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Simultaneous Quantification of Eight Compounds of *Lonicera japonica* by HPLC-DAD

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Abstract – *Lonicera japonica* are recognized in traditional oriental medicine for their notable antiviral, anti-inflammatory, and antibacterial attributes. According to the findings from the previous study, it demonstrates antioxidative and neuroprotective activity. Analytical methods for the simultaneous quantification of eight compounds isolated from *L. japonica*, loganin (**1**), secoxyloganin (**2**), caffeic acid (**3**) rutin (**4**), hyperoside (**5**), lonicerin (**6**), quercetin (**7**) and luteolin (**8**) were established through the utilization of HPLC-DAD. This HPLC analysis was conducted using a Luna C18 column (5 μm, 4.6 mm × 150 mm) at 25°C. The mobile phase, comprising 0.1% trifluoroacetic acid and acetonitrile, was run at a flow rate of 1 mL/min. Validation of the method included assessments for linearity, precision and accuracy. The calibration curve displayed exceptional performance, boasting an r^2 value surpassing 0.9989. Limits of detection (LOD) ranged from 1.11 to 3.18 mg/mL, while limits of quantification (LOQ) spanned from 3.33 to 9.54 mg/mL. In the precision test, both intra- and inter-day assessments revealed minimal relative standard deviations (RSD) values, consistently below 2.91% and 3.48%, respectively. Accuracy test outcomes fell within the 98.22% to 103.47% range, with RSD values consistently under 2.68%. These findings affirm the HPLC-DAD method's high reliability and accuracy in the quantitative analysis of eight compounds in *L. japonica* extract, rendering it well-suited for quality control purposes.
Keywords – *Lonicera japonica*, Lonicerin, HPLC-DAD, Quality control

Introduction

The world is grappling with a burgeoning aging population, largely owing to remarkable advancements in healthcare that have extended the average human lifespan. However, this demographic shift has brought to the forefront a pressing issue: the escalating incidence of neurodegenerative disorders. These conditions are characterized by the relentless and irreversible death of neurons, leading to a decline in both cognitive and motor functions.[1] Notable examples of such disorders include Alzheimer's disease and Parkinson's disease.[2] Although pharmaceutical treatments comprised of chemical compounds exist for these conditions, they often come with limitations and adverse effects. Consequently, there has been a significant surge in research endeavors aimed at identifying natural products with exceptional neuroprotective properties. Therefore, neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, have spurred intensive research into natural products with potential neuroprotective benefits. While promising natural compounds have been identified, the journey from discovery to effective treatment is intricate and necessitates further investigation and development.[3–5]

Since ancient times, herbal medicines have served as valuable resources for preventing and treating various diseases globally.[6] Moreover, herbal medicines are recognized for their relatively low incidence of side effects. In recent years, the growing interest in health has spurred ongoing research on natural products. Consequently, there has been an active pursuit in developing health functional foods using natural products.[7] Nevertheless, the quality of herbal plants can exhibit variability based on factors such as origin, cultivation methods, collection timing, and processing techniques.[8] Recognizing the necessity for more systematic and efficient medicinal herb management, recent efforts have led to the establishment of individual analysis methods for substances utilizing high-performance liquid chromatography (HPLC). However, it

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is crucial to acknowledge that natural products consist of a diverse array of compounds, and their effects can be intricately expressed when utilized as drugs.[9] Many herbal medicines employ individual methods, leading to significant economic and time losses. A more efficient approach to quality control can be realized through the simultaneous analysis of multiple components. This not only streamlines the process but also enhances overall effectiveness.[10]

The flowers and buds of *L. japonica* are well-established in traditional oriental medicine for their notable antiviral, anti-inflammatory, and antibacterial properties, making them widely employed in the treatment of diverse conditions such as upper respiratory tract infections, fever, sores, and swelling.[11,12] The plant is rich in numerous compounds, including alkaloids, cerebrosides, flavonoids, iridoids, polyphenols, and triterpenoid saponins, as reported in various parts of the plant.[13,14] In our previous research, we reported that an 80% MeOH extract of *Lonicera japonica* Thunb. flowers has significant neuroprotective activities against glutamate-induced neurotoxicity in primary cultures of rat cortical cells. And, caffeic acid, lonicerin, kaempferol-3-*O*-rutinoside, quercetin and luteolin had significant neuroprotective activities against glutamate-induced neurotoxicity in primary cultures of rat cortical cells.[15,16]

This study introduced a simultaneous analysis of *L. japonica* using the HPLC-DAD method. The established method underwent validation, and its applicability to *L. japonica* extract for quality control was confirmed.

Materials and Methods

Plant materials – The dried flowers of *L. japonica* were obtained from the medicinal herbs market known as Chunjigayakcho in Seoul, Korea. A voucher specimen (CJ0001M) has been stored in the natural product laboratory at Kangwon National University, Chuncheon, Korea. The solvents used, such as water, methyl alcohol, and acetonitrile, were of HPLC grade and were sourced from J.T. Baker (U.S.A), with trifluoroacetic acid (TFA) purchased from DAE JUNG in Seoul, Korea.

HPLC analysis – The analysis of *L. japonica* solutions was conducted using HPLC-DAD. The HPLC system (Dionex) was equipped with an LPG 3X00 pump, an ACC-3000 auto-sampler, a DAD-3000(RS) diode array UV/VIS detector, and a column oven. Injection and separation of each sample occurred through a Luna C18 column (5 μm, 4.6 mm × 150 mm) at a temperature of 25°C. The mobile phase, consisting of 0.1% trifluoroacetic acid (TFA) in water and acetonitrile, facilitated the process. Sample injections were set at a volume of 10 μL. UV wavelengths were configured at 205, 254, 280, and 330 nm. Chromatograms were acquired at 205 nm to effectively capture all peaks simultaneously.

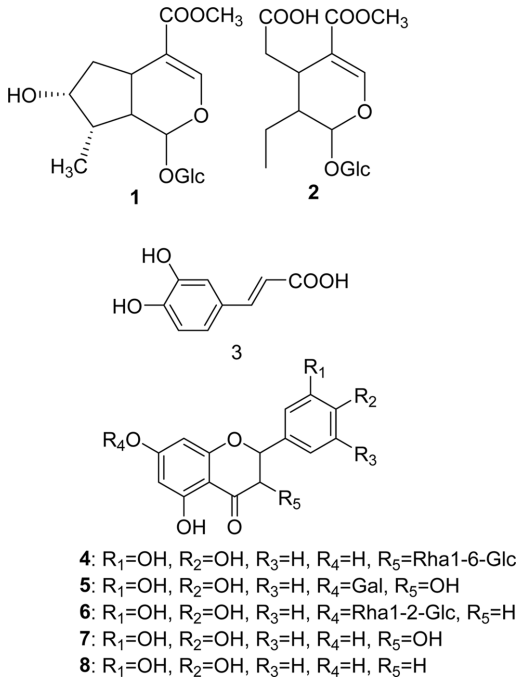

Fig. 1. Chemical structures of compounds **1**–**8** isolated from *L. japonica* extract.

Preparation of standard solutions for HPLC analysis – Standard stock solutions were prepared by dissolving eight isolated compounds loganin (**1**), secoxyloganin (**2**), caffeic acid (**3**), rutin (**4**), hyperoside (**5**), lonicerin (**6**), quercetin (**7**), and luteolin (**8**) in acetonitrile at concentrations of 783.32 μg/mL, 565.21 μg/mL, 656.27 μg/mL, 873.23 μg/mL, 785.43 μg/mL, 561.84 μg/mL, 712.54 μg/mL, and 890.32 μg/mL, respectively (Fig. 1). To prepare working solutions, each standard stock solution was further diluted at 1/2, 1/4, 1/8, and 1/16 ratios in acetonitrile. After filtration through a 0.45 μm pore-sized filter, the resulting working solutions were used in the establishment of the calibration curve.

Preparation of *L. japonica* extract sample – Dried *L. japonica* flowers (100 g) were subjected to extraction using 80% methanol through ultrasonication for 90 minutes, repeated three times. The resulting extracts were concentrated under reduced pressure, forming a powdered substance, which was then dissolved in HPLC grade acetonitrile at a concentration of 20 mg/mL. Following filtration through a 0.45 μm membrane filter, the *L. japonica* sample was introduced into the HPLC system.

Validation of Method

Linearity – Calibration curves were calculated by plotting the peak area against the concentration of individual working solutions. To prepare the working solutions, compounds 1 through 8 were dissolved in methanol at various concentrations: compound **1** (48.96, 97.92, 195.83, 391.66, and 783.32 μg/mL), compound **2** (35.32, 70.65, 141.30, 282.61, and 565.21 μg/mL), compound **3** (41.02, 82.04, 164.07, 328.14, and 656.27 μg/mL), compound **4** (54.58, 109.16, 218.31, 436.62, and 873.23 μg/mL), compound **5** (49.09, 98.18, 196.36, 392.72, and 785.43 μg/mL), compound **6** (35.12, 70.23, 140.46, 280.92, and 561.84 μg/mL), compound **7** (44.54, 89.07, 178.14, 356.27, and 712.54 μg/mL), and compound **8** (55.65, 111.29, 222.58, 445.16, and 890.32 μg/mL). The linear regression equations, represented as $y = ax \pm b$, where x and y denote concentration and peak areas of each compound, were calculated. Linearity was determined using the least squares treatment (R^2). Each working standard concentration was analyzed in triplicate.

Limit of detection (LOD) and limit of quantification (LOQ) – The limit of detection (LOD) was established as the minimum sample concentration, while the limit of quantification (LOQ) was defined as the lowest compound concentration. This determination was based on injecting a diluted standard solution when achieving a signal-to-noise ratio within the range of 3.3 to 10.

Repeatability and precision – The precision of the analytical method was rigorously assessed through intra-day and inter-day injections. Specifically, the intra-day experiment involved three consecutive injections over a span of three days. Both intra-day and inter-day tests were conducted across three distinct concentrations, each of which had been validated through calibration curves. Repeatability and precision were quantified using the relative standard deviation (RSD, %) as the measure of variability.

Accuracy tested by recovery test – The accuracy of the analytical method underwent thorough examination through a recovery study. This involved the addition of precisely measured amounts of compound solutions to the entire *L. japonica* sample. For each of the eight compounds, three different concentrations were employed: compound **1** (48.96, 97.92, and 195.83 μg/mL), compound **2** (35.32, 70.65, and 141.30 μg/mL), compound **3** (41.02, 82.04, and 164.07 μg/mL), compound **4** (54.58, 109.16, and 218.31 μg/mL), compound **5** (49.09, 98.18, and 196.36 μg/mL), compound **6** (35.12, 70.23, and 140.46 μg/mL), compound **7** (44.54, 89.07, and 178.14 μg/mL), and compound **8** (55.65, 111.29, and 222.58 μg/mL). To calculate the recovery percentage, the following equation was employed: (detected amount – original amount)/spiked amount × 100. This methodology allowed for a comprehensive assessment of the accuracy of the method by quantifying the extent to which the detected amounts aligned with the original and spiked amounts.

Sample analysis using established method – The effectiveness of the optimized simultaneous determination method was substantiated through the analysis of the entire *L. japonica* sample. Utilizing the calibration curve established for the eight compounds, we precisely calculated the amounts of each compound within the *L. japonica* extract. Importantly, all eight compounds were successfully detected in the chromatogram, and their respective peaks exhibited no overlap, ensuring accurate and distinct identification in the analytical process.

Statistical analysis – All experiments were meticulously replicated a minimum of three times to ensure the robustness of the results. The data were presented as the mean ± standard deviation (S.D.), and statistical analyses were conducted using one-way analysis of variance (ANOVA) in conjunction with Tukey's test to determine significant differences. Significance levels were denoted as $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. In the context of cell experiments, the data were expressed as a relative percentage, with the control group set at 100% as the reference point. This approach allowed for a comprehensive understanding of the experimental outcomes in relation to the control group.

Results and Discussion

The HPLC experiment was optimized with the aim of achieving enhanced separation efficiency and peak resolution for target compounds within a shorter run time. To attain this objective in *L. japonica*, a series of preliminary tests were conducted to determine effective HPLC-DAD conditions, including the selection of an appropriate Luna C18 column, a reversed-phase column. The chosen mobile phase comprised a multi-step gradient solution system of 0.1% TFA water (A) and acetonitrile (B). The optimal conditions for compound separation were identified as follows: 0–15 min with 10% B, 15–25 min with a gradient of 10–30% B, 25–35 min with a gradient of 30–50% B, and 35–50 min with 50% B, all at a flow rate of 1 mL/min. The gradient employed resulted in the isolation of eight peaks within a 50 minute timeframe. The DAD detector wavelength underwent testing at 205, 254, 280, and 330 nm, and chromatograms were specifically chosen

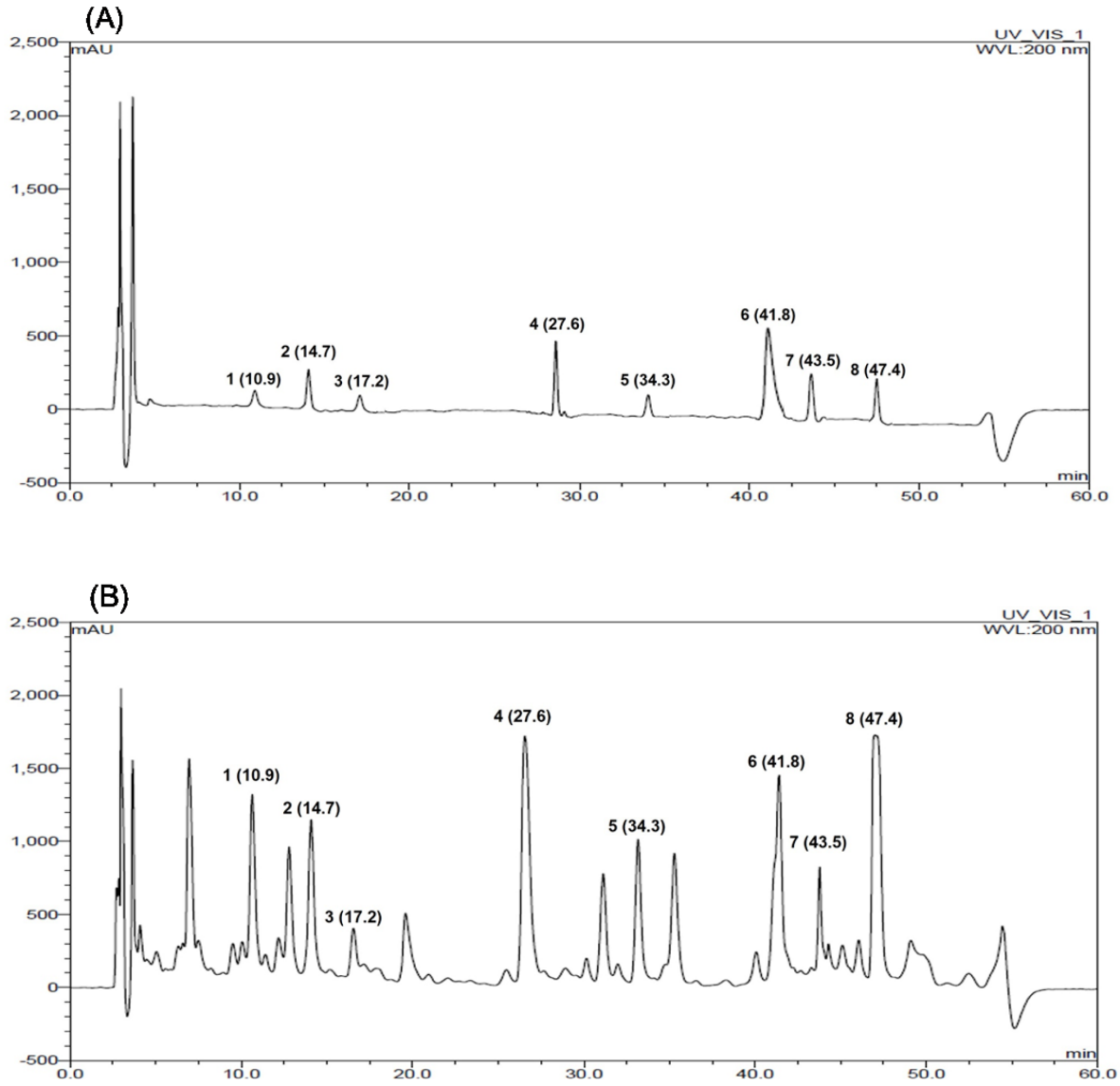

Fig. 2. The HPLC chromatogram of standard mixture (A) and *L. japonica* extract (B).

based on the UV spectrum at 205 nm. Notably, the column temperature exhibited no noteworthy impact on the separation process, prompting the utilization of room temperature. The verification of each compound's peak was ensured through the comparison of retention time and UV spectrum with their respective marker solutions. The chromatograms include all the compounds identified in *L. japonica* (Fig. 2).

To validate this method, experiments were conducted to verify linearity, detection and quantification limits, precision and accuracy, as well as recovery. Regression equations were established through five concentration trials of each standard, conducted in triplicate. In the linear regression equation $y = ax + b$, where x represents the concentration of the marker compounds and y represents the peak area, the slope and intercept of the calibration curve were determined. The high correlation coefficients ($r^2 > 0.9988$) demonstrate excellent linearity of all calibration curves within the specified test ranges. According to this linear regression, the limits of detection (LOD) ranged from 1.11 to 3.18 μg/mL, and the limits of quantification (LOQ) were within the range of 3.33 to 9.54 μg/mL, respectively (Table 1). This implies the method can detect and quantify compounds at minimal amounts.

To assess the repeatability and precision of the method, within-day tests (intra-day analysis, $n = 3$) and intermediate-day tests (inter-day analysis, $n = 3$) were conducted. Intra-day testing was performed three times within a

Table 1. The regression data, LOD and LOQs of eight isolated compounds analyzed by HPLC-DAD

Compound	Regression equation[a]	R^2	LOD (μg/mL)	LOQ (μg/mL)
1	$y = 0.0371x + 0.0116$	0.9989	1.22	3.66
2	$y = 0.11315x + 0.0312$	1	2.15	6.45
3	$y = 0.1643x + 0.0316$	0.9992	2.54	7.62
4	$y = 0.1227x + 0.4621$	0.9993	2.11	6.33
5	$y = 0.0682x + 0.1216$	0.9991	3.18	9.54
6	$y = 0.1243x - 0.0114$	0.9999	2.56	7.68
7	$y = 0.1453x + 0.0193$	0.9995	1.11	3.33
8	$y = 0.1148x + 0.0529$	0.9998	1.16	3.48

[a] y: peak area, x : amount (μg)

Table 2. Intra- and inter- day precision data of eight compounds

Compound	Concentration (μg/mL)	Intra-day			Inter-day		
		Mean (μg/mL)	RSD[a] (%)	Accuracy (%)	Mean (μg/mL)	RSD[a] (%)	Accuracy (%)
1	195.83	199.98 ± 0.23	0.16	102.12	198.20 ± 0.43	0.22	101.21
	97.92	101.03 ± 0.56	0.56	103.19	101.95 ± 0.76	0.75	104.12
	48.96	49.52 ± 1.44	2.91	101.15	49.80 ± 0.54	1.08	101.72
2	141.30	144.58 ± 0.49	0.39	102.32	141.65 ± 0.59	0.42	100.25
	70.65	71.55 ± 0.24	0.36	101.28	70.23 ± 0.54	0.77	99.26
	35.32	35.05 ± 0.46	1.31	99.23	36.25 ± 1.26	3.48	102.64
3	164.07	159.44 ± 0.89	0.59	97.18	166.81 ± 0.64	0.38	101.67
	82.04	83.90 ± 0.67	0.80	102.27	81.41 ± 0.87	1.07	99.23
	41.02	39.45 ± 0.29	0.74	96.17	39.49 ± 0.91	2.30	96.28
4	218.31	225.25 ± 0.43	0.19	103.18	223.09 ± 0.52	0.23	102.19
	109.16	110.57 ± 0.54	0.49	101.29	110.72 ± 0.62	0.56	101.43
	54.58	54.11 ± 0.54	1.00	99.14	55.94 ± 0.91	1.63	102.49
5	196.36	200.60 ± 0.32	0.16	102.16	202.58 ± 0.49	0.24	103.17
	98.18	99.27 ± 0.53	0.53	101.11	99.58 ± 0.33	0.33	101.43
	49.09	49.97 ± 0.21	0.42	101.79	50.35 ± 0.41	0.81	102.57
6	140.46	143.42 ± 0.84	0.59	102.11	143.49 ± 0.53	0.37	102.16
	70.23	71.86 ± 0.44	0.61	102.32	71.22 ± 0.45	0.63	101.41
	35.12	35.89 ± 0.53	1.48	102.16	35.39 ± 0.62	1.75	100.79
7	178.14	182.04 ± 0.72	0.40	102.19	180.49 ± 0.54	0.30	101.32
	89.07	89.21 ± 0.49	0.55	100.16	90.17 ± 0.57	0.63	101.24
	44.54	44.67 ± 0.63	1.41	100.29	44.24 ± 0.72	1.63	99.34
8	222.58	231.02 ± 0.51	0.22	103.79	218.89±0.46	0.21	98.34
	111.29	113.92 ± 0.51	0.48	102.36	113.84 ± 0.48	0.42	102.29
	55.65	56.67 ± 0.28	0.49	101.83	56.85 ± 0.67	1.18	102.16

[a] Relative Standard Deviation

single day, while inter-day testing was carried out on three different days (1st, 3rd, and 5th days). The Relative Standard Deviation (RSD) values for intra-day testing ranged from 0.16% to 2.91%, and for inter-day testing, they ranged from 0.21% to 3.48% (Table 2). These findings indicate that the method exhibits high reproducibility and precision.

The method's accuracy was assessed through a recovery test, where each sample underwent triplicate testing by introducing three distinct concentrations of solutions

Table 3. Recovery of the eight compounds from *L. japonica*

Compound	Spiked (μg/mL)	Found (μg/mL)	RSD (%)	Recovery (%)[*]
1	195.83	198.53 ± 0.83	0.42	101.38
	97.92	100.53 ± 0.57	0.57	102.67
	48.96	50.16 ± 0.99	1.97	102.45
2	141.30	139.24 ± 0.29	0.21	98.54
	70.65	72.20 ± 0.49	0.68	102.19
	35.32	36.52 ± 0.98	2.68	103.41
3	164.07	166.79 ± 1.12	0.67	101.66
	82.04	84.65 ± 0.74	0.87	103.18
	41.02	42.01 ± 0.89	2.12	102.43
4	218.31	225.25 ± 1.65	0.73	103.18
	109.16	111.94 ± 1.11	0.99	102.55
	54.58	55.28 ± 0.45	0.81	101.29
5	196.36	193.40 ± 0.64	0.33	98.49
	98.18	99.27 ± 0.44	0.44	101.11
	49.09	48.93 ± 0.29	0.59	99.68
6	140.46	143.54 ± 0.63	0.44	102.19
	70.23	72.67 ± 0.37	0.51	103.47
	35.12	36.04 ± 0.55	1.53	102.63
7	178.14	179.51 ± 1.19	0.66	100.77
	89.07	90.69 ± 0.51	0.56	101.82
	44.54	45.23 ± 0.78	1.72	101.55
8	222.58	228.46 ± 1.33	0.58	102.64
	111.29	110.91 ± 0.92	0.83	99.66
	55.65	54.66 ± 0.38	0.70	98.22

[a] Recovery (%) = (amount found – original amount) / spiked amount × 100 %

into the comprehensive *L. japonica* standard solution. The mean recovery percentages were determined for each compound, yielding values of 102.67% for compound **1**, 103.41% for compound **2**, 103.18% for compound **3**, 103.18% for compound **4**, 98.49% for compound **5**, 103.47% for compound **6**, 101.82% for compound **7**, and 98.22% for compound **8** (Table 3). Method accuracy was gauged using the relative standard deviation (RSD), with %RSD values for the average recovery being 1.97% for compound **1**, 2.68% for compound **2**, 2.11% for compound **3**, 0.99% for compound **4**, 0.59% for compound **5**, 1.52% for compound **6**, 1.72% for compound **7**, and 0.82% for compound **8** (Table 3). All analyzed compounds demonstrated recovery within the optimal range, and RSDs were consistently low. This data underscores the method's high accuracy. In summary, the comprehensive results affirm the method's suitability for the quantitative analysis of *L. japonica* samples.

The method described earlier proved effective in examining the presence of eight target compounds in *L. japonica*. It is summarized the varying quantities of the tested compounds, with loganin (**1**), rutin (**4**), lonicerin (**6**), and luteolin (**8**) being the dominant components at concentrations of 39.24 mg/g, 53.11 mg/g, 41.23 mg/g, and 87.35 mg/g in the whole sample, respectively (Table 4). The optimized HPLC-DAD conditions allowed for the simultaneous detection of all eight compounds. The developed HPLC-DAD method was employed for the qualitative analysis of compounds in *L. japonica*, enabling the rapid and simultaneous detection of eight compounds

Table 4. Contents of eight compounds in *L. japonica* extract

Compounds	Content (μg/mg)
1	39.24 ± 3.22
2	25.36 ± 2.68
3	12.89 ± 1.22
4	53.11 ± 2.31
5	20.73 ± 2.66
6	41.23 ± 1.21
7	8.25 ± 0.88
8	87.35 ± 2.49

within a 50 minute timeframe. Furthermore, the optimized HPLC-DAD method demonstrated both selectivity and accuracy, as confirmed through validation tests, including assessments of linearity, limits of detection and quantification, repeatability, precision, and accuracy.

In conclusion, a novel method has been employed to expedite the separation of *L. japonica*, resulting in shorter processing times and improved efficiency, leading to heightened peak resolution. To validate this innovative approach, various parameters including linearity, detection and quantification limits, precision, accuracy, and recovery were systematically evaluated. The results demonstrated that the simultaneous analysis method is both highly reproducible and accurate. These findings imply that the qualitative and quantitative analysis method holds potential for enhancing the quality control of *L. japonica* through the simultaneous quantification of eight compounds.

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Conflict of interest statement

The authors have declared that there are no conflicts of interest.

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