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Antihypertensive Activity of Black Garlic Extract in Rats and Its Phytochemical Analysis using GC-MS

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Abstract
***Background**: Hypertension is defined as a medical condition where blood pressure rises above 140/90 mmHg. Black garlic is recognized as a natural remedy that may help lower high blood pressure, primarily due to its abundant antioxidant properties, which are believed to inhibit the function of the angiotensin-converting enzyme (ACE) that is essential for regulating blood pressure. **Objective**: This study aimed to identify the chemical composition of black garlic using GC-MS and assess its antihypertensive effects in rat models. **Methods**: This study characterized the chemical composition of black garlic using GC-MS (Agilent 7890A) and evaluated its antihypertensive effects in rats. Hypertension was induced by oral administration of NaCl at a dose of 3.75 g/20 g body weight (BW) from day 0 to day 14. Blood pressure measurements were taken on days 0, 14, and 21. Black garlic extract was administered at three dose levels 4.2 mg/20 g BW, 8.4 mg/20 g BW, and 12.4 mg/20 g BW to evaluate dose dependent antihypertensive responses. Statistical analysis included the Kolmogorov-Smirnov test for normality, homogeneity testing, One-Way ANOVA **Results**: The GC-MS analysis identified 9-octadecenoic acid as the dominant compound in black garlic, accounting for 34.53% of its total composition. The antihypertensive activity test showed that administering black garlic at a dose of 12.4 mg/20 g BW significantly lowered systolic, diastolic, and mean arterial blood pressure while enhancing nitric oxide levels in hypertensive rats. **Conclusion**: Black garlic has the potential as an effective herbal treatment to lower blood pressure.*

***Keywords:** antihypertension, black garlic, gc-ms, in vivo*

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INTRODUCTION

Hypertension is a condition characterized by an increase in blood pressure above the normal limit, where the systolic pressure exceeds 140 mmHg and the diastolic pressure exceeds 90 mmHg (Wahyuni et al., 2023). Hypertension is a type of multifactorial chronic disease caused by environmental and genetic factors. In addition, this disease is also influenced by various factors such as obesity, excessive stress, lack of physical activity, and excessive salt consumption (Oliveros et al., 2020). The World Health Organization (WHO) reports a global hypertension prevalence of 22%, with Africa highest at 27% and Southeast Asia third at 25%. In Indonesia, there are 63.3 million hypertension cases and 427,218 related deaths. The condition is most common in people aged 55–64. Of the 34.1% prevalence, only 8.8% are diagnosed, with many not taking or not regularly taking medication. Hypertension can be managed through synthetic drugs and lifestyle changes (Kementerian Kesehatan, 2019). The most common antihypertensive drug prescribed to hypertensive patients is captopril (60.1%), followed by amlodipine (29.7%) and hydrochlorothiazide (10.2%) (Diarmika et al., 2018).

Captopril exerts its antihypertensive effect by inhibiting the formation of angiotensin II, a hormone responsible for vasoconstriction. However, as an ACE inhibitor, captopril can lead to bradykinin accumulation, which may cause a dry cough (Straka et al., 2016). This side effect can negatively impact patient adherence to treatment by reducing motivation, lowering awareness, and diminishing willingness to comply with therapy, ultimately increasing the risk of non-compliance (Halim et al., 2015). Therefore, people prefer to use herbal medicine which is considered safer, one of which is black garlic.

Black Garlic is a processed garlic product made through fermentation with high temperatures and humidity of 70-80%. The fermentation process requires a longer fermentation time of one month (Kim et al., 2013). Garlic undergoes characteristic changes during fermentation. The non-enzymatic browning reaction that occurs during this process causes the garlic to turn black. This reaction also produces a sweet taste and gives the garlic a chewy and jelly-like texture (Yuan et al., 2016).

Additionally, black garlic is known to contain S-allyl cysteine (SAC), an active compound which is formed during the fermentation process. The compound can dissolve in water and has strong antioxidant properties (Omar & Al-Wabel, 2010). In vitro and in vivo studies have shown that black garlic has stronger antioxidant properties than white garlic (Lee et al., 2020).

Black garlic has a significantly higher antioxidant capacity, as indicated by its TEAC (Trolox Equivalent Antioxidant Capacity) value of 59.2 ± 0.8 μmol/g wet, compared to fresh garlic, which contains only 13.3 ± 0.5 μmol/g wet. This elevated TEAC value suggests a strong potential for preventing diabetes complications. The antioxidant properties of black garlic are primarily attributed to sulfenic acid (SAC), a compound formed from the decomposition of allicin (Chang & Jang, 2021). In a study conducted by Setyawan & Muflihatin (2019), black garlic has been shown to effectively reduce both systolic and diastolic blood pressure in individuals with hypertension. In a study by Chen et al (2021), black garlic extracts and nano emulsions alleviate DOCA-salt-induced hypertension and improve cognitive function in rats by modulating key biomarkers such as bradykinin, aldosterone, Ang II, NO, AChE, and antioxidant enzymes.

This study aims to evaluate the in vivo antihypertensive activity of black garlic (*Allium sativum* L.) in rats. The expected outcome is to provide scientific evidence on the effectiveness of black garlic as an antihypertensive agent through in vivo analysis in rats.

MATERIALS AND METHODS

Materials

The garlic used in this study was black garlic derived from Solo garlic (*Allium sativum*), obtained from Yogyakarta City, NaCl (Merck), CMC-Na (Sigma), Captopril®, N-(1-naphthyl) ethylene diaminehydrochloride (Sigma- Aldrich), Sulfanilamide (Merck), Ortho-phosphoric acid (Merck), and Sodium Nitrate (Merck).

Extract preparation

Black garlic is produced from Solo garlic (Allium sativum) through a fermentation process at 60–70°C with controlled humidity for 12 days, without any additives. The temperature during fermentation was maintained within a range of 60–70°C, with some variation throughout the process. During fermentation, the garlic undergoes a color change from white to black and develops a soft texture, mild aroma, and a distinctive sweet-sour flavor profile (Yudhayanti et al., 2020). One gram of black garlic was grounded and transferred into a 10 mL volumetric flask. Distilled water was added to the mark, and the mixture was vortexed for 1 minute. The solution was then subjected to sonication for 30 minutes at room temperature to enhance extraction.

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Following sonication, the mixture was centrifuged at 5000 rpm for 10 minutes. The resulting supernatant was collected and used for further analysis (Pramitha & Yani, 2020).

Analysis with gas chromatography-mass spectrometry (GC-MS)

GC-MS analysis was performed using an Agilent 7890A system coupled with an Agilent 5975C mass spectrometer and an HP-5DB capillary column (60 m × 250 µm × 0.25 µm). Helium served as the carrier gas, with an injector temperature of 250°C, an injection volume of 0.2 µL, and a 1:200 split ratio. A temperature gradient was applied to ensure effective separation of volatile compounds. Mass spectra were recorded in the range of 35–550 *m/z*. GC-MS enables the identification of compounds based on their retention times and unique mass spectral patterns, facilitating the characterization of complex mixtures (Pratiwi et al., 2022).

Grouping of test animals

This research, which involved test animals, has obtained research approval from the Research Ethics Commission (KEP) of Ahmad Dahlan University (UAD) under letter number: 012401007. In the planning of administering black garlic to test animals, 3 dosage variations were made: 4.2 mg/20 g BW, 8.4 mg/20g BW, and 12.4 mg/20g BW (Pangala et al., 2022).

Antihypertensive activity test

Antihypertensive activity was evaluated by measuring blood pressure on days 0, 14, and 21. Hypertension was induced by oral administration of NaCl at a dose of 3.75 g/20 g body weight from day 0 to day 14 (Sadik et al., 2021). On the following day, baseline blood pressure of the rats was measured. The animals were then administered black garlic extract at doses of 4.2 mg/20 g BW, 8.4 mg/20 g BW, and 12.4 mg/20 g BW once daily for seven consecutive days. The extract was prepared by diluting the aqueous black garlic extract with distilled water to the appropriate concentrations. Fresh solutions were prepared daily and administered orally via gavage. Blood pressure measurements were repeated on day 21.

Blood collection of rats

Blood samples from the rats were collected on the 21st day. The procedure was performed by holding and pinching the nape of the neck with fingers. Blood was drawn from the ophthalmic vein using a capillary tube and collected into a tube of ± 3 cc. Then, the blood was centrifuged at a speed of 3000 rpm for 15 minutes. The centrifugation produced a serum, which was then prepared for nitric oxide (NO) levels analysis (Ma'ruf et al., 2025).

Measurement of nitric oxide levels

Nitric oxide levels were measured using an ELISA Reader (Asys) following the method proposed by Hunter et al (2013) with modifications. Nitric oxide levels in mouse serum were quantified using the Griess Reaction Assay. The procedure involved preparing two reagents: Griess A (0.1% w/v N-(1-naphthyl) ethylenediamine hydrochloride in distilled water) and Griess B (1% w/v sulfanilamide in 5% ortho-phosphoric acid). A sodium nitrate standard solution (69.0 mg/100 mL) was diluted to generate a nitrite calibration curve. For analysis, 100 µL of serum sample or standard was pipetted into a 96-well plate, followed by sequential additions of 100 µL each of Griess A and B solutions. After a 10-minute incubation for chromogenic development, absorbance was measured at 550 nm using an ELISA microplate reader, with values compared against the standard curve to determine nitrite concentrations

Data analysis

The collected data on systolic and diastolic blood pressure, heart rate pressure, and nitric oxide test, were statistically analyzed using the Kolmogorov-Smirnov test to assess normality and the homogeneity of variance test. The differences between treatment groups were then evaluated using the Tukey test.

RESULTS AND DISCUSSION

Results of Black Garlic Component Analysis with GC-MS

The chromatogram profile of the analysis results reveals the presence of seven components in black garlic. The chromatogram of black garlic is presented in Figure 1. The analysis of black garlic components with GC-MS mass spectra was performed by comparing the base peak with spectra from NIST and WILEY 9 LIB (Pratiwi et al., 2022). The chromatogram profile of black garlic that has been analyzed with GC MS is presented in Table 1 and Figure 1.

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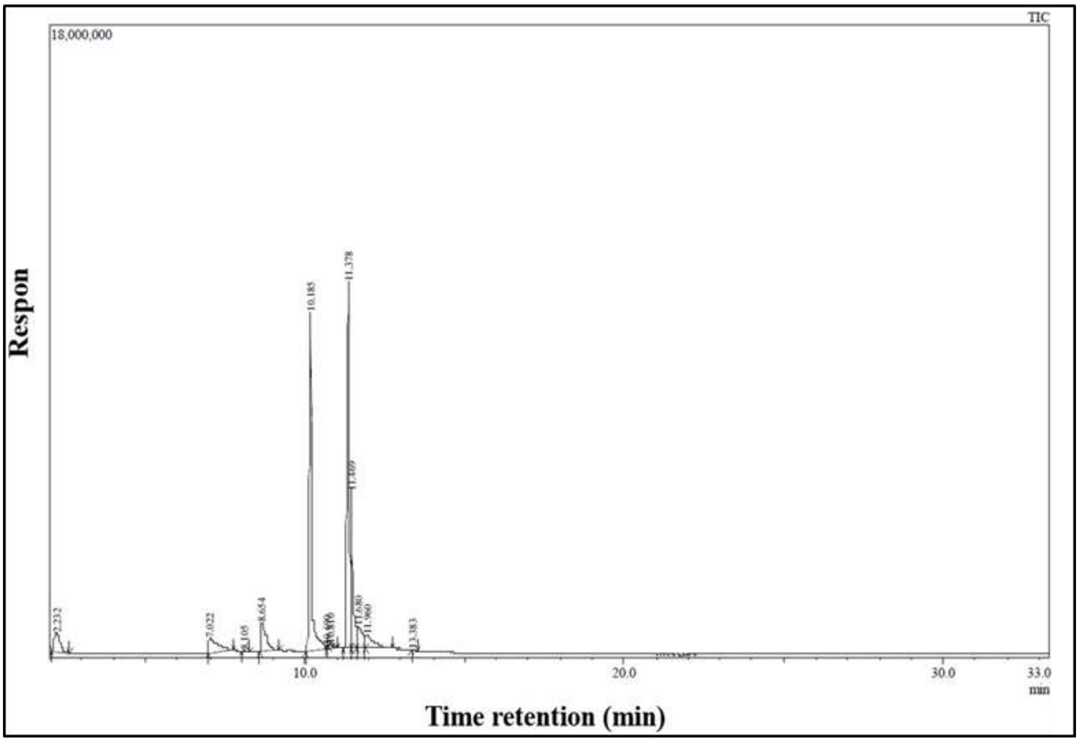

Figure 1. Chromatogram profile of compounds from black garlic

Table 1. Results of black garlic component analysis using GC-MS

No	t_R (minute)	%Area	MW(g/mol)	Molecular Formula	Name
1	11.440	34.53	282.5	$C_{18}H_{34}O_2$	9-Octadecenoic acid
2	11.010	32.67	256.4	$C_{16}H_{32}O_2$	Hexadecanoic acid
3	11.620	9.57	284.4	C18H36O2	Octadecanoic acid
4	9.200	5.06	228.3	C14H28O2	Tetradecanoic acid
5	7.770	4.98	200.3	C12H24O2	Dodecanoic acid
6	11.910	4.88	164.2	C12H20	Cyclododecyne
7	12.730	3.93	280.4	C18H32O2	9,12-Octadecadienoic acid

Note :
tR: Retention Time
MW: Molecular Weight

Based on Table 2 and Figure 2, the largest component of the GC-MS profile of black garlic is 9-Octadecenoic acid (34.53%), followed by Hexadecanoic acid (32.67%), Octadecanoic acid (9.57%), Tetradecanoic acid (5.06%), Dodecanoic acid (4.98%), Cyclododecyne (4.88%), and 9.12-Octadecadienoic acid (3.93%). The results of the black garlic chromatogram profile reveal that dodecanoic acid had the shortest retention time, and the longest was 9.12-Octadecadienoic acid. This is due to the influence of MW and the influence of the boiling point of each different compound (Rohman & Man, 2012).

Black garlic is the result of the fermentation of fresh garlic (Allium sativum) through the Maillard reaction at high temperatures (60–90 °C) and high humidity (70–90%) over a certain period. This process alters the chemical composition and enhances the content of its bioactive compounds. The main bioactive compounds in black garlic include water-soluble sulfur compounds such as S-allyl cysteine and S-allyl-mercapto cysteine, as well as Maillard reaction products such as 5-hydroxymethylfurfural. The levels of polyphenols and volatile compounds also increase significantly compared to fresh garlic, resulting in improved antioxidant, anti-inflammatory, anticancer, hepatoprotective, and immunomodulatory activities (Ahmed & Wang, 2021).

GC-MS analysis of black garlic detects only volatile compounds, excluding non-volatile bioactives such as polyphenols, amino acids, and water-soluble sulfur compounds. Since these compounds play important biological roles, complementary techniques like LC-MS are needed for a more comprehensive chemical profile. Therefore, GC-MS provides only a

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partial overview, highlighting the need for further studies using additional analytical methods (Wonorahardjo et al., 2023).

The results of antihypertensive activity test

The study involved six groups of test subjects, with each group comprising five rats. Blood pressure readings were recorded on the 14th and 21st days of the experiment. The findings from these measurements are presented in Tables 2, 3, and 4.

The data presented in Table 2 revealed that black garlic administration significantly reduced systolic blood pressure, with the most effective dosage being 56 mg/g body weight. This dosage achieved a reduction in blood pressure comparable to the captopril-treated group, highlighting the potent antihypertensive effects of black garlic. These findings underscore the role of black garlic's rich antioxidant content, particularly 9-octadecenoic acid (oleic acid), in modulating blood pressure and supporting cardiovascular health (Massaro et al., 2020).

The statistical evaluation of systolic blood pressure revealed a notable decrease ($p<0.05$) following the administration of the test preparation. These findings suggest that black garlic demonstrates efficacy as an antihypertensive agent in male Wistar strain white rats. This significant reduction in blood pressure underscores the potential of black garlic as a natural treatment option for managing hypertension.

The data on diastolic blood pressure presented in Table 3 indicated that the administration of black garlic significantly reduced diastolic blood pressure levels. Notably, the most effective dosage identified in this study was 56 mg per gram of body weight, which resulted in a decrease that was almost comparable to the reduction observed in the group treated with captopril.

The present study demonstrated that black garlic exhibits an antihypertensive effect, which is attributed to 9-octadecenoic acid (oleic acid), a compound with high antioxidant activity (Massaro et al., 2020). The statistical analysis of systolic blood pressure revealed a significant result ($p<0.05$), indicating a marked reduction in systolic blood pressure after the administration of the test preparation. Therefore, it can be concluded that black garlic serves as an effective antihypertensive agent in male Wistar strain white rats. This finding highlights the potential of black garlic as a natural alternative for the management of hypertension.

Table 2. Results of systolic blood pressure (SBP) measurements on days 14 and 21

Group	Dose (mg/gBW)	Average of SBP (mmHg) ± SD		Decrease of SBP (mmHg)
		Day 14 (NaCl)	Day 21 (Intervention)	
Normal	-	96.4 ± 5.12	95.6 ± 6.98^{b}	-0.80
Control	CMC-Na	129.8 ± 5.63^{a}	129.2 ± 5.26	-0.60
Black Garlic	14	129.4± 7.12^{a}	127.2 ± 5.49^{c}	-2.20
	28	130.0 ± 5.47^{a}	124.2 ± 5.97^{b}	-5.80
	56	129.8 ± 5.40 ^{a}	120.6 ± 6.42^{b}	-9.20
Captopril	4,5	131.0 ± 7.68^{a}	117.8 ± 5.26^{b}	-13.20

Table 3. Diastolic blood pressure (DBP) measurement results on days 14 and 21

Group	Dose (mg/gBW)	Average of DBP (mmHg) ± SD		Decreased of DBP (mmHg)
		Day 14 (NaCl)	Day21 (Intervention)	
Normal	-	83.8 ± 6.30	83.0± 5.56^{b}	-0.80
Control	CMC-Na	89.4 ± 5.94^{a}	88.0 ± 6.20	-1.40
Black Garlic	14	91.0 ± 5.43^{a}	87.6 ± 5.72^{c}	-3.40
	28	89.2 ± 5.89^{a}	82.4 ± 6.73^{b}	-6.80
	56	89.6 ± 7.89^{a}	81.8 ± 5.40^{b}	-7.80
Captopril	4,5	96.0 ± 6.20^{a}	80.4 ± 5.41^{b}	-15.60

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Table 4. Mean arterial blood pressure (ABP) measurement results on days 14 and 21

Group	Dose (mg/gBW)	Average of ABP (mmHg) ± SD		Decreased of ABP (mmHg)
		Day 14 (NaCl)	Day 21 (Intervention)	
Normal	-	88.0 ± 5.69	87.2 ± 5.65[b]	-0.80
Control	CMC Na	102.8 ± 5.68[a]	101.7 ± 5.87	-1.10
Black Garlic	14	103.8 ± 5.93[a]	100.8 ± 5.62[c]	-3.00
	28	102.8 ± 5.55[a]	96.3 ± 6.40[b]	-6.50
	56	103.0 ± 7.05[a]	94.7 ± 5.73[b]	-8.30
Captopril	4,5	107.66 ± 5.31[a]	93.1 ± 5.52[b]	-15.60

Table 5. Results of nitric oxide (NO) level measurements on day 21

Group	Dose (mg/gBW)	Nitrit Oxide Concentration (µM/L)
Normal	-	10.3 ± 2.73
Control	NaCMC	5.6 ± 2.11[a]
Black Garlic	14	6.1 ± 2.44[a]
	28	8.8 ± 2.06[b]
	56	10.1 ± 2.52[b]
Captopril	4.5	11.1 ± 2.50[b]

Table 4 highlights the mean arterial blood pressure scores, showing that black garlic administration effectively lowered blood pressure. The optimal dose of black garlic was 56 mg/g BW, producing results nearly comparable to captopril, the standard antihypertensive drug. This study confirmed the antihypertensive effects of black garlic, attributed to its high antioxidant content, particularly 9-Octadecenoic acid (oleic acid). Statistical analysis showed a significant reduction in systolic blood pressure ($p < 0.05$) after treatment, indicating that black garlic effectively lowers blood pressure in male Wistar rats. This finding supports the potential of black garlic as a natural antihypertensive agent (Massaro et al., 2020).

GC-MS analysis revealed that black garlic contains fatty acids such as 9-octadecenoic acid, hexadecanoic acid, and 9,12-octadecadienoic acid, which contribute to its biological effects, including antiproliferative activity and modulation of lipid metabolism. The fermentation process also reduces the pungent odor of fresh garlic and results in a chewy texture and a distinct sweet flavor. Therefore, black garlic holds therapeutic potential in the prevention and management of various chronic diseases through its strong antioxidant and anti-inflammatory mechanisms (Binici et al., 2025).

The fatty acid, 9-octadecenoid=c acid has been shown to exhibit anti-inflammatory and vasodilation properties, which may contribute to its effects on blood pressure regulation. Its ability to modulate endothelial function and reduce oxidative stress could play a key role in lowering blood pressure (Villaño et al., 2023).

Nitric oxide (NO) level measurement

In determining the NO levels in hypertensive male rats, measurements were made at a wavelength of 550 nm. The average value of NO absorption level in male Wistar rats, measured using ELISA Reader, is listed in Table 5.

The measurement of nitric oxide (NO) levels on the 21st day revealed statistically significant differences among the groups. However, no significant difference was observed between the black garlic 28 mg/gBW, 56 mg/gBW, and Captopril 4.5 mg/gBW groups. This indicates that black garlic at doses of 28 mg/gBW (8.8 ± 2.06 µM/L) and 56 mg/gBW (10.1 ± 2.52 µM/L) can effectively increase NO levels, achieving results comparable to Captopril at a dose of 4.5 mg/gBW (11.1 ± 2.50 µM/L).

According to Astutik et al (2014), nitric oxide (NO) levels in the blood are related to systolic and diastolic blood pressure because NO has vasodilator properties. This may be attributed to endothelial damage due to excessive oxidative stress. As endothelial damage worsens, NO production decreases, and blood pressure increases. As a result, decreased NO availability leads to endothelial- dependent vasodilation disorders in hypertensive patients.

Increased expression of nitric oxide (NO) in hypertensive rats indicates involvement in the regulation

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of Hexadecanoic acid or palmitic acid on myocardial contractility. Palmitic acid supplementation, followed by the addition of NO inhibitors, significantly increase contractility. NO affects myocardial function through mitochondrial protein regulation, reduction of mitochondrial oxygen consumption, and modulation of cardiac metabolism. The combination of NO with mitochondrial protein inhibitors has the potential to inhibit the positive inotropic effect of palmitic acid on hypertensive cardiomyocytes (Tan et al., 2021).

CONCLUSION

The optimal formula contained 0.284% sorbitan monooleate, 3.429% lauryl glucoside, and 0.287% soy lecithin, which showed a close alignment between the observed and predicted data. This formulation achieved the desired characteristics for Nanostructured Lipid Carriers (NLC), as evidenced by their homogeneous consistency, suitable particle size, pH range, and polydispersity index. The physical stability of NLC from the creaming index showed that this combination of surfactant and co-surfactant effectively improved the stability of NLC and produced an optimal formula for further development.

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AUTHOR CONTRIBUTIONS

Conceptualization: DE, MSB, LHN, MM, SY, VS, DP; Methodology: DE, MSB, LHN; Software : MSB, LHN, MM.; Validation : DE, MSB, LHN, MM, SY; Formal Analysis : DE, MSB, LHN, MM.; Investigation : DE. MSB, SY, VS, DP ; Resources : DE, MSB, LHN, MM, SY; Data Curation : DE, MSB, LHN, MM, SY, VS, DP ; Writing - Original Draft : DE, MSB, LHN, MM; Writing - Review &Editing : DE. MSB, SY, VS, DP; Visualization : DE, MSB, LHN, MM, SY, VS, DP; Supervision : DE; Project Administration : DE; Funding Acquisition : DE.

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