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Qualitative and Quantitative Analyses of the Anti-Allergic Constituent of Commercial *Prunus mume* Products in Taiwan

SHOU-FANG WU[1], YUAN-HUSAN CHEN[1], CHIEN-LIANG LIN[1], JUAN-CHENG YANG[1], YING-CHI DU[1], JIA-JUNG LEE[2], YANG-CHANG WU[1]* AND FANG-RONG CHANG[1,3]*

[1.] *Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C.*
[2.] *Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, R.O.C.*
[3.] *Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804, Taiwan, R.O.C.*

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ABSTRACT

The juice extracted from *Prunus mume* (Mei-Gin) is in the form of a highly concentrated dark black syrup. It is a common health supplement in Asia. The active component, 5-hydroxymethylfurfural (HMF), manifested a concentration-dependent effect on the inhibition of *β*-hexosaminidase degranulation upon antigen-sensitized RBL-2H3 cells. In order to investigate HMF (**1**) of *P. mume* extract, HMF was isolated and the HPLC profiles of 23 commercial Mei-Gin products (6 types) were qualitatively and quantitatively analyzed for HMF content. The samples included 10 Taiwanese Mei-Gin products, 3 Japanese Mei-Gin products, 5 specific-processing Mei-Gin products, 2 commercial plum drinks, 1 fresh mature plum extract, and 2 heat-processed samples. The HPLC profiles showed that the commercial products contained various amounts of HMF. Among them, the water extract of *P. mume* showed better yield of HMF. The yields from such products may differ due to different Mei-Gin original materials and different extraction and manufacturing procedures.

Key words: *Prunus mume*, Rosaceae, Mei-Gin, 5-hydroxymethylfurfural (HMF), anti-allergic activity

INTRODUCTION

"Mei" (*Prunus mume* Sieb. et Zucc.), also known as "Ume" or Japanese apricot, is a member of the Rosaceous family. It is widely grown in Taiwan, Japan, and Mainland China[(1)]. The fruit of *Prunus mume* has been used as a traditional drug and health food in Asia. Nowadays, it is widely consumed throughout the world because of its possible health benefits[(2,3)]. *P. mume* contains many basic nutrients, including proteins, carbohydrates, dietary fiber and multiple vitamins. In addition, *P. mume* contains some organic acids, such as malic acid, citric acid, and succinic acid. Based on literature survey, 74 compounds have been reported to be derived from the genus *Prunus*, including 13 phenolic glycosides, 5 flavonoids, 15 flavonoid glycosides, 3 cyanogenic glycosides, 11 benzenoids, 8 organic acid, 2 furanic compounds, 4 phenylpropanoids, 4 triterpenes, 8 steroids, 1 diterpenes and 3 fatty acids[(4-7)]. The fruit of *P. mume* has been used in folk medicine to alleviate fever, cough and intestinal disorders. It also has multiple biological and pharmacological effects, such as anti-oxidation, anti-fatigue, anti-diarrheal, anti-platelet aggregation and anti-cancer effects[(7,8)]. However, the raw fruit is poisonous due to two types of cyanogenic glucosides, prunasin and amygdalin. For this reason, processing is necessary and can be accomplished through pickling the raw fruit in vinegar, soaking it in liquor, or heating and concentrating it into juice or syrup[(9)].

Mei-Gin is the extract of the fruit of *P. mume*, which is a common health supplement in Asia. It is a dark black and highly concentrated syrup with a very sour taste. Mei-Gin was a military supplement for Japanese soldiers who were not in acclimatization during the World War II. Chuda *et al.*[(9)] isolated two compounds, 5-hydroxymethylfurfural (HMF) and mumefural (the citric acid ester of 5-hydroxymethylfurfural), from the methanol extract of the concentrated *P. mume* fruit juice. The flow rate of blood spiked with HMF or mumefural was compared to the flow rate of blood spiked with the two predominant organic acids in the fruit. The results showed that HMF and mumefural were the effective compounds that improved blood fluidity.

* Author for correspondence. Tel: +886-7-312-1101 ext. 2197; Fax: +886-7-311-4773;
E-mail: aaronfrc@kmu.edu.tw, yachwu@kmu.edu.tw

Other reports also indicated the beneficial effects of HMF. However, some harmful effects were also reported. Janzowski *et al.* (2000) reviewed some available data regarding HMF. It is not clear whether human exposure to HMF presents a potential health risk. Some controversial results on the mutagenicity/genotoxicity of HMF were also published[10,11]. However, Janzowski *et al.* finally showed that HMF does not pose a serious health risk, even though the highest concentrations in specific foods approach the biologically effective concentration range in cell systems[10]. Moreover, it may not be a mutagenetic agent but has a weak effect on DNA breaking[11].

Additionally, the extract of the fruit of *P. mume* has been reported to have anti-inflammatory effects based on the inhibition of HMGB1 release[12]. HMGB1 and IL-33 were considered as chromatin-associated nuclear factors that induce the production of pro-inflammatory and allergy-associated cytokines[13,14]. In addition, mast cells are known for regulating both immediate and late-phase allergic reactions. Aggregation of IgE receptor results in the activation and degranulation of mast cells. As part of our ongoing investigation and discovery of new anti-allergic agents, it was found that the ethyl acetate extract of Mei-Gin showed moderate anti-allergic effect. Furthermore, the active components of Mei-Gin extract were investigated. In the current research, HMF was isolated from Mei-Gin. Qualitative and quantitative analyses on the HMF contents of 23 marketed products of *P. mume* collected from Japan and Taiwan were performed.

MATERIALS AND METHODS

I. *Instrumentation and Materials*

IR spectra were measured using a Mattson Genesis II™ FT-IR spectrophotometer. UV spectra were obtained using a JASCO V-530 UV/VIS spectrophotometer. NMR spectra were run using Varian GEMINI200 MHz FT-NMR. The chemical shift (δ) values are in ppm (part per million) with CD_3OD as the internal standard, and coupling constants (*J*) are in Hz. Low resolution ESI-MS spectra were obtained using a VG Biotech Quattro 5022 mass spectrometer in positive mode. Silica gel 60 (40 - 60 mesh, Merck), Geduran® Si 60 (63 - 200 mesh, Merck), LiChroprep® RP-18 (40 - 63 mesh, Merck), Sephadex LH-20, Celite® 545 and Diaion HP-20 were used for column chromatography (CC). Silica gel plates (Kieselgel 60, F254, 0.20 nm, Merck) were used for TLC.

II. *Preparation of Mei-Gin Related Products*

The Mei-Gin extract investigated by separation, isolation and structural elucidation was collected in 2006 from Yi-Qing farm in Nantou County, Taiwan. The Mei-Gin product was produced in a condition of reduced pressure and relatively lower temperature (ca. 95°C). In the standard process, 100 kg of raw fruit was crushed and filtered to yield 60 - 70 L of juice and then concentrated to less than 2 kg of Mei-Gin, and the concentration ratio was ca. 1/50. PM11 - 15 were produced using special processing methods. PM11 and PM12 were extracted with vinegar for four months (< 100°C). PM12 was further concentrated to a ratio of 1/50. PM13 and PM14 were extracted with rice wine (40%) for four months (< 100°C), and PM14 was concentrated to a ratio of 1/50. PM 15 was extracted with water and heated for ca. 50 h (< 100°C) as a juice. In addition, fresh unripe plum (1 kg) was blended in a blender and soaked with water for one day. The water extract solution was filtered and concentrated by a freeze-dry system. The solid water extract of fresh unripe plum (PM21) was obtained. Half of PM21 was used in reflux experiments. The sample was refluxed at 90°C for 24 h and 48 h to obtain PM22 and PM23, respectively.

III. *Extraction and Isolation*

Mei-Gin (5.88 kg, produced from ca. 300 kg of raw fruit) was extracted five times with hot water (ca. 70°C, 3.5 L). The extract solution was partitioned with ethyl acetate (EA). The EA phase was concentrated under reduced pressure and the EA fraction (223.45 g) was obtained. The abundant precipitate of the EA fraction was filtered and the residual solution was subjected to CC gradient elution with mixtures of *n*-hexane: EA : methanol (1/0/0, 2/1/0, 1/1/0, 1/5/0, 0/1/0, 0/30/1, 0/15/1, 0/5/1 and 0/0/1) to yield twenty fractions (PM F1 - PM F20).

Of these twenty fractions, PM F3 (13.05 g) was rechromatographed with gradient mixtures of *n*-hexane : EA : methanol (2/1/0, 1/1/0, 1/5/0, 0/1/0, 0/30/1, 0/15/1, 0/5/1 and 0/0/1) to yield 16 subfractions. Among the 16 subfractions, compound **1** (278.91 mg) was isolated and eluted with *n*-hexane : $CHCl_3$: methanol solvent system by a repeating CC and the structure was confirmed as HMF by NMR spectra.

IV. *Qualitative and Quantitative Analyses of HMF*

(I) *Sample Preparation*

HMF was isolated from Mei-Gin and the structure was elucidated by spectroscopic methods. The reference compound was used for qualitative analysis. Standard stock solution contained 1 mg/mL HMF, which was prepared with 1.0 mg HMF in 1.0 mL of H_2O for quantitative analysis. Standard sample solutions were injected using an injection volume of 20 μL into the HPLC system.

Twenty-three "Mei" products were collected from markets and farms, including ten Taiwan Mei-Gin products, three Japanese Mei-Gin products, five specific-processing Mei-Gin products, two commercial plum drinks, one fresh plum extract and two heat-processed samples (Table 1).

All of these samples were concentrated by removing

water. Each sample (10 mg) of the twenty-three Mei-Gin products was dissolved in H_2O (1 mL) and filtered with a nylon membrane (50-μL injection volume).

(II) *Analytical HPLC*

HPLC analyses were performed with a Shimadzu model LC-10AT *vp* HPLC (Japan), equipped with a two-solvent delivery system, a SIL-20A automatic sample injector and a model SPD-10A *vp* diode array detector. The detection wavelength was set at 254 nm. Chromatography was carried out on an Atlantis® (4.6 × 150 mm i.d.) column. Gradient elution was performed with water-HPLC grade MeOH (0 - 100%, 0 - 60 min) at a flow rate of 1 mL/min. The solvents were filtered through a 0.45-μm filter prior to being used. The total HPLC run time for the assay was 60 min.

(III) *Calibration*

In the standard HPLC chromatogram, six different concentrations of HMF, in the linear range from 0.125

Table 1. Twenty-three Mei-Gin and plum-derived products

Sample type	Name	Code name	Extraction solvent (notes and concentration ratio)
Taiwanese commercial Mei-Gin products	IC-W1	PM01	Raw plum juice, heated for ca. 100 h, concentrated ratio: 1/50
	SI	PM02	
	TS	PM03	
	LMJ	PM04	
	GL	PM05	
	WRL	PM06	
	WRW	PM07	
	WNT	PM08	
	TSG	PM09	
	USM	PM10	
Specific-processing Mei-Gin products	IC-A1	PM11	Plum soaked with vinegar for 4 months
	IC-A2	PM12	Plum soaked with vinegar for 4 months, concentrated to 1/50 (< 100°C)
	IC-E1	PM13	Plum soaked with rice wine (40%) for 4 months
	IC-E2	PM14	Plum soaked with rice wine (40%) for 4 months, concentrated to 1/50 (< 100°C)
	IC-W2	PM15	Raw plum juice, heated for ca. 50 h
Japanese commercial Mei-Gin products	JP-1	PM16	Water (collected from Japan)
	JP-2	PM17	Water (collected from Japan)
	JP-3	PM18	Water (collected from Japan)
Commercial plum drinks	DR-1	PM19	Commercial product
	DR-2	PM20	Commercial product
Fresh plum extract	NP-1	PM21	Water (juice), freeze dried
Heat-processed samples	NP-2	PM22	Juice, refluxed for 24 h at 90°C, freeze dried
	NP-3	PM23	Juice, refluxed for 48 h at 90°C, freeze dried

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to 1 mg/mL, were prepared in H_2O. The experiment was replicated six times (n = 6) for each concentration.

(IV) *β-Hexosaminidase Secretion Assay*

A method for measuring *β*-hexosaminidase release was reported to detect the degree of degranulation in RBL-2H3 cells. The water fraction, EA fraction and HMF were tested for anti-allergic effect using the *β*-hexosaminidase secretion assay in RBL-2H3 cells. This assay was conducted according to procedures recorded in the literature[15,16]. Monoclonal anti-DNP IgE was purchased from Sigma. RBL-2H3 cells were seeded into 96-well plates at a cell density of 5×10^4 cells/well and the cells were then preincubated with drugs at the indicated concentrations for 24 h. Dexamethasone was used as a positive control drug. RBL-2H3 cells were sensitized with 1 μg/mL of anti-DNP IgE in DMEM medium containing FBS (10%), penicillin (100 U/mL) and streptomycin (100 μg/mL). After 18 h of sensitization, the cells were washed twice with 500 μL of Tyrode's assay buffer (135 mmol/L NaCl, 5 mmol/L KCl, 1.8 mmol/L $CaCl_2$, 1 mmol/L $MgCl_2$, 1.19 mmol/L KH_2PO_4, 20 mmol/L HEPES, 5.6 mmol/L glucose, pH 7.2) and stimulated with 1 μg/mL DNP-BSA for 1 h. The supernatant (50 μL) was transferred into a 96-well microplate and incubated with 50 μL of substrate solution (1 mM *p*-nitrophenyl-N-acetyl-D-glucosaminide) in 0.1 M citrate buffer (pH 4.5) at 37°C for 1 h. Towards the end, the reaction was stopped with 200 μL/well of stop solution (0.1 M Na_2CO_3/$NaHCO_3$, pH 10.0). The absorbance was read at 405 nm on an ELISA reader.

RESULTS AND DISCUSSION

HMF was reported as a controversial component that has shown positive and negative effects[9-11]. In addition to the promising results reported in prior literature, the HMF isolated from the target Mei-Gin extract also plays an important role in screening for anti-allergic activity in the *β*-hexosaminidase secretion assay. Based on the results, we concluded that HMF can serve as an important standard for *P. mume* and Mei-Gin commercial products. Hence, the fingerprint profile of HMF as a quality control standard for monitoring the commercial products was established.

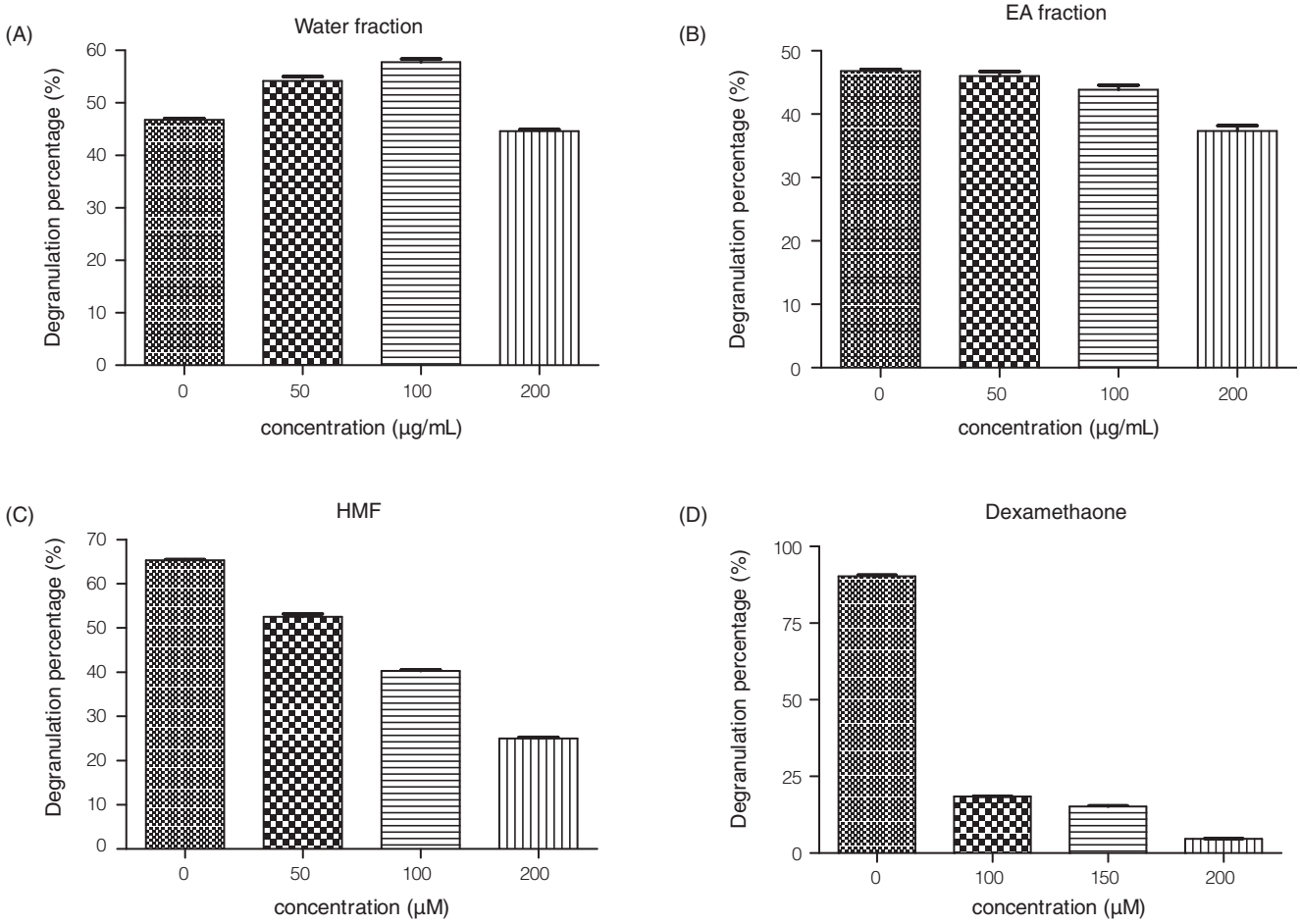

Figure 1. Effects of water fraction, EA fraction and HMF on degranulation in RBL-2H3 cells (n = 3).

I. *Effect of HMF on Degranulation in RBL-2H3 Cells*

Although previous reports indicated that the extract of *P. mume* has potent effects on the inhibition of the pro-inflammatory factor HMGB1, its effects on allergic degranulation were not examined. First of all, the cytotoxicity range of HMF was screened. HMF showed no cytotoxicity against RBL-2H3 cells at high dose (380 μg/mL). As shown in Figure 1, the degranulation levels of the extracts of water and EA fractions (Figure 1A) and HMF (Figure 1C) from Mei-Gin were evaluated by assessing *β*-hexosaminidase release. According to the data, HMF inhibited *β*-hexosaminidase release in a dose-dependent manner. It can be proposed that HMF may contribute to the anti-allergic effects of *P. mume*. All the evidence suggested that HMF could be an important marker to evaluate the quality of *P. mume* or Mei-Gin commercial products.

II. *Qualitative and Quantitative Analysis*

Based on the above reasons, the HPLC fingerprint profile of HMF was established as a quality control standard. HMF (**1**) was obtained from the EA layer, isolated by normal phase chromatography with a MeOH/$CHCl_3$ gradient mixture solvent system. As indicated in the HPLC profiles of Mei-Gin products, all except for PM21, PM22, and PM23 were found to have the signal of HMF at a retention time of 13.7 min.

Calibration curves were established with six concentrations of HMF in the range of 0.125 - 1 mg/mL. The conditions were detailed in the experimental section. The linearity of the plot of concentration (x, mg/mL) for each compound *versus* peak area (y) was investigated. Under these analytical conditions, good linearities for all of the calibration curves were obtained ($R^2 = 0.9997$).

In addition, the quantitative analysis of the 23 Mei-Gin products was performed (Table 2). As the results indicated, the Mei-Gin products contained various amounts of HMF. However, PM21 - 23 have no trace of HMF. PM15 contained the most HMF (0.583%), whereas PM13 and 14 contained the least HMF (< 0.001%). In the Taiwanese market, Mei-Gin products (PM01 - 10) were collected from different companies or farms. PM03 was found to contain 0.553% of HMF. However, PM08 contained only 0.034%. The results indicated that different growing conditions of *P. mume* in different places (Table 1) will influence the yield of HMF products. In addition, HMF was not detected in PM21 (the water extract of raw fruit). This result suggested that HMF formation was affected by factors including temperature and time control during thermal processing and the concentration ratio. According to previous studies, HMF will be transformed from mono- or di-saccharides (glucose, fructose, and sucrose), oligosaccharides (chitosan), polysaccharides (cellulose) and aminosugars (glucosamine) by thermal degradation, followed by dehydration and rearrangement in acidic conditions[17-25]. As shown in this study, organic acids, such as citric acid, will reach a very high concentration level in Mei-Gin products. As it is the most important marker reported thus far in concentrated products of plum juices, HMF content is a key factor in manufacturing.

The specific-processing Mei-Gin products, PM11 - 15, were extracted by vinegar alcohol and water. PM15 (the intermediate product of Mei-Gin water extract, heated below 100°C for 50 h and concentrated to a ratio of 1/50) contained 0.583% of HMF. The vinegar extracts, PM11 and 12 (extracted with vinegar for four months at

Table 2. HMF content (g/kg) in different Mei-Gin and plum-derived products (n = 6)

Sample code	Product name	HMF Content (%)	RSD[a] (%)
PM01	IC-W1	0.469	1.576
PM02	SI	0.067	0.983
PM03	TS	0.553	1.107
PM04	LMJ	0.377	1.454
PM05	GL	0.144	0.445
PM06	WRL	0.189	0.468
PM07	WRW	0.157	1.825
PM08	WNT	0.034	1.966
PM09	TSG	0.446	1.413
PM10	USM	0.093	0.773
PM11	IC-A1	0.197	1.725
PM12	IC-A2	0.194	1.705
PM13	IC-E1	< 0.001	0.872
PM14	IC-E2	< 0.001	1.613
PM15	IC-W2	0.583	0.708
PM16	JP-1	0.067	1.041
PM17	JP-2	0.134	1.463
PM18	JP-3	0.015	0.922
PM19	DR-1	0.013	0.837
PM20	DR-2	< 0.001	3.271
PM21	NP-1	N.D.[b]	
PM22	NP-2	N.D.[b]	
PM23	NP-3	N.D.[b]	

[a] Related standard deviation.
[b] HMF was not detected.

lower than 100°C) contained only 0.197% and 0.194% HMF, respectively. However, the alcohol extracts, PM13 and 14 (extracted with 40% rice wine for four months below 100°C) contained almost no HMF. The results suggested that the production process of the alcohol extracts may not reach the temperature required to form HMF, or HMF production may be disrupted by the existence of alcohol. Hence, the results suggested that water is a more suitable solvent in Mei-Gin production for extracting high HMF content.

In the extracts of reflux experiments on fresh *P. mume* (PM21 - 23), several signals appeared on PM22 and 23 HPLC profiles, but no HMF appeared even after heating at 90°C for 24 and 48 h. Possible reasons are insufficient temperature and acidic concentration[17-25]. Meanwhile, sparse HMF was found in two commercial plum drinks (PM19 - 20).

Based on the above qualitative and quantitative analyses, HMF, one of the most important markers for the quality control of Mei-Gin was established. Moreover, the quality of functional foods or drinks related to Mei-Gin could be monitored by this standard model for the economic uses of *P. mume* products in the market.

CONCLUSIONS

In current study, HMF is the one of major components from Mei-Gin and showed anti-allergic activity in a dose-dependent manner in a β-hexosaminidase secretion assay without cytotoxicity at high dose. Furthermore, we established the HPLC profiles of HMF and performed the quantitative analysis of 23 Mei-Gin products, which were collected from different origins and manufactured using different processes. As the HPLC profiles indicated, HMF was found in PM01 - 20, with variable HMF contents. In this study, we showed that water extracts of Mei-Gin had better yields in the production of HMF, and the yield varies with different manufacturing processes. Based on the results, the thermo systems and organic acid levels are the key points leading to different yields of HMF in Mei-Gin production. Finally, a simple and effective method was established for the quality control of Mei-Gin. This will improve the consistency and standardization of Mei-Gin products.

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