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Antipyretic Activity of Avocado Seed *(Persea americana)* Infusion in Pepton-Induced Fever in Male White Rats *Rattus norvegicus*

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ABSTRAK

Biji alpukat (*Persea americana*) telah lama digunakan dalam pengobatan tradisional dan secara empiris dipercaya dapat menurunkan demam. Penelitian ini bertujuan untuk mengetahui aktivitas antipiretik infus biji alpukat pada tikus putih jantan (*Rattus norvegicus*) yang diinduksi pepton. Infus biji alpukat dibuat menggunakan pelarut aquades pada suhu 90 °C. Pengujian antipiretik dilakukan pada lima kelompok, yaitu kontrol negatif (Na-CMC), kontrol positif (parasetamol), serta tiga kelompok perlakuan yang diberikan infus biji alpukat dengan dosis 100, 200, dan 300 mg/200 g berat badan. Demam diinduksi melalui injeksi intramuskular pepton 5% sebanyak 1 mL/200 g berat badan. Suhu rektal diukur setiap 30 menit selama 3 jam. Hasil penelitian menunjukkan bahwa semua dosis perlakuan menurunkan suhu tubuh pada menit ke-180. Penurunan suhu terbesar ditemukan pada dosis 300 mg/200 g berat badan sebesar 2,16 °C, sehingga dapat disimpulkan bahwa infus biji alpukat memiliki aktivitas antipiretik yang bersifat dosis-dependent.

Kata kunci: *biji alpukat, Persea americana, demam, antipiretik*

ABSTRACT

Avocado seeds (Persea americana) have long been used in traditional medicine and are empirically believed to reduce fever. This study aimed to evaluate the antipyretic activity of an avocado seed infusion in male white rats (Rattus norvegicus) induced with peptone. The infusion was prepared using distilled water at 90 °C. The antipyretic test consisted of five groups: a negative control (Na-CMC), a positive control (paracetamol), and three treatment groups receiving avocado seed infusion at doses of 100, 200, and 300 mg/200 g body weight. Fever was induced by intramuscular injection of 5% peptone (1 mL/200 g body weight). Rectal temperature was recorded at 30-minute intervals for 3 hours. The results showed that all treatment doses reduced rectal temperature after 180 minutes. The greatest reduction was observed at a dose of 300 mg/200 g body weight, with a decrease of 2.16 °C, indicating that avocado seed infusion exhibits dose-dependent antipyretic activity.

Keywords: *avocado seed, Persea americana, fever, antipyretic activity*

1. INTRODUCTION

Lifestyle patterns worldwide have increasingly shifted toward a “back-to-nature” approach, including in the field of medicine. The use of herbal or natural-based remedies offers several advantages, such as effective therapeutic potential, good tolerability, and relatively fewer side effects compared with synthetic drugs[1]. One example is the utilization of avocado seeds (*Persea americana*), which have been reported to exhibit various pharmacological activities, including antioxidant[2], anti-arthritis[3], anti-hyperlipidemic[4], antihyperglycemic[5], antibacterial[6], and wound-healing effects in white rats[7]. Phytochemical screening has further revealed that avocado seeds contain several secondary metabolites, such as saponins,

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tannins, alkaloids, phenolic compounds, and triterpenoids.

Fever is clinically defined as an elevation of body temperature above the normal range of 36.0–37.7 °C[8]. It is commonly initiated by sensations of chills during the rise in temperature and may be accompanied by flushing or redness of the skin surface[9]. As a physiological response, fever serves as an indicator of illness and represents the body's natural defense mechanism against infections[10]. Antipyretics are agents used to reduce elevated body temperature during fever episodes[11], with synthetic drugs such as paracetamol being widely applied. Nevertheless, antipyretic therapy may also be derived from traditional herbal medicines that have been utilized across generations, particularly those originating from medicinal plants[12].

In Ongkaw Village, South Minahasa, North Sulawesi, the infusion of avocado seeds (*P. americana*) has traditionally been consumed as a fever-reducing remedy. The preparation involves washing and peeling the avocado seed, grating it into smaller particles, and boiling it in water until reaching the boiling point. The infusion is then allowed to cool to room temperature before being consumed. This practice reflects local ethnomedicinal knowledge that has been preserved and passed down through generations within the community.

Despite its widespread empirical use, scientific investigations focusing on avocado seeds as an antipyretic agent remain limited. Therefore, this study was conducted to evaluate the antipyretic activity of avocado seed infusion using a peptone-induced fever model.

2. RESEARCH METHOD

Tools and Materials

The equipment used in this research included digital and mercury thermometers, disposable syringes (OneMed) of 1 mL and 3 mL, an analytical balance, a hot plate, an oral probe, and a pH meter.

The materials utilized were male white rats (*Rattus norvegicus*), avocado seeds (*Persea americana*), sodium carboxymethyl cellulose (Na-CMC), paracetamol 500 mg, peptone (Himedia), distilled water (aquadest), 70% alcohol, ethanol, ferric chloride ($FeCl_3$), chloroform, ammonia, magnesium (Mg), concentrated hydrochloric acid (HCl), 2N sulfuric acid (H_2SO_4), glacial acetic acid, concentrated sulfuric acid, as well as Mayer, Wagner, and Dragendorff reagents.

Research Procedure

1. Sample Collection
   Ripe avocado seeds were collected from Ongkaw II Village, Sinonsayang District, South Minahasa Regency, North Sulawesi Province. The seeds were thoroughly washed, peeled to remove the outer skin, cut into smaller pieces, and drained. Subsequently, the seeds were sliced and dried using an oven-drying procedure.
2. Extraction
   A total of 250 g of cleaned and ground avocado seeds were weighed and placed into a beaker. Distilled water (500 mL) was added, and the mixture was heated at 90 °C for 15 minutes. The resulting infusion was then filtered using a flannel cloth.
3. Preparation of 1% Na-CMC Suspension
   The Na-CMC suspension was prepared by dissolving 1 g of Na-CMC powder in 50 mL of hot distilled water in a glass beaker. The mixture was allowed to stand until it became transparent. Distilled water was then added to obtain a final volume of 100 mL.
4. Preparation of 5% Peptone Solution
   A 5% (w/v) peptone solution was prepared by accurately weighing 5 g of peptone and dissolving it in distilled water in a volumetric flask. The volume was adjusted with distilled water to obtain a final volume of 100 mL.
5. Preparation of Paracetamol Suspension
   The standard human dose of paracetamol is 500 mg. Using a conversion factor of 0.018 for dose adjustment from humans to rats, the equivalent dose was calculated as 9 mg per 200 g of body weight.
   Paracetamol tablets were weighed, crushed into powder, and gradually mixed with 1% Na-CMC suspension in a mortar until a homogeneous mixture was obtained. The suspension was then transferred into a 100 mL volumetric flask.

Preparation of Experimental Animals

Fifteen male white rats weighing approximately 200 g were used in this study. The animals were acclimatized for one week in cages with husk bedding and wire covers. During this period, they were provided with pellet feed and water ad libitum.

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Antipyretic Activity Test

Prior to testing, the rats were fasted for approximately 18 hours. Baseline rectal temperature was measured using a digital thermometer. Fever induction was then performed by intramuscular injection of peptone into the thigh muscle to elevate body temperature.

After 1 hour, rectal temperature was measured again. Rats that exhibited a temperature of ≥38 °C compared with baseline were considered febrile.

The animals were subsequently divided into treatment groups and orally administered the assigned treatments: avocado seed infusion at doses of 100 mg/200 g body weight, 200 mg/200 g body weight, and 300 mg/200 g body weight, along with a positive control (paracetamol) and a negative control (Na-CMC).

The antipyretic effect was evaluated by recording rectal temperature at 30, 60, 90, 120, 150, and 180 minutes after administration.

Body temperature served as the dependent variable and was measured rectally using a digital thermometer. The recorded temperatures included baseline temperature, febrile temperature, and post-treatment temperature.

The temperature change (Δt) was calculated as follows:

$$\Delta t = t1 - tn$$

Where:

Δt = change in body temperature after treatment

t_1 = rectal temperature after induction with 5% peptone

t_n = rectal temperature measured at each 30-minute interval after treatment

Data Analysis

The obtained data were statistically analyzed using Analysis of Variance (ANOVA) to determine the effect of avocado seed infusion on temperature reduction. A significance level of $p < 0.05$ was considered statistically significant.

Furthermore, Tukey's HSD post hoc test was applied to identify significant differences among treatment groups. The results are presented in tabular form[13–15].

3. RESULTS AND DISCUSSION

Preparation of Avocado Seed Infusion

The avocado seed infusion used in this study was prepared from oven-dried seeds that were accurately weighed and extracted using 500 mL of sterile distilled water (aquades). Sterile aquades was selected as the solvent to minimize microbial contamination, which could compromise extract quality. The use of sterile solvent was essential to ensure optimal extraction of active constituents while preventing microbial growth[16,17]. The infusion yielded 500 mL of liquid extract, which served as the stock solution for subsequent dosing.

Phytochemical Screening Results

Phytochemical screening was conducted using qualitative test tube reactions, in which the infusion extract was treated with specific reagents to identify the presence of secondary metabolites. Positive reactions were determined based on characteristic color changes or precipitate formation. The screening results are summarized in Table 1.

Table 1. Results of Phytochemical Screening

Group of Compounds	Reagent	Result	Color Change
(1)	(2)	(3)	(4)
Steroid	Glacial acetic acid and concentrated sulfuric acid	-	Color not formed
Saponin	Aquades	+	Bubble/Foam formed
Tanin	Ethanol and 1% $FeCl_3$	+	A bluish black deposit emerged.
Alkaloid	Dragendorff	+	Orange deposits emerged.
	Wagner	+	Brown deposits emerged.
	Mayer	+	White sediment has emerged.
Phenol	$FeCl_3$ 5%	+	Dark green color emerged.

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Flavonoid	HCl Concentrated and Mg	-	Color shift was absent.
Triterpenoid	Glacial acetic acid and concentrated sulfuric acid	+	Orange color emerged.

Steroids, The steroid screening test using glacial acetic acid and concentrated sulfuric acid showed no blue or green coloration, indicating a negative result. Thus, steroid compounds were not detected in the avocado seed infusion and are unlikely to contribute to antipyretic activity.

Saponins, The presence of saponins was confirmed by the formation of stable foam, indicating a positive reaction. Saponins may exert antipyretic effects by inhibiting the binding of exogenous pyrogens to their receptors[18].

Tannins, Tannins were detected through a color change from light brown to bluish-black following reaction with ferric chloride. Tannins may reduce fever by inhibiting arachidonic acid metabolism and suppressing prostaglandin biosynthesis[19].

Alkaloids, Alkaloid screening produced positive results with Dragendorff, Wagner, and Mayer reagents, as shown by orange, brown, and white precipitates, respectively. Alkaloids may exert antipyretic activity by inhibiting arachidonic acid metabolism through the cyclooxygenase pathway, thereby reducing prostaglandin E2 (PGE2) production, a key mediator of fever[20].

Phenols, Phenolic compounds were indicated by a dark green coloration after reaction with FeCl3. Phenols may contribute to antipyretic effects through inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which regulate prostaglandin synthesis21. Additionally, phenolic constituents may suppress lipoxygenase activity, thereby reducing inflammatory mediator production22, ultimately lowering body temperature[23].

Flavonoids, Flavonoid screening yielded negative results, as no dark red coloration was observed. Therefore, flavonoids were not detected in this extract and are unlikely to contribute significantly to antipyretic effects.

Triterpenoids, The triterpenoid test showed a positive orange coloration, confirming their presence. Triterpenoids may reduce fever by inhibiting cyclooxygenase activity within the central nervous system[24,25].

Antipyretic Test

All experimental animals were acclimatized for one week prior to testing. During this period, rats were monitored for normal behavior, stable body weight, and absence of abnormalities, confirming their suitability for the study.

Fever was induced through intramuscular injection of 1 mL of 5% peptone into the thigh muscle. Baseline body temperature was recorded before induction, and febrile status was confirmed one hour after injection. Rats with rectal temperatures ≥38°C were classified as febrile. Normal rat body temperature typically ranges from 35.9°C to 37.5°C26.

Peptone consists of soluble polypeptides and amino acids derived from hydrolyzed proteins[27]. Because proteins may be recognized as foreign substances, peptone acts as an exogenous pyrogen, stimulating the hypothalamus to increase prostaglandin production, leading to elevated body temperature[28,23,29].

Following fever induction, rats received oral administration of avocado seed infusion at doses of 100, 200, and 300 mg/200 g body weight, paracetamol as a positive control, or Na-CMC as a negative control. Temperature measurements were recorded every 30 minutes for 180 minutes. As shown in Table 2, body temperature increased from baseline values of 33.96°C–35.23°C to 37.66°C–38.6°C following peptone induction. Each treatment group exhibited distinct temperature changes throughout the observation period.

Table 2. Results of Average Body Temperature Measurements of Rats Before and After Treatment

Treatment Group	Body Temperature (°C) of White Rats Over Time (Minutes)							
	T0	T1	30'	60'	90'	120'	150'	180'
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Control (-)	34,1	37,96	37,16	37,46	37,9	37,93	37,33	38,06
Control (+)	35,23	38,6	38,06	37,56	37,53	37,26	36,83	36,56
IAS 100 mg/200gr BB	33,96	38,1	37,2	37,26	36,7	37	36,23	36,76
IAS 200 mg/200gr BB	34,26	38,03	37,1	37,4	36,5	36,7	35,9	36,56
IAS 300 mg/200gr BB	34,7	37,66	37,3	36,63	36,43	36,1	36,06	35,5

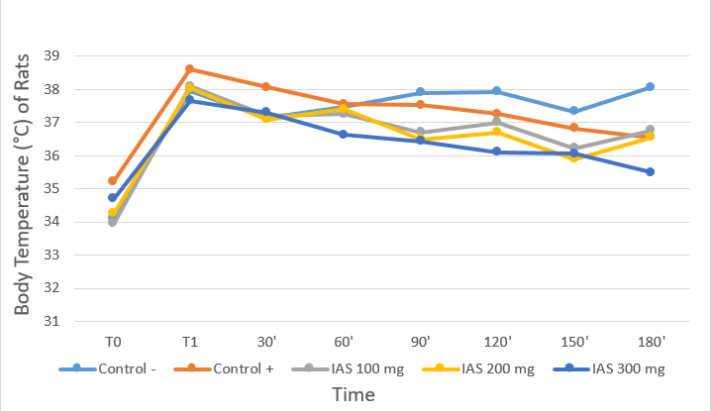

Figure 1. Average Body Temperature Change in White Mice Before and After Treatment

The negative control group (Na-CMC) showed inconsistent fluctuations in temperature, likely influenced by increased water intake during experimentation. In contrast, the positive control group (paracetamol) demonstrated a progressive decline in body temperature until 180 minutes, consistent with its known mechanism of inhibiting prostaglandin biosynthesis and promoting heat loss through sweating.

Administration of avocado seed infusion at doses of 100 and 200 mg/200 g produced fluctuating reductions, whereas the 300 mg/200 g dose resulted in a gradual and sustained temperature decrease comparable to paracetamol. This suggests that higher concentrations of active secondary metabolites contribute to improved antipyretic efficacy.

Temperature reduction was calculated using the formula:

$$\Delta t = t_1 - t_n$$

where *t1* represents temperature after peptone induction and *tn* represents temperature after treatment. Average reductions are presented in Table 3 and Figure 2.

Table 3. Average decrease in body temperature of white rats

Treatment Group	Reduction in Body Temperature (°C) of White Rats Over Time (Minutes))					
	30'	60'	90'	120'	150'	180'
(1)	(2)	(3)	(4)	(5)	(6)	(7)
Control (-)	0,8	0,5	0,06	0,03	0,63	-0,1
Control (+)	0,54	1,04	1,07	1,34	1,77	2,04
IAS 100 mg/200gr BB	0,9	0,84	1,4	1,1	1,87	1,34
IAS 200 mg/200gr BB	0,93	0,63	1,53	1,33	2,13	1,47
IAS 300 mg/200gr BB	0,36	1,03	1,23	1,56	1,6	2,16

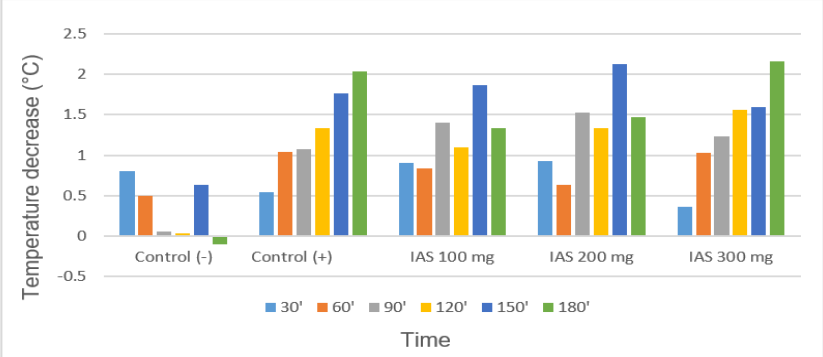

Figure 2. The average temperature decrease for the treatment group

Statistical Analysis

The results of the research on avocado seed infusion as an antipyretic were analyzed using ANOVA. One of the requirements for ANOVA testing is that the treatment variances have to be homogeneous. It turns out that the variance of the 15 treatments is homogeneous, as shown in Table 4 below. The homogeneity variance test yields a value of 0.180, which is more substantial than 0.05; therefore, the requirements for variance analysis were satisfied.

Table 4. Test of Homogeneity of Variances

Levene Statistic	df1	df2	Sig
(1)	(2)	(3)	(4)
1.944	4	10	0.180

Table 5. ANOVA Test

	Sum of Squares	df	Mean Square	F	Sig
(1)	(2)	(3)	(4)	(5)	(6)
Between Groups	10.043	4	2.511	23.537	0.000
Within Groups	1.067	10	0.107		
Total	11.109	14			

Based on Table 5, the significance value is found to be 0.000, which is lower than 0.05. This affirms that there is an antipyretic activity of avocado seed infusion on white rats. To determine which treatments were different, a post hoc test (Tukey's Test) was conducted. Based on Tukey's post hoc test, 3 homogeneous subsets were obtained as shown in Table 6 below.

Table 6. Tukey HSD

Treatment	N	Subset for alpha = 0.05		
		1	2	3
(1)	(2)	(3)	(4)	(5)
IAS 300 mg	3	35.500		
Paracetamol	3		36.567	
IAS 200 mg	3		36.567	
IAS 100 mg	3		36.767	
Na-CMC 1%	3			38.067
Sig.		1.000	0.939	1.000

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Based on Table 6, it can be seen that the negative control is in its own subset, indicating that the negative control differs from the other 4 treatments. Paracetamol IAS 100 mg and IAS 200 mg are in the same subset, which indicates that these three treatments have the same antipyretic effect. IAS 300 mg is also in its own subset, indicating that IAS 300 mg is significantly different from the other 4 treatments (negative control, positive control, IAS 100 mg, and IAS 200 mg). This result shows that IAS 300 mg demonstrates a better antipyretic effect than the other four treatments.

Antipyretic Mechanism of Avocado Seed Infusion

In this study, avocado seeds of P. americana were used as a fever-reducing medicine that contains secondary metabolite compounds such as alkaloids, tannins, saponins, triterpenoids, and phenols that act as antipyretics.

The avocado seeds in this study were carefully extracted through the infusion method involving aquades solvent. Sterile aquades was chosen to prevent microbial contamination that could compromise the quality of the extract. This ensures that the active compounds in the sample can be carefully extracted and safely protected from microorganisms[16,17].

In this study, the antipyretic effect of avocado seeds was tested by inducing 5% peptone intramuscularly (i.m.) at a dosage of 1 mL/200 g body weight. The effect of fever induction in the test animals was determined by measuring the temperature rectally using a digital thermometer. Peptone consists of polypeptides, oligopeptides, and single amino acids that are soluble in water, along with other water-soluble compounds present in the original protein substrate[27].

Pepton is a hydrolyzed protein used to induce fever in rats. Pepton can cause fever by stimulating the hypothalamus to increase prostaglandins, leading to an increase in body temperature[28, 23, 29].

After the injection of peptone for approximately 15 minutes, the rat's body exhibited reactions, namely fever, drowsiness, shivering, and increased thirst. All test animals that experienced an increase in body temperature of 0.6ºC or higher can be categorized as febrile[30].

The results of this study show that the rectal temperature of the test animals increased by more than 0.6ºC for one hour after the injection of peptone. This marked the time that caused the mice to experience optimal fever. An increase in body temperature above the normal threshold indicates fever, which is a physiological response to fight infections or diseases present in the body[31].

The physiological process that causes an increase in the body's set-point temperature usually originates from infections or non-infections, such as inflammation, malignancy, or autoimmune disorders. These processes involve the release of immunological mediators, which trigger the hypothalamic thermoregulatory center, leading to an increase in body core temperature[32].

When the core body temperature rises, it acts as a warning that triggers the immune system to activate various types of cells, such as natural killer cells, dendritic cells, macrophages, neutrophils, T and B lymphocytes, and vascular endothelial cells[33].

In the hypothalamus, the thermoregulatory center performs vasoconstriction to retain heat and induces shivering. The induction of fever results in the inhibition of bacterial development, enhances the bactericidal activity of neutrophils, produces acute phase protein synthesis, and induces other physiological changes such as drowsiness and anorexia.

All of these phenomena confirm that fever plays a different role in the survival of the host during infection[34]. When experiencing fever, the test animals exhibited clinical symptoms, namely decreased activity, lethargy, and apparent drowsiness.

The decrease in body temperature among test animals varies, which can be attributed to the endogenous factors of each test animal related to the fever-inducing agent. This variability is significantly influenced by several non-physical and environmental factors. The repeated rectal temperature measurements may have triggered stress and discomfort in the test animals, therefore leading to the fluctuations in their body temperature[35, 36].

Based on the results of the phytochemical screening conducted on the avocado seed infusion extract, secondary metabolite compounds with antipyretic effects were discovered, namely alkaloids. These bioactive compounds yield antipyretic impacts through

multiple mechanisms. Alkaloids inhibit the metabolism of arachidonic acid through the cyclooxygenase pathway, leading to the production of prostaglandins, especially PGE2 or Prostaglandin E2, which is important in fever production[20]. Similarly, tannins inhibit arachidonic acid in the biosynthesis of prostaglandins[19]. Saponins reduce body temperature by inhibiting the binding of exogenous pyrogens that penetrate the body to their receptors[18], while triterpenoids inhibit cyclooxygenase in the brain[24, 25].

Phenolic compounds inhibit the activity of the COX enzyme. The COX enzyme regulates the formation of prostaglandins. There are two forms of the COX enzyme, COX-1 and COX-2. COX-1, which can be found in platelets, kidneys, endothelial cells, and the stomach. COX-1 is very important for maintaining renal function and gastric mucosal integrity. COX-2, which is produced by inflammatory stimuli and found in fibroblasts, synovial cells, leukocytes, and macrophages[21], also contributes to inhibiting lipoxygenase.

Lipoxygenase is a group of oxidative enzymes that produce lipoxins (anti-inflammatory mediators) or leukotrienes (pro-inflammatory mediators). Lipoxygenase catalyzes the formation of hydroperoxy eicosatetraenoic acid (HPETE) from arachidonic acid.

This HPETE is reduced and transformed into eicosanoids, which signals molecules that play an important role in regulating immune responses and various other physiological processes[22], directly leading to the inhibition of the biosynthesis of prostaglandins and leukotrienes. The end products of the COX and lipoxygenase pathways result in a decrease in body temperature[23].

4. CONCLUSION

This research demonstrates that avocado seed infusion (*Persea americana*) exhibits significant antipyretic activity in male white rats induced with 5% peptone. Phytochemical screening confirmed the presence of secondary metabolites, including saponins, tannins, alkaloids, phenols, and triterpenoids, which may contribute to fever reduction through inhibition of prostaglandin pathways.

The antipyretic test showed that the 300 mg/200 g body weight dose produced the most consistent temperature decrease, comparable to paracetamol. ANOVA results confirmed a significant difference among treatment groups ($p < 0.05$), indicating that avocado seed infusion has potential as a natural antipyretic agent.

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