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ISOLATION AND QUANTIFICATION OF GINSENOSIDES FROM PROCESSED *PANAX NOTOGINSENG* RADIX AND RHIZOME

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Summary

Isolation and Quantification of Ginsenosides from Processed *Panax notoginseng* Radix and Rhizome

From the extract of *Panax notoginseng* radix and rhizome which was processed by steaming at 120°C for 4 hours, eight ginsenosides were isolated, including 20(*R*)-ginsenoside Rh1 (**1**), 20(*R*)-ginsenoside Rg3 (**2**), 20(*S*)-ginsenoside Rg3 (**3**), ginsenoside Rg1 (**4**), notoginsenoside R1 (**5**), ginsenoside Re (**6**), ginsenoside Rd (**7**), and ginsenoside Rb1 (**8**). The chemical structures of these compounds have been determined based on nuclear magnetic resonance spectroscopy (NMR) and compared with published data. The contents of ginsenosides **1, 3-8** in unprocessed and processed *P. notoginseng* samples were determined by the HPLC-PDA method.

Keywords: *Panax notoginseng, Processed, Ginsenoside, HPLC.*

1. Introduction

Panax notoginseng (Buck) F. H. Chen, also known as Kim Bất Hoán in Vietnamese or simply Chinese ginseng, is a valuable medicinal plant belonging to the Araliaceae family and has high economic value [1],[2],[3]. *P. notoginseng* (PN) has a high saponin content and is cheaper than Korean ginseng (*Panax ginseng*) [1]. Similar to other medicinal plants in the *Panax* genus, *P. notoginseng*'s main chemical components are saponins from the dammaran-type including protopanaxadiol (PPD) and protopanaxatriol (PPT) structures, with more than 80 different saponins (ginsenosides) isolated. The major ginsenosides in PN are ginsenoside Rb1 (G-Rb1), G-Rd, G-Rg1, G-Re, and notoginsenoside R1 (N-R1) [4]. Multifunctional properties of unprocessed PN have been documented such as improving symptoms of coronary artery disease, anti-inflammatory effects, anti-tumor effects, lipid-lowering effects, and antiplatelet aggregation [5],[6],[7]. The active ingredients and biological activity of processed PN by steaming at different temperatures and steaming duration have been investigated. Research has indicated significant changes in the physicochemical properties of PN during steaming and drying compared to fresh PN. Many new active ginsenosides have been found in steamed PN [8],[9]. Previous studies have suggested that the processing of PN can facilitate the formation and enhancement of less polar ginsenoside components such as G-Rg3, G-Rh1, G-Rk3, and G-Rh4 [9],[10]. These changes in the content and structure of these saponins have led to differences in pharmacological effects and have various health benefits such as increased antiplatelet aggregation, anticoagulant, neuroprotective, and antioxidant effects [7]. Therefore, it could be used as a potential drug for the prevention and treatment of Alzheimer's disease and cancer [11].

Despite the superior pharmacological effects of processed PN compared to its unprocessed form, most PN products available in the Vietnamese market are either in the form of raw powder or derived from unprocessed PN extracts. Research on processed PN in Vietnam is still limited. Bui Thi Ha et al. conducted research to isolate ginsenosides from PN grown in the Si Ma Cai region of Lao Cai province. The study successfully isolated two compounds, G-Rg3 and G-Rh1, from processed PN that had been steamed at 120°C for 8 hours. However, the accurate determination of the *S*/*R* isomer of these two ginsenosides has not yet been mentioned. Furthermore, the ginsenoside content in both the processed and unprocessed forms has not yet been analyzed in this study [12]. The monographs of *P. notoginseng* in pharmacopeias of various countries typically utilize ginsenosides components, including G-Rb1, G-Rd, G-Rg1, N-R1, and G-Re, as marker compounds for qualitative and quantitative analysis. In processed PN, less polar ginsenosides such as G-Rg3, G-Rh1, G-Rk3, and G-Rh4 are major components [9],[10]. The objective of this study was to isolate and identify major ginsenosides in processed PN

steamed at 120°C for 4 hours. The isolated ginsenosides can serve to assess the content of these components in raw and processed PN, ensuring the quality of raw materials throughout the production process. This research represents a crucial step toward establishing robust quality standards for PN, both in its raw and processed forms.

2. Materials and method

2.1. Materials

Dried *Panax notoginseng* radix and rhizome (1 kg) were purchased from Ha Giang JSC. in July 2020. The voucher specimen (UMP-PN-27-HG) was deposited at the Department of Pharmacognosy, Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh city.

2.2. Standards for qualitative analysis using thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC)

Pure compounds including ginsenoside Rg1, ginsenoside Re, ginsenoside Rd, 20(*R*) ginsenoside Rh1, 20(*S*) ginsenoside Rg3, ginsenoside Rb1, and notoginsenoside R1 (purity > 95%, HPLC-PDA) were isolated from previous research projects [13]. These standards were used as marker compounds for the isolation procedure of target components. The isolated ginsenosides were used for both qualification and quantification.

2.3. Solvents, chemicals and equipment

The solvents used for extraction and isolation were purchased from RCI Labscan Ltd. (Thailand). The solvents for HPLC analysis (acetonitrile - ACN and MeOH) were obtained from J.T.Baker (USA). TLC was carried out using TLC *Silica gel* 60 F_{254} (Merck, Germany), and spots were detected by spraying a solution of 10% sulfuric acid in ethanol followed by heating at 110°C for 5 minutes. The isolation was achieved using open column chromatography with a stationary phase of *silica gel* (40-63 µm, Merck) and reversed-phase *silica gel* Lichroprep (40-63 µm, Merck). HPLC analysis was performed on an UPLC Acquity H-class system equipped with PDA detector (Waters, USA). A Phenomenex Gemini C_{18} chromatography column (150 × 4.6 mm; 3 µm) was used for the separation. The Nuclear Magnetic Resonance (NMR) spectra of isolated compounds were measured on a Bruker 500 MHz spectrometer (USA).

2.4. Extraction and isolation

P. notoginseng radix and rhizome (1 kg) were washed and steamed at 120°C for 4 hours. They were then dried at 60°C to process PN. It was coarsely ground, of which the 50 g powder was finely ground to get the moderately fine powder that passed through a 355 µm mesh sieve for qualitative and quantitative analysis. The coarse powder of processed PN was extracted with 80% MeOH (5 liters x 3 times) by ultrasonication at 60°C for 1 hour. The extracts were combined, and the solvent was evaporated to yield 530 g of MeOH condensed extract. This extract was then dissolved in 2 liters of distilled water and successively partitioned with ethyl acetate (EtOAc) and saturated *n*-butanol (Bu) to yield 29.82 g of EtOAc extract, 122.53 g of Bu extract, and 357.46 g of water extract, respectively. The EtOAc extract (29 g) was fractionated by *silica gel* column chromatography with $CHCl_3$ - MeOH (100:15) as elution solvent to get 13 fractions (EA1-EA13). The Bu extract was also fractionated by *silica gel* column chromatography with $CHCl_3$ - MeOH - H_2O (70:30:10; lower layer) as elution solvent to obtain 21 fractions (Bu1 - Bu21).

TLC was conducted to compare the extracts with G-Rg1, G-Re, G-Rd, G-Rh1, G-Rg3, G-Rb1, and N-R1, to identify the target fractions for isolation. From EA6 and EA7 fractions, which showed a similar TLC spot to G-Rh1, a white precipitate was obtained after removing the solvent. This precipitate was washed with ethyl acetate to yield compound **1** (540 mg). The Bu6 and Bu7 fractions, which showed a TLC spot similar to G-Rg3, were evaporated to yield a white precipitate. This precipitate was refined by hot MeOH extraction, filtration, and recrystallization several times with a $CHCl_3$ - MeOH - H_2O solvent mixture to yield compound **2** (470 mg). The remaining filtrate was evaporated and then recrystallized in MeOH to get compound **3** (217 mg). The Bu9 fraction was further separated by *silica gel* column chromatography with an EtOAc - MeOH - H_2O (200:17:13) elution system to obtain compound **4** (505 mg) from the Bu9.5 fraction. This compound showed a spot with an R_f value similar to G-Rg1 on TLC. From the Bu15 fraction, reversed-phase column chromatography with a MeOH - H_2O (45:55) elution system to get two main fractions including Bu15.1 and Bu15.2. The Bu15.2 fraction, which showed a TLC spot similar to G-Rd, was evaporated to yield compound **5** (670 mg). The Bu15.1 fraction was further separated by reversed-phase column chromatography with a MeOH - H_2O (40:60) elution system to yield 4 main fractions

(Bu15.1.1 - Bu15.1.4). From the Bu15.1.4 fraction, a white precipitate was obtained, which was washed with EtOAc to yield compound **6** (187 mg), showing an R_f value similar to G-Re on TLC. The remaining filtrate was fractionated by reversed-phase column chromatography with an ACN - H_2O (20:80) elution system to yield needle-like crystals. These crystals were washed with MeOH - H_2O to yield compound **7** (507.7 mg), which showed a spot with an R_f value similar to N-R1 on TLC. The Bu18 and Bu19 fractions were combined and further separated by reversed-phase column chromatography with a MeOH - H_2O (65:35) elution system to yield the Bu18.3 fraction; this fraction showed a spot with R_f value similar to G-Rb1 on TLC. This fraction was refined by reversed-phase column chromatography, eluted with ACN - H_2O (20:80 → 30:70), to yield compound **8** (739 mg).

2.5. Determination of purity of isolated compounds using the HPLC-PDA

2.5.1. Chromatographic conditions

The HPLC analysis was operated on an UPLC Acquity H-class system equipped with PDA detector (Waters, USA), Phenomenex Gemini C_{18} chromatography column (150 × 4.6 mm, 3 µm), Phenomenex Gemini C_{18} guard column, detection wavelength at 203 nm, mobile phase A (acetonitrile) and B (water) with a gradient elution program: 0 - 11 min (21% A), 11 - 25 min (21 - 32% A), 25 - 35 min (32 - 40% A), 35 - 40 min (40 - 60% A), 40 - 50 min (60 - 95% A); flow rate was set at 1 mL/min; sample injection volume was 10 µL; column temperature 30°C. The purity of the isolated ginsenosides was determined based on the percentage peak area of all the eluted components on the chromatogram compared to the blank sample, as well as in comparison with the retention time and peak area of the corresponding standards.

2.5.2. Sample preparation

The isolated compounds were dissolved in MeOH at a concentration of about 500 µg/mL. The sample solution was filtered through a 0.22 µm filter before being injected into the HPLC system.

2.6. Determination of some main ginsenosides content in unprocessed and processed PN

2.6.1. Chromatographic conditions

The HPLC analysis was carried out on an Acquity UPLC H-Class system coupled with PDA detector (Waters, USA) and using Phenomenex Gemini C_{18} chromatography column (150 × 4.6 mm, 3 µm), Phenomenex Gemini C_{18} guard column, detection wavelength was set at 203 nm, mobile phase A (acetonitrile) and B (water) with a gradient elution program: 0 - 11 min (21% A), 11 - 25 min (21 - 30% A), 25 - 27 min (30 - 35% A), 27 - 37 min (35 - 39% A), 37 - 50 min (39 - 53% A), 50 - 51 min (53 - 95% A), 51 - 60 min (95% A); flow rate was set at 1 mL/min; sample injection volume was 10 µL, column temperature 30°C. The preliminary determination of the main ginsenoside content in unprocessed and processed PN was based on the retention time and peak area of the corresponding isolated ginsenosides.

2.6.2. Sample preparation

Weigh about 100 mg of raw PN and processed PN (steamed at 120°C for 4 hours) powder into a screw-cap test tube. Add exactly 10 mL of 80% MeOH, screw on the cap, and extract by sonication for 60 mins at 45°C. The sample solution was filtered through a 0.22 µm filter before being injected into the HPLC system.

3. Results and Discussion

3.1. Extraction and isolation

From 80% MeOH extract, by using column chromatography and purifying by recrystallization, eight compounds (**1-8**) were isolated. The flow chart for the isolation and purification was described in **Fig. 1**.

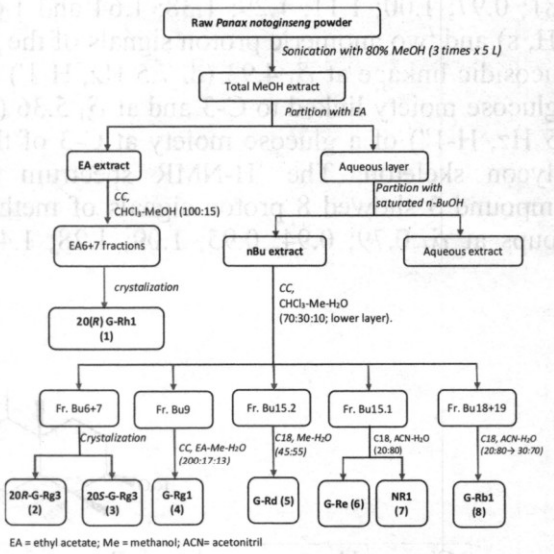


Fig.1. Isolation process of ginsenosides (**1-8**) from processed PN

The structure of the isolated compounds was determined by comparing them with HPLC chromatograms of standard substances and confirmed by comparative analysis of NMR spectroscopy with literature data. The isolated compounds showed the purity higher than 95.0% as determined by HPLC-PDA (Table 1).

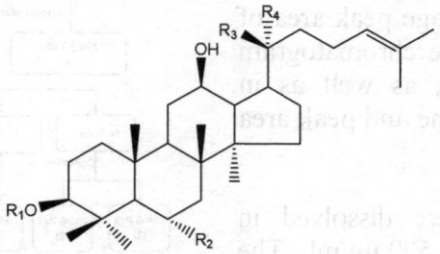
Table 1. Results of isolation and purity of the isolated compounds

Compound	Weight (mg)	Compound name	HPLC purity
1	540	20(*R*)-ginsenoside Rh1 (20*R*-G-Rh1)	98.00%
2	470	20(*R*)-ginsenoside Rg3 (20*R*-G-Rg3)	95.80%
3	217	20(*S*)-ginsenoside Rg3 (20*S*-G-Rg3)	96.00%
4	505	Ginsenoside Rg1 (G-Rg1)	99.50%
5	670	Ginsenoside Rd (G-Rd)	97.50%
6	187	Ginsenoside Re (G-Re)	99.99%
7	507	Notoginsenoside R1 (N-R1)	99.99%
8	739	Ginsenoside Rb1 (G-Rb1)	96.70%

3.2. Structure determination

The ^{1}H-NMR spectrum of compound **1** showed proton signals of 8 methyl groups resonating at δ_H 0.86; 1.05; 1.17; 1.38; 1.60; 1.62; 1.68; 2.07 (3H, *s*) and one proton at δ_H 5.31 (1H, *t*, 7.0) of the double bond in dammarane skeleton. In addition, the ^{1}H-NMR spectrum also showed the presence of a hexose sugar group with an anomeric proton signal resonating at δ_H 5.03 (1H, d, 7.8). The ^{13}C-NMR spectrum of **1** showed an anomeric carbon signal at δ_C 106 of a glucose moiety linked to position C-6. Comparative analysis of NMR data with published references, compound **1** was identified as 20(*R*)-ginsenoside Rh1 [8],[9].

The ^{1}H-NMR spectrum of compound **2** showed 8 proton signals of methyl groups at δ_H 0.81; 0.97; 1.00; 1.11; 1.29; 1.38; 1.64 and 1.67 (3H, s) and two anomeric proton signals of the β-glucosidic linkage at δ_H 4.93 (d, 7.5 Hz, H-1′) of a glucose moiety linked to C-3 and at δ_H 5.36 (d, 7.5 Hz, H-1″) of a glucose moiety at C-3 of the aglycon skeleton. The ^{1}H-NMR spectrum of compound **3** showed 8 proton signals of methyl groups at δ_H 0.79; 0.94; 0.95; 1.09; 1.28; 1.41; 1.61; 1.63 (3H, s) and two anomeric proton signals of the β-glucosidic linkage at δ_H 4.91 (*d*, 7.7, H-1′) and at δ_H 5.36 (d, 7.8, H-1″) of two glucose moieties at C-3 of the aglycon skeleton. The ^{13}C-NMR spectra of compounds **2** and **3** were consistent with the spectral data of G-Rg3 in the references [8]. Furthermore, according to the references, differentiation of the 20(*S*) and 20(*R*) isomers can be based on the neighboring carbon atoms of C-20 [8],[13]. The δ_C shifts of C-17, C-21 and C-22 in the ^{13}C-NMR spectrum of compound **2** were 50.6; 22.8 and 43.3; and for compound **3** were 54.8; 27.1 and 39.5, respectively. The ^{1}H-NMR and ^{13}C-NMR data of compounds **2** and **3** were consistent with the spectral data of 20(*R*) and 20(*S*)-ginsenoside Rg3 in the references [8],[9]. Therefore, the structure of compound **2** was identified as 20(*R*)-ginsenoside Rg3 and compound **3** as 20(*S*)-ginsenoside Rg3. Compounds **4-8** were identified as ginsenoside Rg1 (**4**), ginsenoside Rd (**5**), ginsenoside Re (**6**), notoginsenoside R1 (**7**), and ginsenoside Rb1 (**8**), in accordance with literature data [12].



Ginsenoside	R_1	R_2	R_3	R_4
20*R*-G-Rh1 (**1**)	H	O-Glc	CH_3	OH
20*R*-G-Rg3 (**2**)	Glc^2-^{1}Glc	H	CH_3	OH
20*S*-G-Rg3 (**3**)	Glc^2-^{1}Glc	H	OH	CH_3
G-Rg1 (**4**)	H	O-Glc	O-Glc	CH_3
G-Rd (**5**)	Glc^2-^{1}Glc	H	O-Glc	CH_3
G-Re (**6**)	H	O-Glc^2-^{1}Rha	O-Glc	CH_3
N-R1 (**7**)	H	O-Glc^2-^{1}Xyl	O-Glc	CH_3
G-Rb1 (**8**)	Glc^2-^{1}Glc	H	O-Glc^6-^{1}Glc	CH_3

Glc: β-D-glucopyranosyl, Rha: α-L-rhamnopyranosyl, Xyl: β-D-xylopyranosyl

Fig.1. Structures of ginsenosides isolated from processed PN

Table 2. 13C NMR data (pyridin-d5) of compound 1-3

C	20*R*-G-Rh1 (1)	20*R*-G-Rg3 (2)	20*S*-G-Rg3 (3)	C	20*R*-G-Rh1 (1)	20*R*-G-Rg3 (2)	20*S*-G-Rg3 (3)
1	39.3	38.7	39.1	6-*O*-Glc-1′	105.1		
2	27.7	26.2	26.7	2′	75.2		
3	79.3	89.2	88.9	3′	80.0		
4	40.2	39.3	39.7	4′	71.6		
5	61.3	56.0	56.4	5′	78.0		
6	78.4	18.0	18.4	6′	62.9		
7	45.1	34.7	35.2	3-*O*-Glc-1′		104.5	105.1
8	41.0	39.6	40.0	2′		81.5	83.5
9	50.1	49.9	50.4	3′		77.2	78.4
10	39.6	36.5	36.9	4′		70.8	71.6
11	31.9	31.0	31.3	5′		77.7	78.1
12	70.8	70.5	71.0	6′		62.2	62.9
13	48.7	48.5	48.6	Glc-1″		104.5	106.1
14	51.6	51.3	51.7	2″		76.0	77.2
15	31.2	31.2	32.1	3″		77.8	78.2
16	26.5	27.6	26.8	4″		71.2	71.7
17	**50.4**	**50.0**	**54.8**	5″		77.4	78.0
18	17.5	15.4	16.6	6″		62.0	62.7
19	17.6	15.9	15.8				
20	72.9	72.9	72.9				
21	**22.5**	**22.1**	**27.1**				
22	**43.0**	**42.6**	**35.9**				
23	22.5	22.1	23.0				
24	125.9	125.5	126.7				
25	130.7	130.7	130.7				
26	25.7	25.5	25.8				
27	17.3	16.9	17.7				
28	31.6	29.4	28.1				
29	16.3	16.2	16.3				
30	17.0	17.4	17.0				

3.3. Determination of ginsenoside content in raw and processed PN

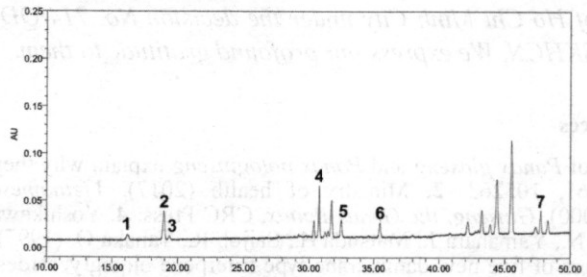


Fig.2. HPLC chromatogram of processed PN. The ginsenosides: N-R1 (**1**), G-Rg1 (**2**), G-Re (**3**), G-Rb1 (**4**), 20*R*-G-Rh1 (**5**), G-Rd (**6**), and 20*S*-G-Rg3 (**7**)

The chromatography of the processed PN, analyzed by HPLC-PDA, is shown in **Fig. 2**. Notably, several new peaks appeared after 40 mins. This suggested a transformation in the ginsenoside composition after the steaming process of PN. The development and validation of the quantification method will be published in a separate study.

Based on the established quantification procedure, the saponin content in the unprocessed and processed PN samples was determined as follows:

Table 3. Contents (n=3) of ginsenosides in unprocessed and processed PN

Sample	Average content (%)							
	N-R1 (1)	G-Rg1 (2)	G-Re (3)	G-Rb1 (4)	G-Rd (6)	20*R*-G-Rh1 (5)	20*S*-G-Rg3 (7)	Total
Raw	1.86	4.39	0.59	4.7	1.03	n.d	n.d	12.57
Processed PN at 120 °C for 4 hours	0.23	1.31	0.11	1.99	0.48	0.83	1.19	6.13

n.d: undetected.

20*R*-G-Rg3 is an isomer that is less soluble in the MeOH than 20*S*-G-Rg3, and the content of the 20(*S*) isomer is significantly higher than the 20(*R*) isomer of G-Rg3 in processed PN. Therefore, this study only analyzes 7 out of the total 8 isolated compounds.

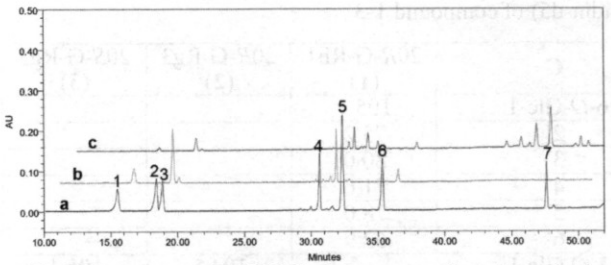


Fig.3. Representative HPLC chromatography of standard mixture (a), raw PN (b), and processed PN (c)

The quantitative analysis results revealed that the major ginsenosides, including N-R1, G-Rg1, G-Re, G-Rd, and G-Rb1, exhibit relatively high concentrations in unprocessed PN, of which 2.5-fold greater than the quality standard outlined in the Vietnamese Pharmacopoeia V [2]. Conversely, the total ginsenoside content, encompassing G-Rg1, G-Re, N-R1, G-Rb1, and G-Rd in processed PN, decreased to one-third compared to raw PN. This reduction is particularly pronounced for protopanaxatriol (PPT) structure ginsenosides such as N-R1, G-Rg1, and G-Re, which exhibit decreased stability at elevated temperatures, leading to significant decomposition during the steaming process. Following the heating process, two new components emerged in processed PN including 20*R*-G-Rh1 and 20*S*-G-Rg3 with a combined content of up to 2%. These ginsenoside components have demonstrated biological activities such as antiplatelet aggregation and anticancer effects. Consequently, the present study provided a detailed ginsenoside profile of processed PN, which is valuable information for the establishment of quality standards for processed PN materials.

4. Conclusions

In conclusion, the extraction of processed PN yielded eight ginsenosides with a purity exceeding 95%, successfully isolated and identified. The result of HPLC analysis revealed a significant reduction in the content of polar ginsenosides, specifically G-Rg1, G-Re, and N-R1, during heat-processing. Conversely, the concentration of less polar ginsenosides such as 20*R*-G-Rh1 and 20*S*-G-Rg3 remarkably increased in steamed PN. Consequently, the heating processing effectively enhances the presence of less polar ginsenosides, which have exhibited greater activity in processed PN, particularly in terms of anticancer properties. The successful isolation of these ginsenosides in substantial quantities may prove invaluable in establishing quality standards for both raw and processed PN materials.

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