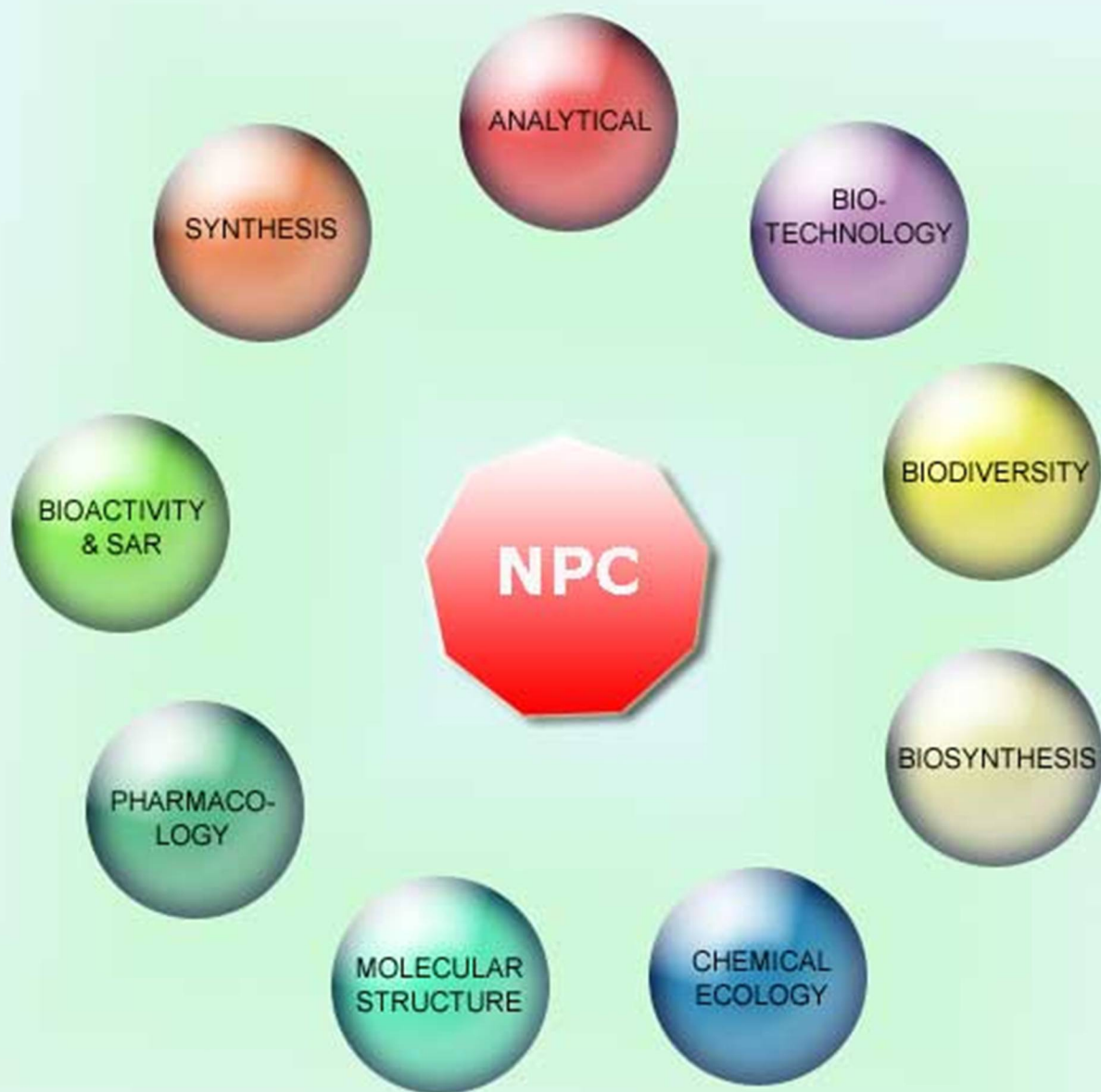


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Classification Using NMR-based Metabolomics of *Sophora flavescens* Grown in Japan and China

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We demonstrate that NMR-based metabolomics can be used to identify the country of growth (Japan or China) of *Sophora flavescens* plants. Principle Component Analysis (PCA) conducted on extracts of *S. flavescens* grown in China provided data distinct from that of extracts of plants grown in Japan. Loading plot analysis showed signals characteristic of Japanese *S. flavescens*. NMR analyses showed these signals to be due to kurarinol (1) and kushenol H (2). These compounds were confirmed by HPLC analysis to be distinctive markers for Japanese *S. flavescens*.

Keywords: NMR, Metabolomics, PCA, *Sophora flavescens*.

The herbal drug “Sophorae Radix” (苦参), derived from the dry roots of *Sophora flavescens* Aiton (Leguminosae), is a common traditional medicine used to combat gastric disturbance, and for its antifebrile, anodyne and anthelmintic activities [1]. Systematic chemical studies revealed that the major constituents of Sophorae Radix are matrine alkaloids and a series of prenylated and lavandulated flavonoids [2, 3]. *S. flavescens* is native to Japan, China, Siberia and the Korean peninsula. To our knowledge, there have been no studies aimed at identifying differences in the components of *S. flavescens* grown in Japan and China.

Metabolomics is defined as the qualitative and quantitative analysis of all metabolites in an organism [4]. Nuclear magnetic resonance (NMR) is a powerful method for such analyses because it allows simultaneous detection of diverse groups of primary and secondary metabolites [5]. The advantage of ¹H NMR spectrometry over other metabolomics techniques is that the signal intensity is only dependent on the molar concentration of each compound in the solution, which allows the direct comparison of the concentrations of all compounds present in the sample [6].

We used ¹H NMR-based metabolic analysis to evaluate differences in the chemical components of Japanese and Chinese *S. flavescens*. Methanolic extracts of the roots were partitioned between diethyl ether and H₂O. The diethyl ether soluble fractions were dissolved in dimethyl sulfoxide (DMSO)-*d*₆ at a concentration of 10 mg/mL for ¹H NMR measurements. Sixteen batches of root of *S. flavescens* grown in different areas of Japan and China were used (Table 1). Since various flavonoids showing structural diversity were isolated and identified from *S. flavescens* in a previous study [3], we here focused on the diethyl ether soluble fraction of the methanolic extracts in order to study a different set of flavonoids.

¹H NMR spectral data were processed using the program ‘Alice2 for Metabolome’ version 5.0 (JEOL). This program can integrate

NMR spectroscopy and multivariate pattern-recognition methods, such as Principle Component Analysis (PCA), into a single interface.

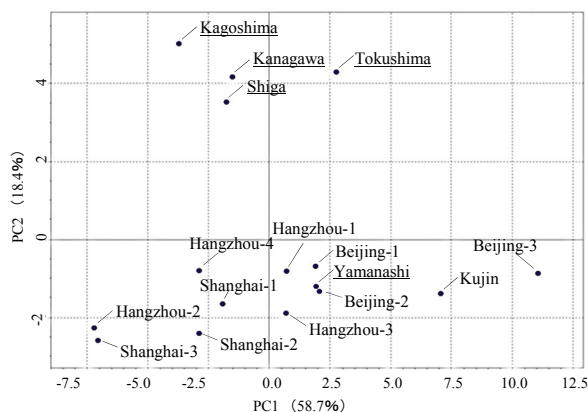
The present study is part of a series of analyses of crude material mixtures from natural resources. We previously reported the categorization of mulberry leaves using ‘Alice2 for Metabolome’ [7]. We have also reported the identification of *Glycyrrhiza* species by direct analysis using real time mass spectrometry (DART-MS) [8], the application of diffusion ordered spectroscopy (DOSY), and relaxation ordered spectroscopy (ROSY) to analyze chalcones from *Angelica keiskei* [9].

Sixteen ¹H NMR spectra were subjected to PCA. All the 348 variables in the bucketed regions (see Experimental Procedures) were equally accounted for in the data sets. PCA models were depicted as score plots and consisted of two synthetic variables: principal component (PC) 1 (the greatest variance of data) and PC2 (the second greatest variance of data, orthogonal with PC1). The PCA score plot of PC1 and PC2 showed a clear independent cluster formation (Figure 1). The scores of PC1, PC2 and PC3 and the residuals were 58.7, 18.4, 6.9 and 16.0%, respectively. The values of PC1 and PC2 were used to identify the origin (country and region) of each batch of roots. The score sum of PC1 and PC2 was 77.1%, which is sufficient to identify the origin of the plant, with the exception of roots originating from Yamanashi in Japan. In the loading plot showing the most relevant variables for the differentiation of the two clusters of PCA score plot, presented in Figure 2, interesting signals at δ 0.92 and δ 0.96 aided classification, as they were clearly observed only in extracts of plants grown in Japan (Figure 3).

To identify the origin of the signals at δ 0.92 and δ 0.96, extracts of Japanese *S. flavescens* were fractionated, the components isolated, and their characteristic signals monitored using ¹H NMR

Table 1: Origins of batches of roots of *S. flavescens*.

No	Sample name	Growing area	Harvest time (Month, Year)
1	Kagoshima	Japan	10.2010
2	Shiga	Japan	10.2010
3	Tokushima	Japan	10.2010
4	Kanagawa	Japan	3.2011
5	Yamanashi	Japan	3.2008
6	Beijin-1	China	10.2010
7	Beijin-2	China	10.2010
8	Beijin-3	China	3.2008
9	Shanghai-1	China	10.2010
10	Shanghai-2	China	10.2010
11	Shanghai-3	China	3.2011
12	Hangzhou-1	China	10.2010
13	Hangzhou-2	China	3.2011
14	Hangzhou-3	China	3.2008
15	Hangzhou-4	China	9.2009
16	Kujin	China	----

**Figure 1:** PCA score plot of PC1-PC2, in which 348 variables were equally accounted for in the data sets. The underlined samples were harvested in Japan.

spectroscopy. Dried root of *S. flavescens* harvested in Sagami-hara, Japan was extracted with methanol. The methanolic extract was dissolved in water, partitioned with diethyl ether, and the diethyl ether fraction chromatographed on a silica gel column eluted with chloroform – methanol mixtures. ^1H NMR analysis of these elutes showed distinctive signals at δ 0.92 and δ 0.96 in the chloroform – methanol (10:1) fraction. This was purified using reversed phase HPLC to obtain compounds **1** and **2**, identified by NMR and MS as kurarinol [10] and kushenol H [11], respectively. The characteristic

signals at δ 0.92 and δ 0.96 were attributed to methyl groups arising from lavandulyl in both compounds by comparing the ^1H NMR spectra of the isolates. The extract of *S. flavescens* harvested in Yamanashi in Japan, which was categorized as belonging to the cluster of Chinese *S. flavescens*, did not show the distinctive signals at δ 0.92 and δ 0.96. Our results indicate that these signals are important in discriminating between Japanese and Chinese *S. flavescens*.

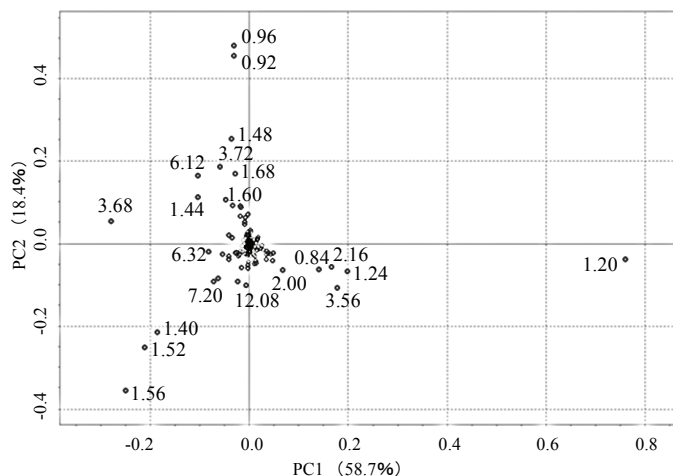
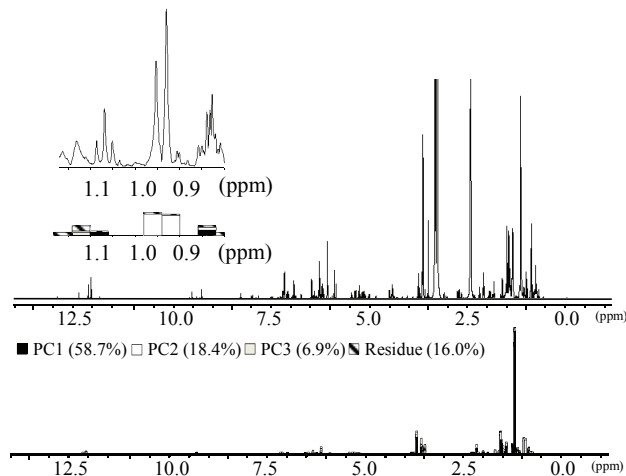
To verify these NMR metabolomics results using another method, we conducted HPLC analysis of Japanese and Chinese *S. flavescens*. Diethyl ether soluble fractions prepared as before were analyzed by reversed phase HPLC. Previously isolated kurarinol and kushenol H were used as authentic samples. Compounds **1** and **2** were selectively detected in extracts of Japanese *S. flavescens*, except for the roots harvested in Yamanashi, as was the case with the NMR metabolomics analysis.

In conclusion, NMR-based metabolomics (^1H NMR spectral analysis coupled with PCA) was used to identify the country (Japan or China) and place of origin of *S. flavescens*. Loading plot analysis showed that compounds **1** and **2** were typical of Japanese *S. flavescens*. This study demonstrated that NMR-based metabolomics can generally differentiate between Japanese and Chinese *S. flavescens*.

Experimental

Sample collection: Sixteen batches of roots of *S. flavescens* were collected from different regions of Japan and China (Table 1). The harvest times of these samples are also listed in Table 1. All the voucher specimens, identified by Professor Yoshiaki Shirataki and Dr Tatsuo Fukuda, were deposited in the laboratory of Pharmacognosy & Natural Medicines, Faculty of Pharmaceutical Science, Josai University, Japan. Sample No. 16 (*Sophorae Radix* 苦参, kujin) grown in Hebei, China, was obtained from UCHIDA WAKANYAKU Ltd (Tokyo, Japan).

Apparatus and chromatographic conditions: A Shimadzu LC20A system was used comprised of a quaternary solvent delivery system, an on-line degasser, a column temperature controller, and a PDA detector coupled with an analytical workstation. A PEGASIL ODS column (Senshu Pak, 5 μm , 150 x 4.6 mm) was used. The sample injection volume was 10 μL , the detection wavelength

**Figure 2:** Loading plot derived from the ^1H NMR spectra of *S. flavescens* harvested from various areas. The black, white, gray and shaded squares correspond to the contribution of PC1, PC2, PC3 and the residuals, respectively.

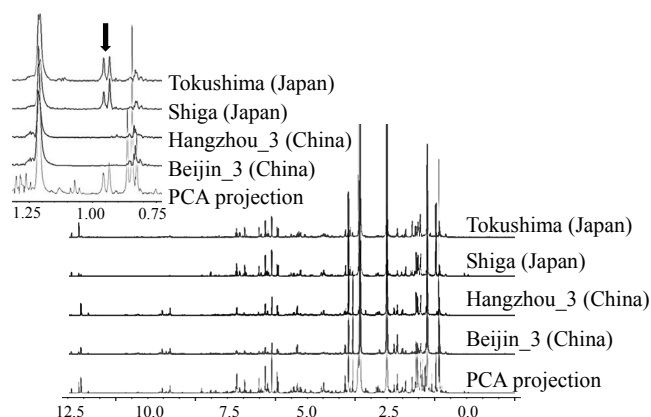


Figure 3: ^1H NMR spectra of the diethyl ether soluble fraction of Japanese and Chinese *S. flavescens*. An arrow indicates characteristic signals for Japanese *S. flavescens*.

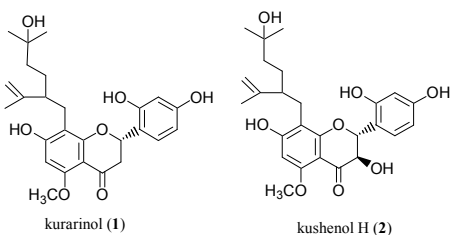


Figure 4: The structures of kurarinol (1) and kushenol H (2).

220 nm, the flow rate 1.0 mL min^{-1} , and the column temperature was maintained at 30°C . Gradient elution was achieved with solvent A (0.1% formic acid in water, v/v) and solvent B (acetonitrile containing 0.1% formic acid, v/v). The gradient program was: 5% solvent B for 3min, 5% to 100% over 15min, then 100% B for 15min.

Preparation of *S. flavescens* root extracts for NMR analysis:

Each of 16 batches of dried root of *S. flavescens* was extracted with methanol for 3 h under reflux. The methanolic extract was

evaporated *in vacuo* and the residue dissolved in water. The aqueous soluble fraction was partitioned with diethyl ether. After evaporation of the diethyl ether, $\text{DMSO-}d_6$ was added to provide a residue concentration of 10 mg/mL. The samples were analyzed using ^1H NMR spectroscopy.

NMR spectroscopy: ^1H NMR spectra were recorded at room temperature on a 400 MHz Agilent-400MR-vnmrs 400 spectrometer (Agilent). Each spectrum consisted of 65,536 complex data points and a spectral width of 6,410.3Hz, obtained by 16 scans with a repetition time of 5.0 sec and a relaxation delay of 1.50 sec per scan. The detection pulse flip angle was set at 45° .

NMR data reduction procedures and pattern recognition analysis:

Each NMR spectrum was regiminted into 375 regions, 0.04 ppm wide, over the range -1.50 to 13.5 ppm. Each segment of the spectral regions (bucket) was integrated. Any integrated regions from 2.40 to 3.45 ppm that contained solvent or water signals were eliminated from the data table, then the total data were reduced to 348 regions. The remaining integral values of each spectrum were normalized over 100 total summed integrals to compensate for any differences in concentration between *S. flavescens* extracts. Spectral processing was performed using ALICE2 for Metabolome version 5.0 software (JEOL).

Isolation and identification of kurarinol (1) and kushenol H (2):

Dried roots of *S. flavescens* (256.3 g), collected at Sagamihara, Japan, were extracted with methanol (300 mL) for 3 h under reflux. This extraction was repeated 3 times. The combined methanolic extract (33.7 g) was suspended in water and fractionated between diethyl ether and water to give the corresponding soluble layers. The diethyl ether layer (1.0 g) was chromatographed on a silica gel 60 (Merck) column using gradient elution with a chloroform-methanol mixture (chloroform: methanol = 100:1 \rightarrow 50:1 \rightarrow 10:1 \rightarrow 1:1) to afford 4 fractions (Fr. A 262.2 mg, Fr. B 113.1 mg, Fr. C 419.1 mg and Fr. D 108.8 mg). Fr. C was further purified using ODS HPLC (Senshu Pak ODS-4151-N, $\phi 10 \times 150 \text{ mm}$, 40% aqueous acetonitrile, isocratic) to give compounds 1 (8.7 mg) and 2 (6.4 mg).

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