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Antipyretic Activity of The Combination of *Momordica charantia* L. and *Carica papaya* L. on Male Mice *(Mus musculus)*

ACTIVITAS ANTIPIRETIK KOMBINASI PARE (*MOMORDICA CHARANTIA* L.) DAN PEPAYA (CARICA *PAPAYA* L.) PADA MENCIT *(MUS MUSCULUS)* JANTAN

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ABSTRACT

Fever or pyrexia is a symptom of an illness. Disease infections such as dengue fever, typhus, malaria, liver inflammation, and other infectious diseases are examples of diseases that often cause fever symptoms. To reduce this negative impact means that fever needs to be treated with antipyretics. This study was aimed to determine the antipyretic effectiveness of a combination of papaya and leaf extracts of pare. A total of 15 healthy male mice (*Mus musculus*) of the ddY strain were 2-3 months old with a weight of 20-30 g were used in this study. Treatment in five groups is group I; ibuprofen 400 mg, group II; Carboxymethyl Cellulosa or CMC-Na 1%, group III (100:100) mg/kg BW, group dose IV (50:150) mg/kg BW, and group dose V (150:50) mg/kg BW, induced fever using the diptheria, pertussis, tetanus (DPT) vaccine with a volume of 0.1 cc (IP) and carried out three repetitions. Observations were made by measuring the rectal temperature of mice using a digital thermometer before DPT vaccine injection or average temperature, 0 minutes (after DPT vaccine injection), 30, 60, 90, and 120 minutes after administering test materials. The combination of papaya leaves and pare leaves can reduce the body temperature of mice. The dose (150:50) mg/kg BW provides the reduction in weight loss body temperature of mice; however, it was not significantly different from ibuprofen.

Keywords: *Momordica charantia* L.; *Carica papaya* L.; antypiretic

ABSTRAK

Demam atau pireksia merupakan salah satu gejala suatu penyakit. Penyakit infeksi seperti demam berdarah, tifus, malaria, pembengkakan pada liver, dan penyakit menular lainnya merupakan contoh penyakit yang sering menimbulkan gejala demam. Dalam hal ini, pemberian obat antipiretik digunakan untuk menekan dampak negatif dari kondisi demam. Penelitian ini bertujuan untuk mengetahui efektivitas antipiretik kombinasi ekstrak pepaya dan daun pare. Dalam penelitian ini digunakan 15 ekor mencit (*Mus musculus*) jantan sehat strain ddY berumur 2-3 bulan dengan bobot badan 20-30 g. Perlakuan pada lima kelompok adalah kelompok I; ibuprofen 400 mg, kelompok II; natrium karboksimetil selulosa atau Na-CMC 1%, kelompok III (100:100) mg/kg BB, kelompok dosis IV (50:150) mg/kg BB, dan kelompok dosis V (150:50) mg/kg BB, yang diinduksi demam menggunakan vaksin difteruia, pertusis, tetanus (DPT) dengan volume 0,1 mL (IP) dengan tiga kali pengulangan. Pengamatan dilakukan dengan mengukur suhu rektal mencit menggunakan termometer digital sebelum penyuntikan vaksin DPT, 0 menit (setelah penyuntikan vaksin DPT), 30, 60, 90, dan 120 menit setelah pemberian bahan uji. Kombinasi daun pepaya dan daun pare dapat menurunkan suhu tubuh mencit. Dosis IV (150:50) mg/kg BB, memberikan penurunan suhu tubuh tikus terbaik dan tidak berbeda secara signifikan dengan antipiretik ibuprofen.

Kata-kata kunci: *Momordica charantia* L.; *Carica pepaya* L.; antipiretik

INTRODUCTION

According to Kusmana and Hikmat (2015), 40% of plants and 25% of flowering plant species are endemic or indigenous to Indonesia. These numerous plant species are extensively utilized in conventional medicine. Traditional medicine is a recognized form of care that relies on medicinal herbs. It symbolizes a return to nature consciousness that aims to promote overall health and naturally treat various conditions. Traditional medicine has several advantages, such as low cost due to the simplicity of getting raw materials, the ability to produce even therapeutic plants on one's property, and relatively mild side effects that make them safe to use. The majority of traditional medicine use is still managed by the people themselves, in the sense that they choose the medicinal types, mix and prepare the medicine, and utilize it. The effectiveness of traditional medicine in treating sickness is still largely unknown because our knowledge of its efficacy is based mainly on empirical experience passed down from generation to generation.

A pyrexia or fever is a sign of an illness. Fever symptoms are common in infectious diseases such as dengue fever, typhus, malaria, liver inflammation, and other infectious diseases. Dehydration, a lack of oxygen, nerve damage, discomfort like headaches, decreased appetite (anorexia), weakness, and muscle aches are some of the negative symptoms of fever. Antipyretics must be used to treat fever to lessen this adverse effect (Fadhil *et al*., 2017).

Papaya leaves (*Carica papaya* L.), which can be used as medicine, are one of the medicinal plants. Young leaves can be added to milk to alleviate toothaches and treat tooth fever, leucorrhea, and acne (Sukardiman and Wiwied, 2013). The alkaloid substances karpas, caricaksantin, violaxanthin, papain, saponins, flavonoids, polyphenols, and saponins are all found in papaya leaves. In addition, papaya leaves are rich in calcium (Ca), iron (Fe), and vitamins, all of which are essential for the production of hemoglobin (Nuryanti, 2017).

The Cucurbitaceae family of plants, including the bitter gourd (*Momordica charantia* L.), is extensively distributed in the tropics as wild species and cultivated crops and is frequently spotted in gardens and yards. Indonesians frequently cultivate the *pare* plant, and bitter gourd leaves are typically utilized in cooking. According to empirical evidence, Indonesians can utilize the leaves of *pare* as an antipyretic or febrifuge. Bitter Gourd Leaves (*Momordica quarantine* L.) can relieve intestinal worms, jaundice, and increased hunger. Saponins, momordisin, momordin, quarantine, resin, tricosanoic acid, resinic acid, and vitamins A and C can be found in bitter gourd leaves (Cahyaningsih *et al*., 2021). Bitter gourd leaves contain a variety of secondary metabolites and active chemicals that are beneficial to overall health and the treatment of several ailments. The presence of flavonoids, tannins, saponins, steroids, alkaloids, and terpenoids was shown to cure wounds based on the findings of the phytochemical content test (Wijaya *et al*., 2014).

The antipyretic effect test of the combination of the ethanol extract of *Belimbing Wuluh* (*Averrhoa bilimbi* L.) leaves and the ethanol extract of *Sambiloto* (*Andrographis paniculata*) herb as well as the antipyretic effect test of papaya leaf extract (*Carica papaya*) were also performed. Based on prior research from numerous journals and research papers, the best dose was used in the study to test the effectiveness of their activity. In this study, the antipyretic effects of papaya and pare leaf extracts, as well as the effects of their combination and the optimal dose, were investigated. This research was aimed to determine the antipyretic effect of papaya and leaf extracts the effective dose as an antipyretic.

RESEARCH METHODS

Preparation of Extract from Pare and Papaya Leaves

Papaya leaf simplicia (*Carica papaya* L.) 200 g and pare leaves (*Momordica charantia* L.) 200 g, put into each glass container, then add 10 parts of filter liquid (70% ethanol). Cover and marinate for six hours, stirring occasionally, then let stand for 18 O'clock. Separate the macerate by precipitation or filtration. Repeat the filtering process at least twice with the type and the same amount of solvent. Results of maceration of papaya leaves and then collect all the macerate from the pare leaves. Then it was concentrated using a vacuum rotary evaporator (Buchi b-740, Büchi Labortechnik AG, Flawil, Switzerland) until a thick extract was obtained (Samudra, 2017).

Phytochemical Screening

The phytochemical screening which was carried out in this study followed the method proposed by Harborne (1987), as presented below:

Flavonoid Test. The extract was weighed 0.1 g and added to 0.2 g of magnesium (Mg) powder, then added 5 mL of concentrated hydrochloric acid (Hydrochloride solution® Merck, Darmstadt, Jerman). If an orange, red, or yellow color is formed, it indicates the presence of flavonoids.

Saponin Test. The extract was weighed for 0.1 gand added to water, and heated. The solution is cooled and then shaken. The appearance of foam for 30 seconds indicates the presence of saponins.

Alkaloid Test. The extract was weighed for 0.1 g, and added three drops of 2 N sulfuric acid (Merck, Darmstadt, Jerman). then tested with Dragendorff reagent (Merck, Damstadt, Jerman). An orange-red precipitate formed after adding three drops of Dragendorff's reagent indicated a positive alkaloid.

Tannin Test. The extract was weighed for 0.1 g and added to 10 mL of distilled water, filtered, and the filtrate added 5 mL of 1% $FeCl_3$ reagent (Merck, Darmstadt, Jerman). Dark blue or black color indicates the presence of tannins.

Antipyretic Test

After becoming accustomed to life at the study site for seven days, male white ddY strain mice weighing 20-30 g and aged between 2-3 months were fasted for about 18 hours. The following step involved randomly assigning three male white mice to each of the five groups comprised of 15 male white mice. Rectal temperature was monitored by digital thermometer (Thermometer Microlife MT-200®, Microlife, Taipei, Taiwan). before and 30 minutes after administered each dose of the diphtheria, pertussis, tetanus hepatitis B, and haemophilus influenzae type b (DPT–HB-Hib) (Pentabio®, Biofarma, Bandung, Indonesia) vaccine.

The variable observed in this study was the increase in body temperature that occurred after vaccination. A dose of the DPT (0.1 cc) vaccine administered intramuscularly in the thigh of mice. This dose is a dose that has been converted for use in experimental animals.

Each group received therapy orally as a solution when the fever was set 30 minutes after the vaccination. Experimental animals belonging to

Group I were given Ibuprofen 400 mg (Ibuprofen®, PT First Medipharma, Sidoarjo, Indonesia); Group II, were given 1% Na CMC or Sodium Carboxy Methyl Cellulose (Calbiochem®, Merck, Darmstadt, Jerman); Group III were given a combination of pare and papaya leaf extracts (100: 100); Group IV were given a combination of pare and papaya leaf extracts (150:50); and Group V were given a combination of pare and papaya leaf extracts (50:150); all doses were equal to 200 mg/kg BW.

The temperature of the rectum was rechecked 30 minutes after treatment and after that every 30 minutes, until the experiment entered 120th minute.

Data Analysis

This study was analyzed using the Way Analysis of Variance statistical method and then re-analyzed using the Tukey test to see the effect of decreasing temperature of mice on the administration of the extract.

RESULTS AND DISCUSSION

The pharmacological activity of some secondary metabolite chemicals found in extracts can be ascertained through phytochemical screening. By adding chemical reagents depending on compound class, papaya leaf extract (*C. papaya* L.) and pare (*M. charantia* L.) were subjected to phytochemical screening

The papaya leaf extract (*C. papaya* L.) contains alkaloids, flavonoids, saponins, and tannins, according to the findings of the aforementioned phytochemical screening. Alkaloids, flavonoids, and saponins can also be found in the leaves of pare (*M. charantia* L.). This demonstrates that secondary metabolites, including flavonoids and tannins, which are expected to have pharmacological actions as antipyretics, are present in the extracts of papaya leaves (*C.* papaya L.) and pare leaves (*M. charantia* L.). A prior study (Maulana *et al*., 2022) yielded the results of this phytochemical screening, which revealed that papaya leaf extract includes secondary metabolites in alkaloids, flavonoids, saponins, and tannins. According to (Azizah and Widyawati, 2018), secondary metabolites in alkaloids, flavonoids, and saponins can be found in pare leaf extract.

Based on the preliminary test, 0.1 cc (IP) of a mixture of papaya leaf extract (*C. papaya* L.) and pare leaf (*M. charantia* L.) (150:50) mg/kg BW) was used as a fever inducer in the volume antipyretic activity test and route of administration of the DPT vaccine. There were

Table 1 Secondary Metabolite Results

Secondary Metabolite	References	Results	Extract (papaya)	Extract (pare)
Alkaloids	*Bourchardat:* brown precipitate forms	There is a brown deposit	+	+
			+	−
	Mayer: A white precipitate forms	No white precipitate	+	+
	Dragendorff: A red-orange precipitate is formed	Orange-red precipitate		
Flavonoids	Forms an orange, red, or yellow color	Yellow	+	+
Saponins	Foam forms for 30 seconds	Foam forms for 30 seconds	+	+
Tannin	Dark blue or black	Black	+	−

five test groups in this study: the group I, which received 400 mg of ibuprofen; in group II, which received 1% Na-CMC; and the test material group, which received three different doses of papaya and pare leaves (100:100, 150:50, and 50:150 mg/kg BW, respectively). The mice's rectal temperatures were recorded for 120 minutes after treatment, and it measure every 30 minutes. Table 2 shows, all mice getting the DPT vaccine experience a febrile response, with temperatures ranging from 1.0-1.7ºC. The endogenous pyrogens (IL-1 and TNF) produced by cells called polymorphonuclear cells can be stimulated by the DPT vaccine, which acts as a pyrogen and causes a rise in body temperature in mice. This pyrogen affects the body temperature by stimulating the synthesis of prostaglandins (Zampronio, 2015). Compared to group I and group II treatments, mice given a combination of test preparations containing papaya leaf (*Carica papaya* L.) and pare (*Momordica charantia* L.) extracts showed distinct temperature variation.

As presented in Table 2, mice in both group I and test material groups had lower average body temperatures than mice in group II. As evidenced by the declining average body temperature toward a normal rectal body temperature of 36.6–38°C, antipyretic activity is becoming more effective. For 120 minutes throughout this test, the treatment groups I, III, IV, and V the average rectal temperature ranged from 37.23°C to 37.14°C. The average rectal temperature for group II was 38.21°C. This demonstrates the antipyretic effect of treatments I, III, IV, and V. Treatment group V, which had antipyretic action and an average temperature of 37.14°C, obtained results that were comparable to those of treatment group I, which had an average temperature of 37.23°C.

This is supported by the statistical results of the ANOVA test to find out the data is usually distributed and followed by the Tukey test to compare whether there is no significant difference between groups where the statistical

Table 2. Average Results of Mice Rectal Temperature Measurements

Treatment Group	Rectal Temperature of Mice (ºC)						Average	*p-value*
	T	T0	T1	T2	T3	T4		
I	37.37	38.63	37.47	36.83	36.33	36.73	37.23±0.807	P>0.05
II	37.53	38.53	38.37	38.20	38.27	38.37	38.21±0,352	
III	37.37	38.33	37.30	37.94	37.93	37.93	37.80±0,392	
IV	37.23	38.63	38.10	37.53	37.20	36.87	37.59±0,655	
V	36.83	38.20	37.77	37.00	36.67	36.37	37.14±0,700	

Description : **T:** initial body temperature; **T0:** body temperature, in the 30th minute after being induced by the DPT vaccine; **T1:** body temperature, in the 30th minute after being given the test material; **T2:** body temperature, in the 60th minute after being given the test material; **T3:** body temperature, in the 3rd minute 90 after being given the test substance; **T4:** body temperature, in the 120th minute after being given the test substance

results show a value of P>0.05, namely H0 is accepted. Based on the results of the average rectal temperature measurement of mice. The average rectal temperature reduction was calculated to determine the ability of treatments I, III, IV, and V to reduce the rectal temperature of mice. The average decrease in temperature illustrates the antipyretic activity of the test material in reducing the body temperature of mice, obtained by calculating the temperature 30 minutes after induction of the DPT vaccine reduced by the temperature after giving the treatment at a certain point.

According to Table 3, the average decrease of rectal temperature in mice varied every 30 minutes for 120 minutes, depending on the therapy. Despite being in the same treatment group, not every mouse's temperature decreased in the same way after treatment. According to Putra *et al*. (2015), various influencing elements, including hormones, the environment, and gastrointestinal conditions, contribute to this fluctuating reduction in temperature. It may also be brought on by psychological issues, such as stress brought on by routine rectal temperature checks, and compared to treatment groups I, II, III, and IV, treatment group V demonstrated more substantial antipyretic effects. Nevertheless, the statistical analysis results between treatment groups I and V did not significantly differ from the antipyretic activity. Treatment Group V performed better than treatment Group I, with an average decrease rate of 0.48 compared to 0.46. Therapy group V is believed to work almost identically with ibuprofen in lowering fever by blocking the cyclooxygenase enzyme.

Treatment groups III and IV differed significantly from treatment group V. This might result from treatment group V's dose concentration higher than that of treatment groups III and IV. Consider the average time between the start of drug action, the duration of action derived from the start occurrence of antipyretic activity, and the amount of time the drug provides the therapeutic effect. Antipyretic activity is thought to occur because of the presence of secondary metabolites in the extract, which are suspected of having a mechanism of antipyretic activity that works synergistically to reduce body temperature better. Table 3 shows that the IV and V treatment groups have better doses than the III treatment group because of their comparable I treatment group-like averages for the start and duration of medication activity. This is because the IV and V treatment groups had the highest concentration, resulting in a more extended period of antipyretic production.

According to studies, these flavonoids and saponins are also suggested to prevent the formation of prostaglandin (PGE-2) (Saptarini and Deswati, 2015). These prostaglandins' presence contributes to the feverish impact. The findings of this study are also corroborated by earlier studies that showed the ability of plants to inhibit cyclooxygenase activity by possessing flavonoid chemicals, a phenolic group of substances. Inhibiting eicosanoids can block the cyclooxygenase pathway, preventing arachidonic acid from converting to endoperoxide. This disruption results in the formation of prostaglandin E2 in peripheral tissues, which cannot interact with the brain directly and lowers the set point in the hypothalamus (Sulistia and Wilmana, 2020). Tannins can act as antipyretics by blocking the manufacture of prostaglandins from arachidonic acid, (Kumar *et al*., 2012). According to Arman *et al*. (1985), alkaloid secondary metabolites inhibit the COX enzyme and use prostaglandin synthesis to produce antipyretic action. Matrien-type alkaloids are believed to function by preventing the release of dopamine, which prevents prostaglandin formation. Flavonoids, steroids, tannins, and saponins are expected to function in concert to lower the fever-induced rectal temperature in experimental mice (Agustin

Table 3. Results of Average Reduction in Mice Rectal Temperature

Treatment Group	Total Reduction in Mice Rectal Temperature (minutes)				
	Δ0-30	Δ30-60	Δ60-90	Δ90-120	Average
I	1.17	0.57	0.50	-0.40	0.46[a]
II	0.17	0.17	-0.07	-0.10	0.04
III	1.03	-0.03	0.17	0.00	0.29
IV	0.53	0.57	0.33	0.33	0.42
V	0.43	0.77	0.33	0.37	0.48[a]

Description : [a](not significantly different) ; +(experiencing a decrease in temperature) ; −(experiencing an increase in temperature)

et al., 2017). To support the safety level of using a combination of pare leaves and papaya leaves as an antipyretic, more research must be done on the antipyretic activity of papaya leaf extract combinations and pare leaves with various fever inducers. This research must include clinical trials, acute toxicity, and chronic toxicity tests.

CONCLUSION

The dose that exhibits antipyretic activity in lowering the body temperature of mice (*Mus musculus*) and is not substantially different from Ibuprofen 400 mg is the dose with the combination of pare and papaya leaf extracts (150:50), all doses were equal to 200 mg/kg BW.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS DECLARATION

The authors hereby declare that the work presented in this article is original and that they will bear any liability for claims relating to the content of this article.

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