

# Tyrosinase Inhibitory and Antioxidant Activity of *Paederia foetida* L.

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## Tyrosinase Inhibitory and Antioxidant Activity of *Paederia foetida* L.

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### ABSTRACT

*Paederia foetida* L. is a tropical Asian plant containing bioactive compounds and often used as functional food. The aim of this study was to determine the antioxidant capacity and inhibitory activity of *P. foetida* leaves extract on tyrosinase activity. In addition, the total phenolic content (TPC) and total flavonoid content (TFC) were determined. TPC and TFC were evaluated by the Folin-Ciocalteu and the aluminum chloride (AlCl<sub>3</sub>) colorimetric method, respectively. The 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), and cupric reducing antioxidant capacity (CUPRAC) methods were used to determine antioxidant capacity. Trolox equivalent antioxidant capacity (TEAC) and ascorbic acid equivalent capacity (AEC) were used to express antioxidant capacity (AAEC). The tyrosinase inhibitory activity was conducted by enzyme-linked immunosorbent assay (ELISA) using L-tyrosine as a substrate and measured at 490 nm by ELISA reader. TPC in the crude extract, fraction A, and fraction B was 173.18 ± 3.99, 553.95 ± 5.70 and 405.37 ± 33.90, respectively. TFC in the crude extract, fraction A, and fraction B was 12.79 ± 0.25, 143.16 ± 9.27, 143.50 ± 6.90, respectively. The best antioxidant capacity of the extract was shown in the DPPH method (15.71 ± 1.6 mg TEAC/g and 100.77 ± 8.5 mg AAEC/g). Meanwhile, fraction B showed the best antioxidant capacity by the FRAP (11.48 ± 1.5 TEAC/g and 8.39 ± 1.2 mg AAEC/g) and CUPRAC (116.34 ± 1.9 mg TEAC/g and 66.11 ± 1.3 mg AAEC/g) methods. Tyrosinase inhibitory activity exhibited that the IC<sub>50</sub> of fractions A (13.67 µg/mL) and B (13.37 µg/mL) were not significantly different with the IC<sub>50</sub> of arbutin. Our molecular docking study showed that the arbutin could suppress the function of the tyrosinase enzyme. Therefore, we assumed that the tyrosinase inhibitor effect of both fractions was most likely due to the arbutin content.

**Keywords:** Antioxidant capacity, tyrosinase, DPPH, FRAP, CUPRAC

### INTRODUCTION

Tyrosinase is a critical enzyme of the biosynthetic melanin pathway and has been the obvious target for preventing the over-expression of melanin in epidermal layers (Lin et al., 2012). Furthermore, excessive accumulation of this pigment can lead to the development of skin disorders, including freckles, melanoma, blotches, lentigo, (Sarkar et al., 2013). Tyrosinase catalyzes the hydroxylation of L-tyrosine to L-

DOPA and the oxidation of L-DOPA to dopaquinone by monophenolase and diphenolase activity (Ramsden & Riley, 2014). Moreover, it is noteworthy that free radicals also play an essential role in melanin biosynthesis. Increasing the activity of the free radicals in living systems can also lead to the production of melanin (Alam et al., 2012; Cui et al., 2018).

Many tyrosinase inhibitors have been identified, but only a few are currently used in

topical dermatological products due to a lack of clinical efficacy, limiting their use in humans (Masyita et al., 2021; Zolghadri et al., 2019). Therefore, research on new agents, particularly using natural products, is of utmost relevance. Moreover, the utilization of natural products add a not only economic value but also utilizes organic waste (Fawwaz et al., 2018; Fawwaz et al., 2019).

*Paederia foetida* L. belongs to the Rubiaceae family, which is also known as 'sembukan' in Indonesia. The leaves of *P. foetida* have an odorous sulfur-smelling (Wang et al., 2014). *P. foetida* possesses pharmacological activities such as anti-inflammatory, anti-arthritis, anti-cancer, 5-tidiarrheal, and gastroprotective effects (Chung et al., 2021; Kumar et al., 2015; Pradhan et al., 2019). However, the anti-melanogenic and antioxidant activity of this plant have not been thoroughly investigated. Therefore, this study aims to investigate the antioxidant and inhibitory activity of *P. foetida* leaves extract on tyrosinase. The total phenolic and flavonoid content of the extracts have also been analyzed because these two components are closely related to the antioxidant activity of natural products.

The *P. foetida* leaves extract antioxidant activity was tested using three different methods: 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), and cupric reducing antioxidant capacity (CUPRAC), respectively. The inhibitory activity on tyrosinase was conducted by enzyme-linked immunosorbent assay (ELISA).

## MATERIALS AND METHODS

### General

The solvents and other chemicals used were of the analytical quality. Arbutin, trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), vitamin C, 2,2-Diphenyl-1-picrylhydrazyl (DPPH), mushroom tyrosinase, and L-tyrosine were purchased from Sigma-Aldrich (St. Louis, MO, USA). 2,4,6-Tripyridyl-S-triazine (TPTZ) was purchased from Merck Tbk (Jakarta, Indonesia). A Millipore-Q50 Ultrapure water system was used to obtain deionized water (Sartorius).

### Sample preparation

The *P. foetida* leaves were collected from Samata, Gowa, South Sulawesi, Indonesia on February 2020 at 10.00 - 12.00 am to obtain optimum compound level. The leaves were washed in running water, cut into small pieces, and dried

for three days in an oven at 40-50°C. The dried leaves were then ground with a blender and passed through a 40/60 mesh, then stored in a container. The plant identification was carried out at the Botanical Laboratory, Department of Biology, Mathematics, and Natural Sciences, Universitas Negeri Makassar, Indonesia.

### Extraction and fractionation

The extraction of *P. foetida* leaves was conducted by the maceration method as described previously (Rifai et al., 2020). Maceration or cold extraction was used because this method is effective for compounds that are not heat resistant (degraded due to heat), the equipment used is relatively simple, inexpensive, and easy to obtain. To obtain ethanol crude extract, the extract was concentrated under reduced pressure at 50 °C. The crude extract was mixed with water (250 mL). The mixture was extracted with hexane and ethyl acetate in that order. To remove particles, all crude extracts were filtered separately through Whatman No. 41 filter paper. To obtain the dry extract, the particle-free extract was concentrated under reduced pressure.

Vacuum liquid chromatography (VLC) was used for the fractionation of extract. The ethyl acetate extract (15 g) was re-dissolved in ethyl acetate and mixed with 30 g silica gel. The solvent was evaporated and grounded in a mortar to obtain a homogenous powder. The column (12 × 40 cm) was packed with 900 g silica gel on top of the silica gel-containing extract and covered with sea sand to ballast the sample (Seelinger et al., 2012). The mobile phases were a mixture of chloroform and methanol (20:1, 15:1, 10:1, 5:1, 3:1, 1:1, 1:3, 1:5, 1:10, 1:15, 1:20) passed through by application of reduced pressure. After checking the collected fractions by thin layer chromatography (TLC), those with similar bands were recombined, resulting in two combined fractions (fractions A and B).

### Thin layer chromatography

The fractionation was controlled by TLC. The stationary phase was silica GF254, and the mobile phase was the mixture of hexane and ethyl acetate (3:1). Spots on the plate were detected before and after a 10% sulphuric acid spray. The sprayed plate was heated at 100°C for five minutes before the compounds were detected using UV254 and visible light. Unless otherwise specified, the plate was treated with 7 µL of extract or fraction solution.

### Total phenolic content (TPC)

TPC was evaluated by the Folin-Ciocalteu method according to the previous study with slight modifications (Nayaka, Fidrianny, Sukrasno, Hartati, & Singgih, 2020). Gallic acid (30–125 µg/mL) was used as a standard substance. The absorbances were measured at 765 nm after 30 minutes incubation at 45 °C. The results were expressed as g of gallic acid equivalents (GAE) per 100 g extract (g GAE/100 g).

### Total flavonoid content (TFC)

TFC was determined by the aluminum chloride (AlCl<sub>3</sub>) colorimetric method (Chang et al., 2002). Quercetin (10–50 µg/mL) was used as a reference standard to obtain a calibration curve. Following the 30 min incubation at room temperature, the absorbances were measured at 415 nm. TFC were expressed as g of quercetin equivalents (QE) per 100 g extract (g QE/100 g).

### DPPH radical-scavenging activity

DPPH radical-scavenging activity was determined as described previously with slight modification (Fawwaz et al., 2021). The samples (5 µg/mL) were correctly diluted and separately added to 5 mL of freshly prepared 0.1 mM DPPH solution in methanol. The samples were then vortexed and incubated at room temperature for 50 minutes, protected from light. The absorbances at 517 nm were measured after the incubation period. The standard substances (0–100 µg) were trolox and vitamin C, respectively. The results were given in milligrams of trolox and vitamin C equivalents per gram of dry weight (DW).

### Ferric reducing antioxidant power

The FRAP method was performed as described previously with slight modifications (Nadri et al., 2014). Briefly, 50 µL of samples were mixed with 3 mL of FRAP reagent (acetate buffer pH 3.1: 0.02 M FeCl<sub>3</sub>: 0.01 M TPTZ = 10:1:1). The absorbances were measured at 595 nm after a 6-minutes incubation at 37 °C. The standard substances (0–100 µg) were trolox and vitamin C, respectively. The results were given in milligrams of trolox equivalent antioxidant capacity (TEAC) and ascorbic acid equivalent capacity (AAEC) per gram of DW.

### Cupric reducing antioxidant capacity

The working solution for the CUPRAC assay was made by combining 1 mL of 10 mM CuCl<sub>2</sub>, 7.5 mM neocuproine, and 1 M ammonium acetate

buffer (pH 7.0) solutions. After thorough mixing, 0.5 mL of sample solution was added, and the final volume was 4.1 mL with a 1:9 water-acetone mixture. After 30 minutes of incubation at room temperature, the absorbances were measured at 450 nm. (Nadri et al., 2014). The standard substances (0–100 µg) were trolox and vitamin C, respectively. The results were reported as mg TEAC dan AAEC per g of DW.

### Mushroom tyrosinase inhibitor activity

The previously described method was used to assess tyrosinase activity (Chen et al., 2015). Briefly, 80 mL of 67 mM potassium phosphate buffer (NaH<sub>2</sub>PO<sub>4</sub>-Na<sub>2</sub>HPO<sub>4</sub>, pH 6.8), 25 mL of the desired inhibitor concentration, and 125 mL of 5 mM L-tyrosine were mixed and added to each well of a 96-well ELISA plate before incubating at 25 °C for 5 minutes. Then, to a final volume of 250 mL, 20 mL of 1250 U/mL mushroom tyrosinase solution was added to each well and incubated at 25 °C for 5 minutes. Furthermore, the absorbances were measured at 490 nm with a microplate reader. In this study, arbutin was used as a control.

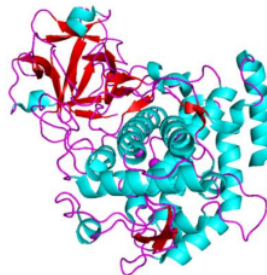


Figure 1. The tertiary structure of tyrosinase. The structures of alpha-helix and beta-sheet are displayed by cyan and red colors in cartoon models, respectively.

### Molecular docking

Molecular docking employed the AutoDock Vina package to assess the ligand-receptor complex (Morris et al., 2009; Trott & Olson, 2010). The molecule of arbutin was retrieved from the PubChem database (CID: 440936). The ligand was downloaded and saved to the sdf extension. In receptor preparation, the three-dimensional (3D) structure of tyrosinase was obtained from the RCSB Protein Data Bank (PDB) database (PDB ID: 2Y9X) (Figure 1). The polar hydrogen and Kollman's united atom charges were computed to the receptor. Afterward, the receptor was saved in

pdbqt format. All the docking results were processed and visualized in Open-Source PyMOL v 2.3 software (Arwansyah et al., 2021; Delano, 2020).

### Statistical analysis

The presented data are the means and standard deviations (SD) of at least three independent experiments. GraphPad Prism 8.0 was used for statistical analysis. Two-way ANOVA was used to analyze group differences, followed by Tukey's multiple-comparison test.

Table I. Total phenolic and flavonoid content of *P. foetida* leaves extract

<i>Paederia foetida</i>	Total phenolic content (g GAE/100 g)	Total flavonoid content (g QE/100 g)
Extract	173.18 ± 3.99	12.79 ± 0.25
Fraction A	553.95 ± 5.70	143.16 ± 9.27
Fraction B	405.37 ± 33.90	143.50 ± 6.90

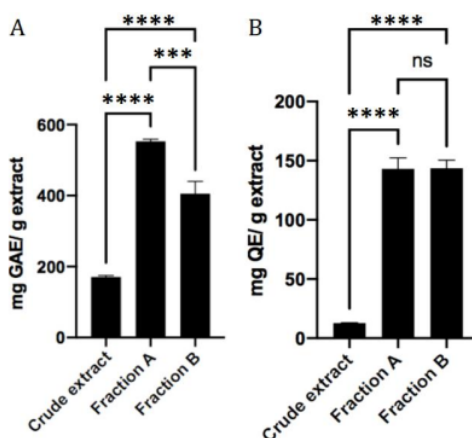


Figure 2. (A) Total phenolic and (10) total flavonoid content of *P. foetida* extract. \*\*\* $p = 0.0002$ , \*\*\*\* $p < 0.0005$ , not significant (ns)  $p > 0.5$ .

## RESULTS AND DISCUSSION

### Total phenolic and flavonoid content

Determining total phenolic and flavonoid content in *P. foetida* leaves showed that fractions A and B had higher phenolic and flavonoid content than that of crude extract (Table I). The total phenolic content in fraction A was significantly higher than that of fraction B. However, fractions A and B had the same total flavonoid content

(Figure 2). A previous study found that the total phenolic content of methanolic extract of *P. foetida* dried and fresh leaves were 35.52 and 62.64 mg ferulic acid equivalent/g sample, respectively (Osman et al., 2009). Another study exhibited that ethanolic extract of *P. foetida* leaves varied between 1.95 – 4.07 mg GAE/g (Shaswat et al., 2018). Our study exhibited that the total flavonoid content of *P. foetida* leaves extract is much lower than that of the total flavonoid content. In contrast, Shaswat et al. found that the total flavonoid content of *P. foetida* leaves extract was higher than that of the total flavonoid (Shaswat et al., 2018). These results indicate that the chemical compound of *P. foetida* leaves extract varies greatly depending on the growth site, the preparation of the extract, and the equivalency used for calculation.

### Antioxidant capacity

The antioxidant capacity determination exhibited that fractions A and B had better antioxidant capacity than extracts based on the FRAP and CUPRAC methods (Table II). However, the DPPH method showed that the extract has a better antioxidant capacity than the two fractions. Between fractions A and B, we can state that fraction B has better antioxidant activity than fraction A (Figure 3). The higher levels of phenolic compounds in *P. foetida* extract correlate with its antioxidant capacity. These findings are consistent with those of the previous study (Afroz et al., 2006; Holmes, 1892).

Trolox is a water-soluble vitamin E analog. It, like vitamin E, is an antioxidant that is used in biological or biochemical applications to reduce oxidative stress or damage. (TEAC) is a Trolox-based antioxidant strength measurement measured in Trolox Equivalents (TE), e.g. micromolTE/100 g. Because measuring individual antioxidant components of a complex mixture (such as blueberries or tomatoes) is difficult, Trolox equivalency is used as a standard for the antioxidant capacity of such a mixture (Pellegrini et al., 1999). Vitamin C (ascorbic acid) is a water-soluble vitamin. Vitamin C is an antioxidant vitamin that can protect against a variety of extracellular free radicals (Każmierczak-Barańska et al., 2020).

The antioxidant capacity test using the DPPH method showed that the extract had the highest antioxidant capacity compared to both fractions A and B. This indicated that the extract had a greater ability as a proton radical scavenger or as a hydrogen donor (Ibrahim et al., 2015).

Table II. Antioxidant capacity of *P. foetida* leaves extract.

Sample	mg TEAC/g DW			mg AAEC/g DW		
	DPPH	FRAP	CUPRAC	DPPH	FRAP	CUPRAC
Extract	15.71 ± 1.6	6.41 ± 0.3	65.05 ± 5.5	100.77 ± 8.5	4.35 ± 0.3	32.53 ± 2.0
Fraction A	1.02 ± 1.6	7.00 ± 0.1	72.59 ± 1.9	23.96 ± 8.3	4.82 ± 0.1	36.53 ± 1.3
Fraction B	0.39 ± 0.3	11.48 ± 1.5	116.34 ± 1.9	20.80 ± 1.6	8.39 ± 1.2	66.11 ± 1.3

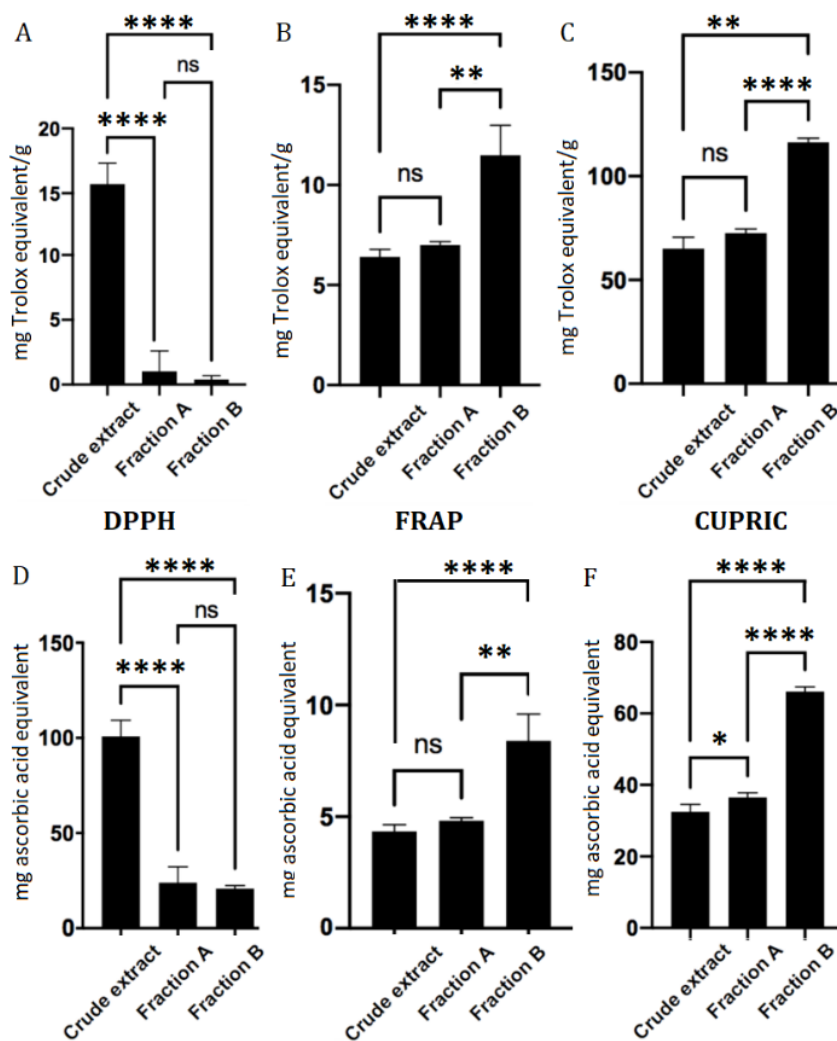


Figure 3. Antioxidant capacity of *P. foetida* extract. (A) DPPH assay, (B) FRAP assay, (C) CUPRAC assay (using Trolox as reference standard). (D) DPPH assay, (E) FRAP assay, (F) CUPRAC assay (using ascorbic acid as reference standard). \*\*  $p < 0.005$ , \*\*\*\*  $p < 0.0005$ , not significant (ns)  $p > 0.5$ .

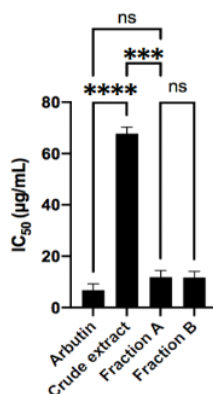


Figure 4. Mushroom tyrosinase inhibitory activity of *Paederia foetida* extract. \*\*\*\* $p < 0.0001$ , \*\*\* $p = 0.0001$ , not significant (ns)  $p > 0.5$ .

Table III. Hydrogen bonds of ligand in complex with tyrosinase obtained by molecular docking.

Residue	AA	Distance H-A (Å)	Distance D-A (Å)	Donor Angle	Donor Atom	Acceptor Atom
280	MET	3.1	3.65	117.37	4276 [O3]	2281 [O2]
260	ASN	2.17	2.96	137.56	4281 [O3]	2129 [O2]
268	ARG	2.73	3.21	110.77	2195 [N]	4290 [O3]
280	MET	3.1	3.65	117.37	4276 [O3]	2281 [O2]

Table IV. The hydrophobic interactions of ligand in complex with tyrosinase obtained by molecular docking.

Residue	Amino acid	Distance	Ligand atom	Protein atom
283A	VAL	3.89	4285	2302

Meanwhile, both fractions showed the ability of antioxidants to reduce  $\text{Fe}^{3+}$  ions to  $\text{Fe}^{2+}$  which was marked by a change in color from green to blue so that the antioxidant power of a compound was analogous to the reducing ability of the compound. The cupric method shows the ability of the sample to reduce  $\text{Cu}^{2+}$  complexes to  $\text{Cu}^+$  complexes, which is characterized by a color change from blue to yellow at the spot compounds that have antioxidant activity (Alam et al., 2013). In this case the method of measuring antioxidant activity will detect different characteristics of the sample, this explains that different methods of measuring activity will refer to the observation of different mechanisms of action of antioxidants.

#### Mushroom tyrosinase inhibitor activity

To investigate the inhibitory effects of the samples on mushroom tyrosinase, the  $\text{IC}_{50}$  values

were determined. We found that fractions A and B were not significantly different in inhibiting the mushroom tyrosinase, with  $\text{IC}_{50}$  values 13.67  $\mu\text{g}/\text{mL}$  and 13.37  $\mu\text{g}/\text{mL}$ , respectively (Figure 4). Furthermore, the  $\text{IC}_{50}$  of arbutin exhibited not significantly different toward those fractions A and B. Overall, our results suggested that *P. foetida* leaves extract may be considered a promising candidate for use as a skin whitening ingredient and hyperpigmentation disorders. These results agree with those of a previous study, in which *P. foetida* leaves extract hold great potential as an anti-melanogenic effect via MAPK signaling-mediated MITF downregulation (Chung et al., 2021).

#### Molecular docking

Based on the tyrosinase test, the  $\text{IC}_{50}$  value was not significantly different between arbutin and

the two fractions. Therefore, we assumed that the tyrosinase inhibitor effect of both fractions was most likely due to the arbutin content. The ability of arbutin to suppress the function of the tyrosinase enzyme can be proven through molecular docking analysis, which shows that the energy required to form the arbutin-tyrosinase complex is minimal (-5.4 kcal/mol). In addition, the interaction between the ligand-receptors is in the form of hydrogen and hydrophobic bonds. The detailed information on the hydrogen bond and hydrophobic interactions between ligand and receptor were summarized in Tables 3 and 4, respectively. The binding pose of ligands into the site of the receptor was visualized in Figure 5. Based on these results, we strongly encourage further research to isolate important chemical components that play a role in inhibiting the action of the tyrosinase enzyme, such as arbutin.

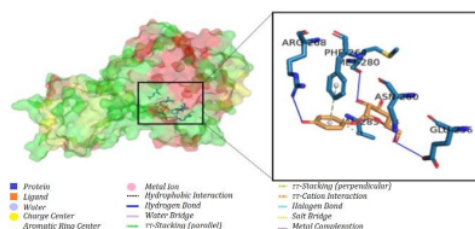


Figure 5. The binding poses between ligand and receptor. The conformation pose of each complex is visualized by PLIP program (Salentin, Schreiber, Haupt, Adasme, & Schroeder, 2015) combined with Pymol v 2.3 program packages.

## CONCLUSION

In conclusion, *P. foetida* leaf extract showed significant antioxidant capacity and tyrosinase inhibitory activity. These activities are closely related to the sample's high phenolic and flavonoid content. Thus, *P. foetida* leaf extract has great potential in preventing hyperpigmentation disorders and antioxidant activity. However, further research is needed to identify the main chemical components in *P. foetida* leaf extract responsible for its antioxidant and anti-melanogenic effects.

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