evaporation is carried out through a water bath with a temperature of 60ºC until viscous extract can be obtained. This viscous extract was used for further testing.

Plant determination

All the plants were determined in Herbarium Jatinangor, Department of Biology, Padjadjaran University with the samples number of *Psidium* guajava 27/HB/12/2023, Carica *papaya* 28/HB/12/2023, *Amaranthus hybridus* 29/HB/12/2023, *Moringa oleifera* 30/HB/12/2023, *Syzygium polyanthum* 31/HB/12/2023.

Macroscopic, phtochemical screening, and yield determination

To determine the simplicia characteristic we conducted macroscopic, phytochemical screening and yield determination. The macroscopic observation includes color, smell, taste, and shape. The phytochemical screening includes alkaloid, flavonoid, polyphenol, saponin, tannin, quinone, monoterpene/sesquiterpene, and steroid/triterpenoid. Meanwhile, yield is obtained by dividing the weight of a dry extract by the weight of the dry plant biomass and multiplying it by 100.

Antidiarrheal activity test

The male mice swiss webster strain were obtained from the Department of Pharmacology and Clinical Pharmacy Bakti Tunas Husada University. All the animals were acclimatized for 5 days and placed in an animal laboratory with a temperature of 25ºC, humidity 60%-80%, and 12 hours of light/day cycle. Moreover, all the animals were ad libitum for drinking or eating. However, before 8 hours of testing, all the animals were fasted.

The total 50 mice were divided into two groups, the first group for behavior observation procedure, and the second group for intestinal transit time. Every group consisted of 25 mice and was divided randomly into 5 groups given below (table 1). Each group contained 5 mice.

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Table 1. Treatment Groups

Groups	Treatment
Negative (-)	Na-CMC 1%.
Positive (+)	Mice were given Diapet orally at a dose of 3.12 mg / 20 gram of mice.
Dose I	Mice were given a combination extract of herbal leaves plants as much as 1.56 mg / 20 gram of mice (*Psidium guajava* leaves (19%), *Carica papaya* leaves (10%), *Amaranthus hybridus* leaves (19%), *Moringa oleifera* leaves (14%) and *Syzygium polyanthum* (38%)).
Dose II	Mice were given a combination extract of herbal herbal leaves plants as much as 3.12 mg / 20 gram of mice (*Psidium guajava* leaves (19%), *Carica papaya* leaves (10%), *Amaranthus hybridus* leaves (19%), *Moringa oleifera* leaves (14%) and *Syzygium polyanthum* (38%)).
Dose III	Mice were given a combination extract of herbal leaves plants leaves as much as 6.24 mg / 20 gram of mice (*Psidium guajava* leaves (19%), *Carica papaya* leaves (10%), *Amaranthus hybridus* leaves (19%), *Moringa oleifera* leaves (14%) and *Syzygium polyanthum* (38%)).

All the groups for behavior observation were induced by castor oil (0.5 mL p.o), and continued by given treatment depending on each group, then following to observe every 30 minutes for 6 hours for diarrhea onset, frequency, feces consistency, duration of diarrhea, and feces weight. Meanwhile, all the groups for the intestinal transit time procedure were induced by castor oil (0.5 mL p.o) and continued by giving treatment depending on each group, followed by norit. After 65 minutes, all the groups were sacrificed through cervical dislocation to remove the intestine. The parameter observed including the length of the intestine that norit exceeds the pylorus is measured to the sign of intestine transit time. In addition, we also measured the entire length of the intestine from the pylorus to the rectum (Juliastini et al., 2023). All procedures of this study were approved by the Ethical Committee of BTH University with approval number 013/E.02/KEPK-BTH/II/2024.

Data Analysis

The data obtained was analyzed using SPSS 26, including normality, homogeneity, ANOVA, and post-hoc test LSD. The level of confidence used was 95%.

RESULTS AND DISCUSSION

The macroscopic analysis of the combined simplicia from *Psidium guajava, Carica papaya, Amaranthus hybridus, Moringa oleifera, and Syzygium polyanthum* leaves revealed a yellowish-green color, a distinctive smell, and a bitter taste, with a final extract yield of 23.8% (Table 2). Subsequent phytochemical screening confirmed the presence of key secondary metabolites, including alkaloids, flavonoids, tannins, saponins, polyphenols, monoterpenes/sesquiterpenes, quinones, and steroids/triterpenoids, in both the simplicia and the extract preparations (Table 3). Crucially, the maceration and evaporation procedures did

not alter this metabolite profile, suggesting the extraction process preserved the key chemical composition. The presence of these metabolites, especially those with established roles, indicates a potential multi-target mechanism for the observed antidiarrheal activity.

The previous several studies showed the ability of flavonoids to activate opioid receptors, noradrenergic and inhibit muscarinic receptors (Ferraz et al., 2020; Swaminathan et al., 2014a: 2014b). In addition, the tannin contained in this combination may have a crucial role as an antidiarrheal that may through a protein precipitation effect or astringent effect protect the mucosa against further stress factors from toxic substances, which resulting the decrease of water hypersecretion (Salama-Müller & Roese, 2023a; 2023b). In other study showed the activity of sesquiterpenes to inhibit Ca^{2+} activity Cl^{-} channel that attenuated gastrointestinal motility, and the activity of quinone as a redox cofactor with antioxidant activity that prevented gut damage (Qu et al., 2023). The antidiarrheal action of alkaloids is commonly attributed to their spasmolytic or anticholinergic effects, which directly slow gut motility, thereby decreasing diarrhea severity. Meanwhile, the contribution of steroids and triterpenoids is often linked to their potent anti-inflammatory activity and role as antimicrobial agents against enteropathogens, which help in restoring normal intestinal function and reducing inflammation. The synergistic effect of these compounds likely plays a critical role in the final pharmacological activity of the extract.

The study utilized a castor oil-induced diarrhea animal model—a common method where castor oil triggers intestinal irritation/inflammation, leading to the secretion of chemical mediators like prostaglandin and acetylcholine, which ultimately prevent water reabsorption and induce peristalsis (Praveen et al, 2010; Tunaru et al., 2012a; 2012b). The most effective dose, Dose III (6.24 mg/20 g BW), of the combined leaf extract demonstrated superior antidiarrheal activity compared to all control groups, including the positive control, across all measured parameters: frequency, consistency, fecal weight, diarrhea duration, and onset of feces (Table 4, Figure 1). This superior efficacy, exceeding that of Diapet (which previously showed similar activity to loperamide (Sheila, 2015)), suggests a potent mechanism of action involving the decrease of peristaltic movement. This reduction in gut motility likely occurs through the inhibition of castor oil's irritant effects, inhibition of chemical mediator secretion, and/or inhibition of receptors that regulate peristalsis, such as cholinergic, serotonin, or neurokinin receptors, or through the activation of opioid receptors (Sharma et al., 2010; Browning & Travagli, 2014).

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Table 2. Macroscopic Powders of Simplicia

Parameters	**Results**
Color	Yellowish Green
Smell	Distinctive Smell
Taste	Bitter
Shape	Powder
Yield	23.8%

Table 3. Phytochemical Screening Results

Secondary Metabolites	**Simplicia Combination**	**Extract combination**
Alkaloids	+	+
Flavonoids	+	+
Saponin	+	+
Tannin	+	+
Polyphenol	+	+

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Secondary Metabolites	Simplicia Combination	Extract combination
Monoterpenes	+	+
Sesquiterpenes	+	+
Steroids	+	+
Triterpenoids	+	+
Quinone	+	+

(+) : Identified; (-) : unidentified

Table 4. The Parameters for Antidiarrheal Activity Determination

Treatment	Average ± Standard Deviation				
	Frequency	Feces Consistency	Feces Weight (gram)	Diarrhea Duration (minute)	Appearance of Feces (minute)
Negative Control (NA-CMC 1%)	8.80 ± 0.84	3.6 ± 0.54	0.17 ± 0.01	312.2 ± 20.25	26.6 ± 11.86
Positive Control (Diapet)	4.40 ± 1.14*	2.0 ± 0.70*	0.11 ± 0.03*	229.8 ± 57.51*	52.8 ± 29.48
Dose I (1,56 mg/20 g of mice)	6.40 ± 1.14*	2.6 ± 0.54*	0.17 ± 0.01	240.0 ± 42.76*	67.8 ± 28.30*
Dose II (3.12 mg/20 g of mice)	6.00 ± 1.22*t	1.8 ± 0.83*	0.07 ± 0.02*t	194.4 ± 36.89*	104.6 ± 36.20*t
Dose III (6.24 mg/20 g of mice)	3.00 ± 1.00*t	0.6 ± 0.54*t	0.04 ± 0.02*t	120.0 ± 46.30*t	176.6 ± 58.84*t

*showed a significant difference compared to negative control (p<0,05); t showed a significant difference compared to positive control (p<0.05).

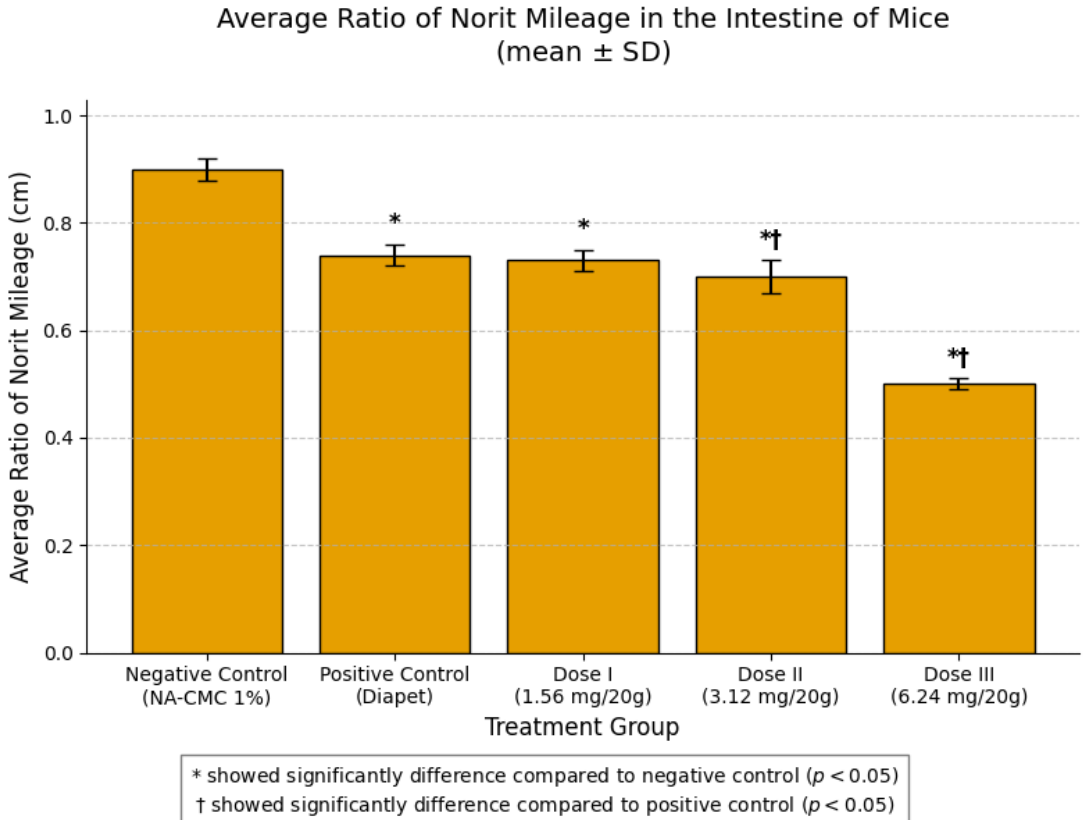

Figure1. The Average Ratio of Norit Mileage in the Intestine of Mice

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CONCLUSION

The dose III ethanolic extract combination of the *Psidium guajava* leaves, *Carica papaya* leaves, *Amaranthus hybridus* leaves, *Moringa oleifera* leaves, and *Syzygium polyanthum* has a potent antidiarrheal activity through the decrease of the intestinal peristaltic movement and showed superiority compared to drugs that available in the marker, therefore the dose III is potential to be further developed for clinical testing.

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