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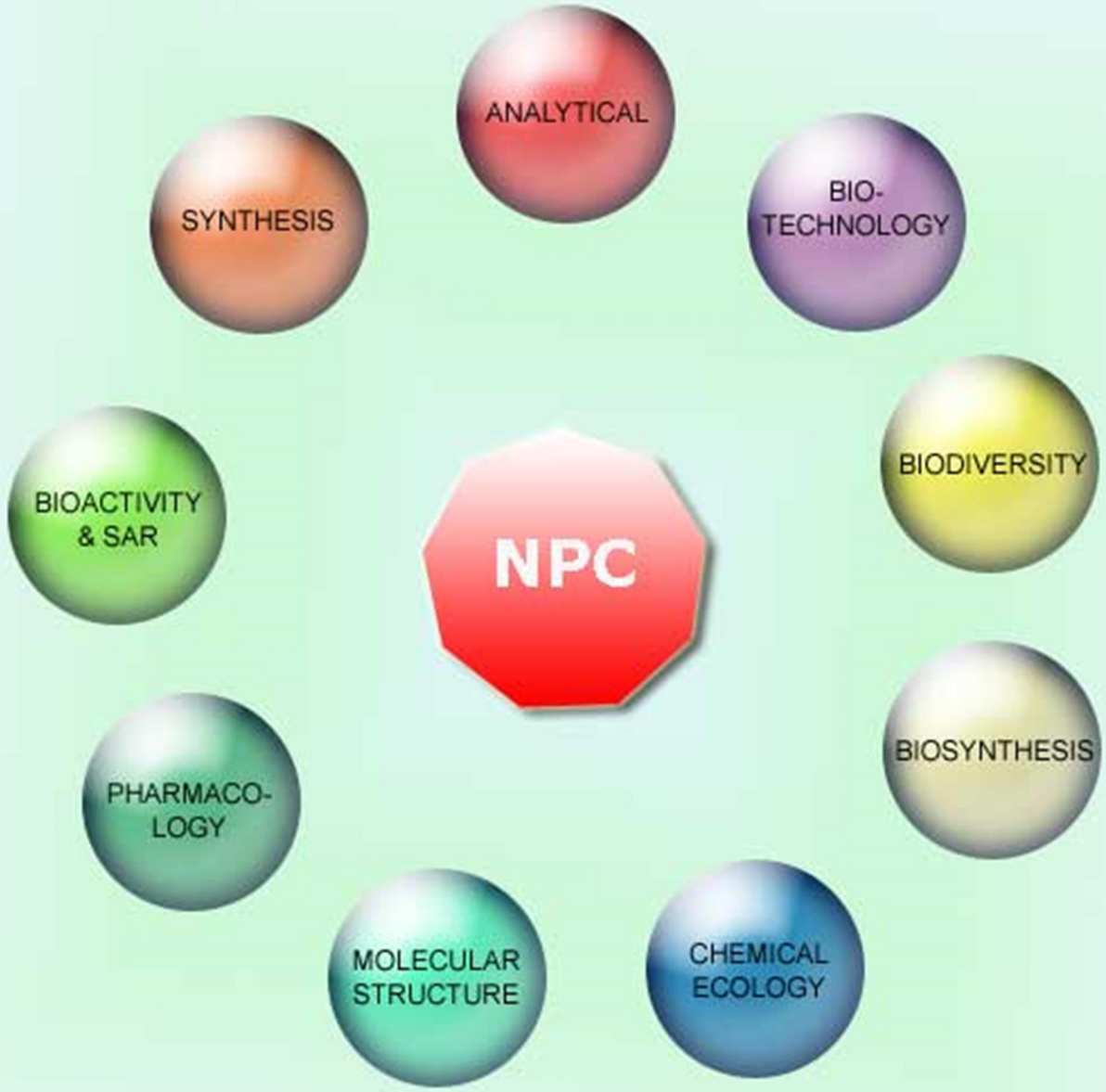

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Identification of a Xanthine Oxidase-inhibitory Component from *Sophora flavescens* using NMR-based Metabolomics

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We demonstrate that NMR-based metabolomics studies can be used to identify xanthine oxidase-inhibitory compounds in the diethyl ether soluble fraction prepared from a methanolic extract of *Sophora flavescens*. Loading plot analysis, accompanied by direct comparison of ^{1}H NMR spectra exhibiting characteristic signals, identified compounds exhibiting inhibitory activity. NMR analysis indicated that these characteristic signals were attributed to flavanones such as sophoraflavanone G and kurarinone. Sophoraflavanone G showed inhibitory activity towards xanthine oxidase in an *in vitro* assay.

Keywords: *Sophora flavescens*, Xanthine oxidase, NMR-based metabolomics, Flavanone.

A traditional drug, the root of *Sophora flavescens* (Sophorae Radix), is used because of its antifebrile, anodyne and anthelmintic activities [1]. Comprehensive chemical studies have revealed that the major active constituents of the root of *S. flavescens* are matrine alkaloids and a series of prenylated flavonoids [2, 3]. In our previous report, we demonstrated that nuclear magnetic resonance (NMR)-based metabolomics could be used to identify the country of growth (Japan or China) of this plant. Principal component analysis (PCA) conducted on extracts of *S. flavescens* grown in China provided data distinct from that of the extracts of plants grown in Japan. Moreover, loading plot analysis showed compounds characteristic of Japanese *S. flavescens* [4].

Metabolic profiling techniques were used to find possible correlations between the metabolic profile of a compound and its biological activity [5, 6]. Loading plot analysis comprises a useful strategy for the identification of biological compounds. NMR is a powerful method for such analysis because it allows the simultaneous detection of diverse groups of primary and secondary metabolites [7]. In addition, NMR can provide much more structural information about metabolites than other analytical techniques such as mass spectrometry (MS).

In this paper, we used ^{1}H NMR-based metabolic analysis to evaluate differences in xanthine oxidase-inhibitory activity of *S. flavescens* roots grown in various geographical locations. Methanolic extracts of the roots were partitioned between diethyl ether and H_2O. The diethyl ether soluble fractions were dissolved in dimethyl sulfoxide (DMSO)-d_6 at a concentration of 10 mg/mL for ^{1}H NMR measurements. These diethyl ether soluble fractions were also examined for inhibitory activity against xanthine oxidase according to a previous report [8, 9]. During the last step of purine metabolism, xanthine oxidase catalyzes the oxidation of xanthine and hypoxanthine into uric acid [10]. Superoxide anion radicals generated by xanthine oxidase are involved in various pathological states such as hepatitis, inflammation, ischemia-reperfusion, carcinogenesis, and aging [11]. Therefore, a xanthine oxidase inhibitor could be a candidate therapeutic agent against not only hyperuricemia, but also lifestyle-related diseases caused by superoxide anion radicals. Twenty batches of *S. flavescens* roots harvested from plants growing in different areas were used in this research (Table 1).

Table 1: Twenty batches of roots of *S. flavescens* and their inhibitory activity against xanthine oxidase.

No.	Sample name	Growing area	Harvest time (Month. Year)	Inhibition (%)
1	Hangzhou-1	China	10.2010	2.8
2	Hangzhou-2	China	3.2011	48.5
3	Hangzhou-3	China	3.2008	79.3
4	Hangzhou-4	China	9.2009	93.7
5	Beijing-1	China	10.2010	1.5
6	Beijing-2	China	10.2010	26.8
7	Beijing-3	China	3.2010	54.9
8	Shanghai-1	China	10.2010	38.1
9	Shanghai-2	China	10.2010	38.7
10	Shanghai-3	China	3.2011	46.7
11	Kujin	China	-----	27.9
12	Yamanashi	Japan	3.2008	62.6
13	Kagoshima	Japan	10.2010	84.0
14	Tokushima	Japan	10.2010	7.9
15	Shiga	Japan	10.2010	30.7
16	Kanagawa	Japan	3.2011	14.7
17	Chiba	Japan	7.2011	38.5
18	Saitama-Ogose	Japan	7.2012	17.6
19	Saitama-Moroyama	Japan	7.2012	98.2
20	Seoul	Korea	8.2011	19.5
21	Allopurinol			70.7

^{1}H 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 PCA into a single interface.

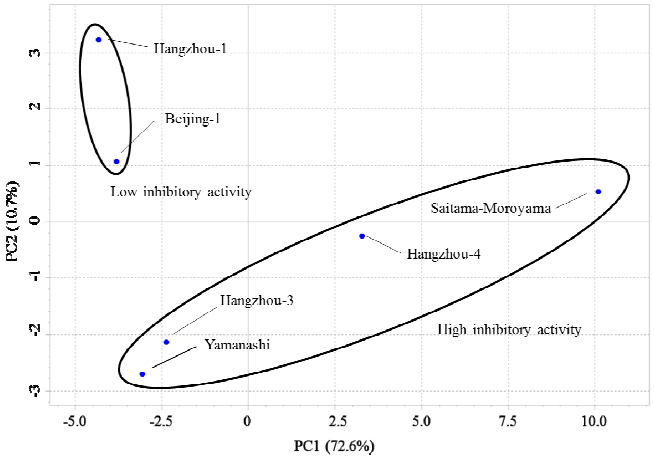

Figure 1: PCA score plot of PC1-PC2, in which 138 variables were equally accounted for in the data sets.

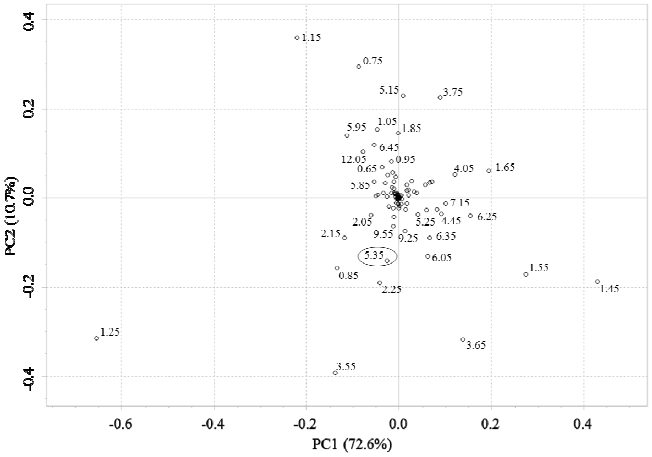

Figure 2: Loading plot derived from the ^{1}H NMR spectra of *S. flavescens* indicating low and high inhibitory activities against xanthine oxidase.

The present study is a part of a series of analyses of crude material mixtures obtained from natural sources. We previously reported the categorization of Sophorae Radix [4] and mulberry leaves by NMR-based metabolomics [12], the identification of *Glycyrrhiza* species using direct analysis by real time mass spectrometry (DART-MS) [13], and the analysis of chalcones from *Angelica keiskei* by applying diffusion ordered spectroscopy (DOSY) and relaxation ordered spectroscopy (ROSY) [14].

We investigated the xanthine oxidase-inhibitory activity of diethyl ether soluble fractions of methanolic extracts from *S. flavescens* harvested from various places. The results in Table 1 show that the fraction listed as "Saitama-Moroyama" prepared from *S. flavescens* grown in Moroyama Town, Saitama prefecture (Japan), showed the strongest inhibitory activity, whereas the fraction listed as "Beijing-1" prepared from a plant grown in Beijing (China) showed very little inhibitory activity (Table 1). A previous paper reported that methanol extracts of *S. flavescens* did not show inhibitory activity against xanthine oxidase [8]. As the results of our present study indicate, the inhibitory activity of extracts from *S. flavescens* towards xanthine oxidase may depend on their place of cultivation and the time of harvest.

To identify the inhibitory active components, the diethyl ether soluble fractions were subjected to NMR-based metabolomics studies. We selected four diethyl ether soluble fractions showing inhibitory activity (Hangzhou-3, Hangzhou-4, Saitama-Moroyama and Yamanashi) and two that did not (Beijing-1 and Hangzhou-1). The ^{1}H NMR spectra were subjected to PCA. All 138 variables in the bucketed regions (see Experimental Procedures) were equally accounted for in the data sets. The PCA score plot of principal component (PC) 1 (the greatest variance in the data) and PC 2 (the second greatest variance in the data, orthogonal with PC1) showed clear independent cluster formation (Figure 1). The scores of PC1, PC2, PC3 and the residuals were 72.6, 10.7, 9.3 and 7.3%, respectively. The values of PC1 and PC2 were used to identify the inhibitory components against xanthine oxidase in each batch of roots. The score sum of PC1 and PC2 was 83.1%, which was sufficient to identify active components. Loading plot analysis was proposed for identifying potential components exhibiting inhibitory activity towards xanthine oxidase in *S. flavescens* extracts.

As shown in Figure 2, loading plot analysis showed the most relevant variables for the two clusters in the PCA score plot. We have searched for characteristic signals using data present in Figure 2, that appeared only in diethyl ether soluble fractions showing high inhibitory activity against xanthine oxidase. Direct comparison of their ^{1}H NMR spectra was conducted based on the results of loading plot analysis.

The signal at δ 5.35 (circled in Figure 2) was observed clearly in ^{1}H NMR spectra of inhibitory active fractions (Figure 3). The signal at δ 2.80 was also detected selectively in ^{1}H NMR spectra of active fractions. This signal appeared near the DMSO signal (δ 2.49). The integrated region from 2.30-3.50 ppm contained solvent signals that were removed for PCA. Thus, the δ 2.80 signal was not detected in the loading plot. The signals indicated with arrows in Figure 3 are characteristic of H-2 and H-3 in flavanones, as already reported [15].

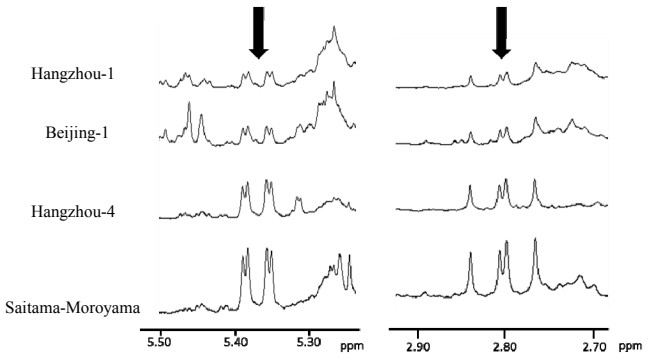

Figure 3: ^{1}H NMR spectra of the diethyl ether soluble fraction of *S. flavescens*. Arrows indicate signals characteristic of the flavanone structure. Hangzhou-4 and Saitama-Moroyama showed high inhibitory activity against xanthine oxidase.

In previous studies several flavanones, for example, sophoraflavanone G and kurarinone (Figure 4), were isolated from *S. flavescens* [15].

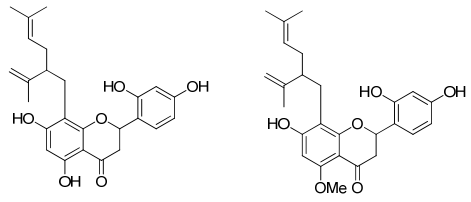

Figure 4: Structure of sophoraflavanone G and kurarinone.

Table 2: Xanthine oxidase inhibitory activities of flavanones.

	Inhibition (%)		
	1μM	10μM	100μM
Sophoraflavanone G	25.4	35.6	53.8
Kurarinone	0	0	36.4
Allopurinol	69.4	—	—

Thus, sohoraflavanone G and kurarinone were examined for their inhibitory activity against xanthine oxidase. As shown in Table 2, sophoraflavanone G provided 53.8% inhibition (100 μM).

In conclusion, we have demonstrated that analysis of the component pattern of *S. flavescens* is a useful tool for finding active compounds that inhibit xanthine oxidase.

Experimental

Sample collection: Twenty batches of roots of *S. flavescens* were collected from different regions (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. 11 (Sophorae Radix, Kujin) was purchased from UCHIDA WAKANYAKU Ltd (Tokyo, Japan).

Preparation of* S. flavescens *root extracts for NMR analysis: Each of 20 batches of dried root of *S. flavescens* was extracted in 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 diethyl ether, DMSO-d_6 was added to provide a residue concentration of 10 mg/mL. The samples were analyzed using ^{1}H NMR spectroscopy.

NMR spectroscopy: ^{1}H 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 6,410.3 Hz, 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^o.

NMR data reduction procedures and pattern recognition analysis: Each NMR spectrum was regimented into 150 regions, 0.1 ppm wide, over the range -1.50 to 13.5 ppm. Each segment of the spectral regions (bucket) was integrated. Any integrated regions from 2.30 to 3.50 ppm that contained solvent and water signals were eliminated from the data table, then the total data were reduced to 138 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).

Assay of inhibitory activity towards xanthine oxidase: Xanthine oxidase inhibitory activity was assayed under aerobic conditions, based on the procedure reported by Noro *et al* [9]. Assay mixtures consisting of 10 μL of test sample solution, 230 μL of 70 mM phosphate buffer (pH 7.5), and 85 μL of enzyme solution (0.01 units/mL in 70 mM phosphate buffer, pH 7.5) were prepared. After preincubation at 25^{o}C for 15 min, the reaction was initiated by the addition of 170 μL of substrate solution (150 μM xanthine in 70 mM phosphate buffer, pH 7.5). The assay mixture was incubated at 25^{o}C for 30 min. The reaction was stopped by adding 70 μL of 1N HCl, and the generated uric acid was measured by HPLC analysis. A blank control was incubated without the enzyme solution. After the addition of 1N HCl to stop the reaction, the enzyme solution was added. Xanthine oxidase inhibitory activity was expressed as the percent inhibition, calculated as (1-B/A)×100, where A and B are the activities of the enzyme without and with test sample, respectively. The crude extracts were dissolved in DMSO to give final concentrations of 50 μg/mL. Allopurinol, a known inhibitor of xanthine oxidase, was dissolved in phosphate buffer at a final concentration of 1 μM. Experiments were carried out in duplicate.

Apparatus and HPLC analysis conditions: A Shimadzu LC20A system comprised 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 SP100AQ column (Senshu Pak, 5 μm, 150×4.6 mm) was used. The sample injection volume was 10 μL. The detection wavelength was 254 nm, the flow rate was 1.0 mL min^{-1}, and the column temperature was maintained at 30^{o}C. Gradient elution was achieved with solvent A (20 mM phosphate buffer) and solvent B (60% aqueous methanol). The gradient program was: 0% solvent B for 5 min, 0% to 25% over 15 min, further increased from 25% to 100% over 1 min, and then 100% B for 10 min.

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References

[1] Shirataki Y, Motohashi N. (**2009**) Flavonoids in *Sophora* species. In *Bioactive Heterocycles VII: Flavonoids and Anthocyanins in Plants, and Latest Bioactive Heterocycles II (Topics in Heterocyclic Chemistry)*. Vol. 16, Motohashi M. (Ed.). Springer, Heidelberg, Germany, 41-91.

[2] Ueno A, Morinaga K, Fukushima S, IItaka Y, Koiso Y, Okuda S. (**1975**) Studies on lupin alkaloid. VI. Isolation and structure of (+)-isomatrine. *Chemical and Pharmaceutical Bulletin*, ***23***, 2560-2566.

[3] Hatayama K, Komatsu M. (**1971**) Studies on the constituents of *Sophora* species. V. Constituents of the root of *Sophora angustifolia* Sieb. et Zucc. (2). *Chemical and Pharmaceutical Bulletin*, ***19***, 2126-2131.

[4] Suzuki R, Ikeda Y, Yamamoto A, Saima T, Fujita T, Fukuda T, Fukuda E, Baba M, Okada Y, Shirataki Y. (**2012**) Classification using NMR-based metabolomics of *Sophora flavescens* growing in Japan and China. *Natural Product Communications*, ***7***, 1453-1455.

[5] Fujimura Y, Kurihara K, Ida M, Kosaka R, Miura D, Wariishi H, Maeda-Yamamoto M, Nesumi A, Saito T, Kanda T, Yamada K, Tachibana H. (**2011**) Metabolomics-driven nutraceutical evaluation of diverse green tea cultivars. *PLoS ONE*, ***6***, e23426.

[6] Ohno A, Oka K, Sakuma C, Okuda H, Fukuhara K. (**2011**) Characterization of tea cultivated at four different altitudes using ^{1}H NMR analysis coupled with multivariate statistics. *Journal of Agricultural and Food Chemistry*, ***59***, 5181-5187.

[7] Verpoorte R, Choi HY, Mustafa RN, Kim KH. (**2008**) Metabolomics: back to basics. *Phytochemistry Reviews*, ***7***, 525-537.

[8] Nguyen MT, Awale S, Tezuka Y, Tran QL, Watanabe H, Kadota S. (**2004**) Xanthine oxidase inhibitory activity of Vietnamese medicinal plants. *Biological and Pharmaceutical Bulletin*, ***27***, 1414-1421.

[9] Noro T, Oda Y, Miyase T, Ueno A, Fukushima S. (**1983**) Inhibitors of xanthine oxidase from the flowers and buds of *Daphne genkwa*. *Chemical and Pharmaceutical Bulletin*, ***31***, 3984-3987.

[10] Massey V, Brumby PE, Komai H. (**1969**) Studies on milk xanthine oxidase. Some spectral and kinetic properties. *The Journal of Biological Chemistry*, ***244***, 1682-1691.
[11] Cos P, Ying L, Calomme M, Hu JP, Cimanga K, Van Poel B, Pieters L, Vlietinck AJ, Vanden Berghe D. (**1998**) Structure−activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. *Journal of Natural Products*, ***61***, 71-76.
[12] Fukuda E, Yoshida M, Baba M, Uesawa Y, Suzuki R, Kamo O, Tsubono K, Arifuku K, Yatsunami K, Okada Y. (**2011**) Application to classification of mulberry leaves using multivariate analysis of proton NMR metabolomic data. *Natural Product Communications*, ***6***, 1621-1625.
[13] Fukuda E, Baba M, Uesawa Y, Kamo O, Arifuku K, Tsubono K, Okada Y. (**2012**) Application of mixture analysis to crude materials from natural resources (III): NMR spectral studies to analyze chalcones from *Angelica keiskei*. *Natural Product Communications*, *7*, 21-23.
[14] Fukuda E, Baba M, Iwasaki N, Uesawa Y, Arifuku K, Kamo O, Tsubono K, Okada Y. (**2010**) Identification of *Glycyrrhiza* species by direct analysis in real time mass spectrometry. *Natural Product Communications*, ***5***, 1755-1758.
[15] Yamahara J, Kobayashi G, Iwamoto M, Chisaka T, Fujimura H, Takaishi Y, Yoshida M, Tomimatsu T, Tamai Y. (**1990**) Vasodilatory active principles of *Sophora flavescens* root. *Journal of Ethnopharmacology*, ***29***, 79-85.

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