# Determination of salvinorin A and salvinorin B in *Salvia divinorum*-related products circulated in Japan

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## ABSTRACT

Two major salvinorins, salvinorin A (SalA) and salvinorin B (SalB), in three *Salvia divinorum* dried leaf products and nine of its "concentrated extract" products circulated in Japan were determined. These ingredients were extracted twice with acetonitrile and decolored with graphite carbon powder. SalA and SalB were confirmed by liquid chromatography–tandem mass spectrometry in product ion scan mode, and quantified by high-performance liquid chromatography with UV detection (for SalA) and by mass spectrometry in single ion monitoring mode (for SalB). The SalA/SalB contents ($\mu$g/mg) were in the range of 3.2–5.0/0.10–0.17 in the dried leaf products and 4.1–38.9/0.26–2.42 in the "concentrated extract" products. These findings would be useful for analysis of *S. divinorum*-related products circulated in the drug market.

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## 1. Introduction

*Salvia divinorum* (Lamiaceae), which is native to Oaxaca in Mexico, has been used for traditional medicine and spiritual practices because of its hallucinogenic properties [1]. In recent years, this plant has been widely used as a herbal dietary supplement or a herbal hallucinogen due to internet trading [2]. Singh has reported a psychiatric emergency case with paranoia, déjà vu, and blunted affect due to drug's abuse [3]. This plant has been circulated as not only whole or pulverized leaf but also as "concentrated extract" products. The buying and selling of *S. divinorum* and its active ingredients have been controlled in several countries, including Japan [4].

Several neoclerodane diterpenoids (salvinorins A–I, divinatorins A–E, and salvidivins A–D) were isolated from *S. divinorum* [5–11]. In these diterpenoids, salvinorin A (SalA, Fig. 1) is mainly involved in the psychiatric activity. This compound is a potent and selective κ-opioid receptor agonist in *in vitro* [12]. Salvinorin B (SalB, Fig. 1), a deacetylated form of SalA, is another important constituent, despite the deficiency of obviously pharmacological

activity, because this compound is presumed to be a major metabolite of SalA in rhesus monkey blood [13].

There have been several reports of chemical analysis of SalA in *S. divinorum* and its related products. For example, Siebert analyzed the chloroform extract of the fresh leaf by thin layer chromatography [14]. In the method of Giroud et al., the ground fresh leaf in saturated ammonium buffer (pH 9.5) was extracted by chloroform–2-propanol (9:1, v/v), and the extract was analyzed by gas chromatography–mass spectrometry (GC–MS) after acetyl-derivatization [15]. The same authors analyzed methanol extract of the dried leaf by GC–MS without derivatization [15]. Gruber et al. [16] and Wolowich et al. [17] analyzed the respective chloroform extracts of the lyophilized leaf and the "concentrated extract" product by high-performance liquid chromatography (HPLC) with UV detection. Medana et al. extracted the leaf by acetonitrile–water (1:1, v/v), and the extract was analyzed by liquid chromatography–tandem mass spectrometry (LC–MS/MS) [4].

The extraction procedures shown in the aforementioned References ([14–17,4]) were not fully examined. For example, selection of extraction solvent, extraction efficiency, and how to remove pigments were not examined. Moreover, SalA concentrations in the "concentrated extract" products have been reported in only one study [17].

The aims of this study are (i) to examine the analytical method of SalA and SalB in the *S. divinorum*-related products and (ii) to analyze these products circulated in Japan. The present method

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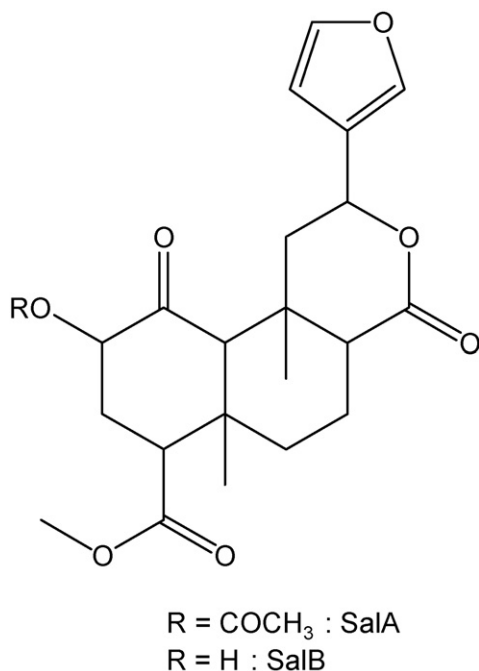*E-mail address:* tujikawa@nrips.go.jp (K. Tsujikawa).

**Fig. 1.** Chemical structures of SalA and SalB.

utilized acetonitrile extraction followed by graphite carbon powder (GCP) treatment. This extraction procedure gave good recovery of SalA and SalB. Moreover, this procedure was superior to the previously reported methods in the point of the cleanness of the extract. By this method, we analyzed SalA and SalB in the *S. divinorum*-related products circulated in the Japanese drug market. SalA and SalB were confirmed by LC–MS/MS, and quantified by HPLC with UV detection (for SalA) and liquid chromatography–mass spectrometry (LC–MS) in single ion monitoring (SIM) mode (for SalB).

## 2. Experimental

### 2.1. Samples and chemicals

Twelve samples (two dried whole-leaf products, one dried pulverized-leaf product, and nine "concentrated extract" products) sold as *S. divinorum*-related products were used in this study. These samples were obtained via the internet in Japan. As for the dried leaf products, their morphologic features observed under a scanning electron microscope were almost fully in accordance with the description in Ref. [14]. On the package of the "concentrated extract" product, its "concentration ratio" was described in the range between 2× and 25×. This ratio was afterward called as "labeled potency".

Garden species of *Salvia* were purchased at gardening shops in Japan. These species used in this study were as follows: *Salvia elegans* "Scarlet Pineapple", *Salvia forskaohlei*, *Salvia* "Indigo Spires", *Salvia glutinosa*, *Salvia guaranitica*, *Salvia blepharophylla*, *Salvia mexicana* "Limelight", *Salvia buchananii*, *Salvia splendens*, and *Salvia farinacea*.

SalA was isolated from *S. divinorum* leaves as previously described with several modifications [18]. SalB was prepared from SalA according to a previously reported method [18]. These two compounds were identified by [1]H-nuclear magnetic resonance and electron ionization mass spectrometry. The purities were confirmed to be 97.6% (for SalA) and 98.3% (for SalB) by HPLC with UV detection. The major impurity in SalA was SalB, and that in SalB was SalA.

GCP was obtained from Wako Pure Chemical (Osaka, Japan). Acetonitrile (HPLC grade), methanol (HPLC grade), acetone (residual PCB grade), and chloroform (residual PCB grade) were obtained from Wako Pure chemical.

### 2.2. Standard solutions

Standard solutions were prepared regarding the purities of SalA and SalB as 100%. SalA (1 mg/mL) and SalB (0.25 mg/mL) solutions in acetonitrile were prepared as stock solutions. Their working standard solutions were prepared from the stock solutions by sequential dilution with acetonitrile. Concentrations of the

working standard solutions were as follows: 5–200 μg/mL for SalA and 0.5–50 μg/mL for SalB. These solutions were stored at 4 °C.

### 2.3. Extraction procedure

The whole-leaf samples were ground to a fine powder in a mortar before extraction. The other samples (a dried pulverized-leaf product and "concentrated extract" products) were supplied for extraction without pulverization.

Two milliliters of acetonitrile was added to 50 mg of the sample in a test tube, followed by shaking for 1 min and ultrasonication for 5 min. After centrifugation at 3000 rpm for 3 min, the supernatant was transferred to a volumetric flask. The residue was extracted once more with 2 mL of acetonitrile, shaken, ultrasonicated, centrifuged, and transferred in the same way. The combined extracts were made up to 5 mL with acetonitrile. In addition, most of the combined extracts originated from the "concentrated extract" products were appropriately diluted by acetonitrile. This dilution was carried out by that 1 mL of the combined extracts was transferred into another test tube, then 1, 3, or 9 mL of acetonitrile was added into this test tube and mixed well (respective dilution factor: 2, 4, and 10). The dilution factor selected for the each extract was the minimum necessary one to decolor it by the after-mentioned GCP treatment.

One hundred and sixty milligrams of GCP were added to 1 mL of these extracts (after dilution if necessary), followed by shaking for 1 min and centrifugation at 3000 rpm for 1 min. The upper layer was transferred to a separate vial. An equivalent volume of distilled water was added to this extract, then filtered through a 0.45-μm membrane (UNIFILTER, Whatman, Clifton, NJ, USA), and a 20 μL aliquot was used for the confirmation and quantitative analysis.

### 2.4. Quantitative analysis

SalA was quantified by HPLC with UV detection (210 nm) by an external standard method. A calibration curve was constructed by injection of working standard solutions diluted by an equivalent volume of distilled water. The injection amounts were 50, 100, 200, 500, 1000, and 2000 ng, which correspond to 0.5, 1, 2, 5, 10, and 20 μg/mg sample (in the case of no dilution). SalB was quantified by LC–MS in SIM mode at $m/z$ 389 by a standard addition method. The spiked amounts were 0, 5, 10, 20, and 50 ng/20 μL of the injection solution, which correspond to 0, 0.05, 0.1, 0.2, and 0.5 μg/mg sample (in the case of no dilution).

### 2.5. Chromatographic and mass spectrometric conditions

Chromatographic separation was performed with a Mightysil RP-18 column (2.0 mm × 150 mm, 5 μm, Kanto Chemical, Tokyo, Japan) maintained at 40 °C. The mobile phase was 0.05% formic acid in water and acetonitrile with a constant flow rate of 0.2 mL/min. The acetonitrile percentages were 0–1 min, 40%; 1–16 min, linearly from 40% to 70%; 16–18 min, linearly from 70% to 100%; 18–21 min, 100%; 21–35 min (re-equilibration step), 40%.

The confirmation analysis was carried out using a Thermo Fisher Scientific Accela series HPLC system (San Jose, CA, USA) and a Thermo Fisher Scientific LCQ Fleet ion trap mass spectrometer with an electrospray ionization (ESI) interface in the positive mode. MS data were collected in product ion scan mode. The precursor ions, collision energy, and scan ranges were $m/z$ 373, 25%, $m/z$ 100–400 for SalA and $m/z$ 391, 25%, $m/z$ 115–500 for SalB. Product ions used for identification were $m/z$ 313, 341, and 355 for SalA and $m/z$ 373, 355, and 259 for SalB. The main mass conditions were spray voltage (5 kV), capillary voltage (50 V), capillary temperature (250 °C), sheath gas flow rate (60 arb), auxiliary gas flow rate (10 arb), and sweep gas flow rate (10 arb).

Quantitative analysis was carried out using a Waters 2690 series HPLC system (Milford, MA, USA) equipped with a Waters 2996 diode array detector and a Waters ZQ single-quadrupole mass spectrometer with an ESI interface in the negative mode. MS data were collected in SIM mode at $m/z$ 389. The main mass conditions were cone voltage (60 V), capillary voltage (4500 V), cone gas flow (50 L/h), desolvation gas flow (350 L/h), and desolvation temperature (300 °C).

## 3. Results and discussion

### 3.1. Selection of an extraction solvent

Selection of an extraction solvent was based not only on extraction efficiency but also on cleanness of the extract, because pigments such as chlorophylls extracted with the SalA/SalB would cause pollution of an HPLC column and an MS system. In the extraction solvents used in the previous reports, methanol [15], acetone [18], and acetonitrile/water (1:1, v/v) [4] were directly injectable solvents to a reverse-phase HPLC system. However, not
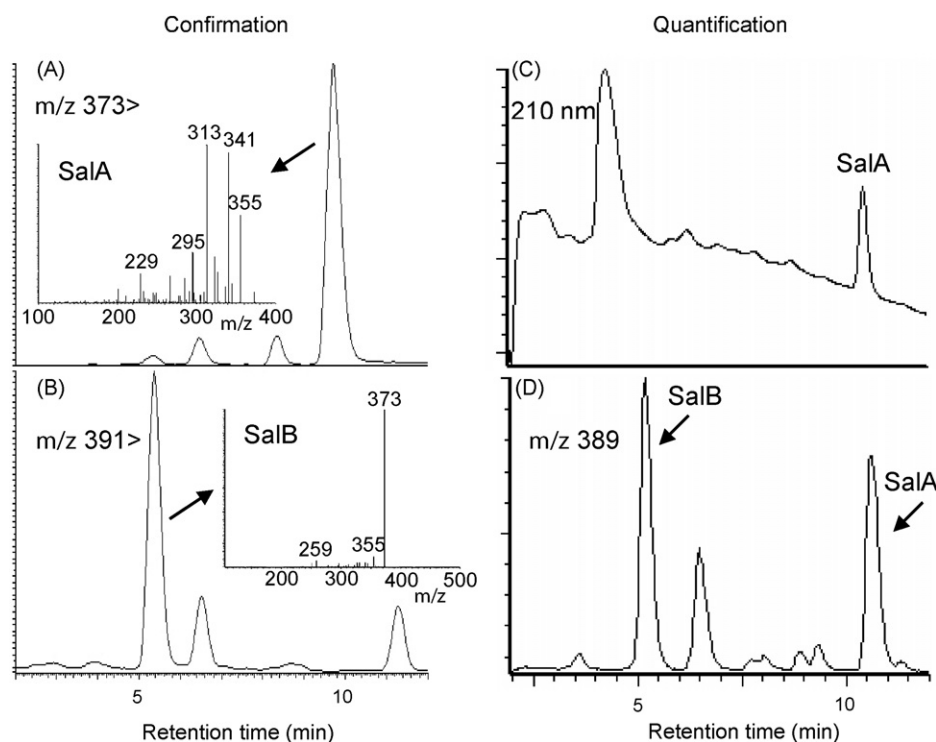
**Fig. 2.** HPLC analysis of the extract of a dried *S. divinorum* leaf product (sample #1). (A) Total ion chromatogram in the product ion scan mode using *m/z* 373 and product ion spectrum at *m/z* 373 for the 9.7-min peak. (B) Total ion chromatogram in the product ion scan mode using *m/z* 391 and product ion spectrum at *m/z* 391 for the 5.4-min peak. (C) Chromatogram at 210 nm. (D) SIM chromatogram at *m/z* 389.

these solvents but acetonitrile was selected as an extraction solvent for the following reasons:

(i) Acetonitrile gave a clearer extract than these solvents.
(ii) Extraction efficiency of acetonitrile was approximately equivalent to those of these solvents.

### 3.2. HPLC analysis of SalA and SalB

#### 3.2.1. Confirmation analysis

Fig. 2(A and B) shows typical MS/MS chromatograms and the MS/MS spectra obtained from a *S. divinorum* sample (sample #1, dried *S. divinorum* leaf product). The MS/MS spectra obtained from peaks eluted at 9.7 min and 5.4 min matched with those of SalA and SalB, thus confirming the presence of SalA and SalB.

#### 3.2.2. Quantitative analysis

Quantification of SalA was performed by UV detection, as the sensitivity of UV detection is more stable than that of MS detection because the latter may suffer from phenomena such as ion suppression and contamination of the sample cone, causing a deterioration of sensitivity. Although UV detection is usually less sensitive than MS, the SalA levels in the samples were sufficient to be determined by UV detection. In contrast, SalB was quantified by LC–MS in SIM mode because the SalB content in the samples was insufficient to be detected by UV detection in a preliminary study.

Fig. 2(C and D) shows typical UV and SIM chromatograms obtained from a *S. divinorum* sample (sample #1, dried *S. divinorum* leaf product), respectively. The peaks for SalA and SalB had retention times of 10.5 min and 5.2 min, respectively. These peaks were not detected in the extract of the garden species of *Salvia*.

### 3.3. Extraction efficiency of SalA/SalB

In a preliminary study, SalA/SalB in the samples was extracted four times with acetonitrile to investigate the extraction efficiency. Nearly all SalA and SalB were recovered from the samples by two extractions with acetonitrile. Hereafter, two-time extraction was used for the subsequent analysis of SalA/SalB.

### 3.4. Removing pigments by GCP treatment

Pigments such as chlorophylls in the extract may interfere with the chromatographic analysis. GCP is often used to remove the pigments in the field of residual pesticide analysis. Decoloring effects and loss of SalA/SalB by GCP treatment were investigated.

Adding 160 mg of GCP to 1 mL of the extract was sufficient to remove the pigments in the extract originated from the *S. divinorum* leaf samples without dilution. However, this GCP amount was insufficient for decoloring the extract originating from most of the "concentrated extract" products. In such cases, the extract was successfully decolored by GCP treatment after the appropriate dilution (maximum dilution factor: 10) with acetonitrile.

The recoveries of SalA/SalB during GCP treatment were investigated by adding 160 mg of GCP to 1 mL of their solution.

**Table 1**
Precision of SalA concentration (μg/mg) evaluated using three *S. divinorum*-related products

| Sample | Intra-assay (*n* = 5) | Inter-assay (*n* = 3) |
| --- | --- | --- |
| A | 4.8 ± 0.1 | 4.9 ± 0.2 |
| B | 3.0 ± 0.1 | 3.0 ± 0.2 |
| C | 9.5 ± 0.8 | 11.1 ± 1.4 |

Each data represents mean ± S.D.

**Table 2**
SalA/SalB contents in the S. divinorum-related products

| Sample no. | [a]Labeled potency | [b]Dilution factor | Content (μg/mg) | | [c]Standardized SalA content (μg/mg) |
|---|---|---|---|---|---|
| | | | SalA | SalB | |
| Dried leaf products | | | | | |
| 1 | 1× | 1 | 5.0 | 0.17 | 5.0 |
| 2 | 1× | 1 | 3.2 | 0.1 | 3.2 |
| 3 | [a]1× | 1 | 3.3 | 0.17 | 3.3 |
| "Concentrated extract" products | | | | | |
| 4 | 2× | 2 | 4.1 | 0.27 | 2.1 |
| 5 | 7× | 2 | 6.6 | 0.26 | 0.9 |
| 6 | 10× | 1 | 11.7 | 0.32 | 1.2 |
| 7 | 10× | 2 | 10.0 | 0.57 | 1.0 |
| 8 | 10× | 2 | 12.7 | 0.77 | 1.3 |
| 9 | 14× | 4 | 15.5 | 0.64 | 1.1 |
| 10 | 20× | 4 | 27.3 | 1.8 | 1.4 |
| 11 | 20× | 4 | 20.5 | 1.3 | 1.0 |
| 12 | 25× | 10 | 38.9 | 2.4 | 1.6 |

[a] Labeled potency of the dried leaf products was expressed as 1×.
[b] Dilution factor 1 means no dilution.
[c] Standardized SalA content (μg/mg): SalA content (μg/mg)/labeled potency.

The SalA and SalB recoveries were $99.0 \pm 1.2\%$ and $96.5 \pm 0.8\%$ (mean ± S.D., 50 μg/mL each in acetonitrile, $n = 5$), respectively. This result indicated that the loss by GCP treatment was negligible.

The stability of SalA/SalB in the acetonitrile extract in a refrigerator (at 4 °C, without light shielding) was evaluated using the extracts originating from a S. divinorum dry leaf product. Fig. 3 illustrates the time course of the residual ratios of SalA/SalB. There was obviously degradation of SalA/SalB in the nonGCP-treated extracts. In contrast, this degradation was not observed in the GCP-treated extracts. This finding suggested that any pigments prompted the degradation of SalA/SalB in acetonitrile solution, and that removing them by GCP treatment was effective to prevent the degradation.

### 3.5. Calibration curves and method validation

Calibration curves of SalA were constructed by an external standard method because matrix effects for SalA were not observed. The calibration curves were linear in the range of 50–2000 ng (equivalent to 0.5–20 μg/mg sample in the case of no dilution) on a column with correlation coefficients that were routinely greater than 0.993. Table 1 indicates intra- and inter-assay precision evaluated using three S. divinorum-related products. The coefficient of variance for the intra-assay ($n = 5$) and inter-assay ($n = 3$) was between 1.9% and 12.4% for the three samples.

Calibration curves of SalB were constructed by a standard addition method to resolve matrix effects originating from the matrix heterogeneity. Regression curves for SalB were linear in the range of 0–50 ng as spiked amounts per 20 μL of the injection solution (equivalent to 0–0.5 μg/mg sample in the case of no dilution). The correlation coefficients of the linear regression curves were always greater than 0.993. The relative standard errors of the slopes and intercepts were within 6.9% and 10.1%, respectively.

### 3.6. SalA/SalB contents in the S. divinorum-related products

Table 2 summarizes the labeled potencies, the dilution factors before the GCP treatment, and the SalA/SalB contents in the S. divinorum-related products. The SalA/SalB contents (μg/mg) in the three dried leaf products were 3.2–5.0/0.10–0.17 μg/mg. The reported contents in dried leaf samples were 7.6–7.8 μg/mg [4] and 0.89–3.70 μg/mg [16] for SalA, as well as 4.2–10.4 μg/mg for SalB [4]. The SalA contents in our samples were roughly in accordance with these reported values. In contrast, the SalB contents in our samples were obviously lower than the reported values. Unfortunately, the cause of this difference was unclear.

The SalA/SalB contents (μg/mg) in the "concentrated extract" products were 4.1–38.9/0.26–2.4. These concentrations tended to increase in proportion to the labeled potency. Wolowich et al. have reported that the SalA contents in four "concentrated extract" products (labeled potency: 5×–20×) were 0.126–0.951 μg/mg [17]. SalA concentrations in our samples were obviously higher than the reported values.

To evaluate adequacy of the labeled potencies in the "concentrated extract" products, SalA contents in them were standardized by their labeled potencies. This standardization was carried out by dividing the SalA contents by the labeled potencies. If the labeled potencies are adequate, it is expected that the standardized SalA contents are almost equal to those of the dried leaf products. However, the standardized SalA contents were significantly lower than those of the dried leaf products ($p = 0.046$, two-tailed unpaired $t$-test). This result indicates that their labeled potencies were lower than the expected ones.
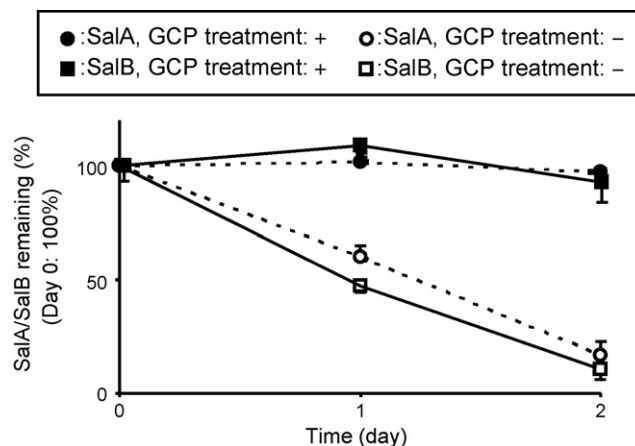


**Fig. 3.** Stability of SalA/SalB in the extracts with and without the GCP treatment. The extracts were stored at 4 °C without light shielding. Each data point represents mean ± S.D. ($n = 3$).

Smoking of 200–500 μg of SalA produces profound hallucinations lasting up to 1 h [19]. This potency is similar to the highly active synthetic hallucinogen LSD. Based on the SalA concentrations in our samples, it is estimated that smoking approximately 40–70 mg of the *S. divinorum* dried leaf products would be sufficient to cause hallucinogenic effects. On the other hand, the smoking dosage of the "concentrated extracts" products was dependent on their potencies. The range of the estimated dosage was from approximately 5 mg (for sample #12, 25×) to 50 mg (sample #4, 2×). Considering the low estimated dosage, high-concentrated samples such as samples #10–#12 have a high risk of intoxication or accidents.

## 4. Conclusion

We have developed an improved analytical procedure for SalA and SalB in *S. divinorum*. This procedure was successfully applied to the determination of SalA and SalB in *S. divinorum*-related products. The present results indicate that all products contained levels of SalA high enough to cause hallucinogenic effects. In particular, some "concentrated extracts" products contained very highly concentrated SalA. These results will be very useful for increasing our understanding of drugs circulated in the Japanese illicit drug market.

## References

[1] L.J. Valdés III, J.L. Díaz, A.G. Paul, Ethnopharmacology of *Ska María Pastora* (*Salvia divinorum*, Epling and Játiva-M), J. Ethnopharmacol. 7 (1983) 287–312.

[2] C.E. Dennehy, C. Tsourounis, A.E. Miller, Evaluation of herbal dietary supplements marketed on the internet for recreational use, Ann. Pharmacother. 39 (2005) 1634–1639.

[3] S. Singh, Adolescent salvia substance abuse, Addiction 102 (2007) 823–824.

[4] C. Medana, C. Massolino, M. Pazzi, C. Baiocchi, Determination of salvinorins and divinatorins in *Salvia divinorum* leaves by liquid chromatography/multistage mass spectrometry, Rapid Commun. Mass Spectrom. 20 (2006) 131–136.

[5] A. Ortega, J.F. Blount, P.S. Manchand, Salvinorin, a new *trans*-neoclerodane diterpene from *Salvia divinorum* (Labiatae), J. Chem. Soc., Perkin Trans. I (1982) 2505–2508.

[6] L.J. Valdés III, W.M. Butler, G.M. Hatfield, A.G. Paul, M. Koreeda, Divinorin A, a psychotropic terpenoid, and divinorin B from the hallucinogenic Mexican mint, *Salvia divinorum*, J. Org. Chem. 49 (1984) 4716–4720.

[7] L.J. Valdés III, H.-M. Chang, D.C. Visger, M. Koreeda, Salvinorin C, a new neoclerodane diterpene from bioactive fraction of the hallucinogenic Mexican mint *Salvia divinorum*, Org. Lett. 3 (2001) 3935–3937.

[8] T.A. Munro, M.A. Rizzacasa, Salvinorins D–F, new neoclerodane diterpenoids from *Salvia divinorum*, and an improved method for the isolation of salvinorin A, J. Nat. Prod. 66 (2003) 703–705.

[9] A.K. Bigham, T.A. Munro, M.A. Rizzacasa, R.M. Robins-Browne, Divinatorins A–C, new neoclerodane diterpenoids from the controlled sage *Salvia divinorum*, J. Nat. Prod. 66 (2003) 1242–1244.

[10] D.Y.W. Lee, Z. Ma, L.-Y. Liu-Chen, Y. Wang, Y. Chen, W.A. Carlezon Jr., B. Cohen, New neoclerodane diterpenoids isolated from the leaves of *Salvia divinorum* and their binding affinities for human *k* opioid receptors, Bioorg. Med. Chem. 13 (2005) 5635–5639.

[11] O. Shirota, K. Nagamatsu, S. Sekita, Neo-clerodane diterpenes from the hallucinogenic sage *Salvia divinorum*, J. Nat. Prod. 69 (2006) 1782–1786.

[12] B.L. Roth, K. Baner, R. Westkaemper, D. Siebert, K.C. Rice, S. Steinberg, P. Ernsberger, R.B. Rothman, Salvinorin A: a potent naturally occurring nonnitrogenous κ opioid selective agonist, Proc. Natl. Acad. Sci. U.S.A. 99 (2002) 11934–11939.

[13] M.S. Schmidt, T.E. Prisinzano, K. Tidgewell, W. Harding, E.R. Butelman, M.J. Kreek, D.J. Murry, Determination of salvinorin A in body fluids by high performance liquid chromatography–atmospheric pressure chemical ionization, J. Chromatogr. B 818 (2005) 221–225.

[14] D.J. Siebert, Localization of salvinorin A and related compounds in glandular trichomes of the psychoactive sage, *Salvia divinorum*, Ann. Bot. 93 (2004) 763–771.

[15] C. Giroud, F. Felber, M. Augsburger, B. Horisberger, L. Rivier, P. Mangin, *Salvia divinorum*: an hallucinogenic mint which might become a new recreational drug in Switzerland, Forensic Sci. Int. 112 (2000) 143–150.

[16] J.W. Gruber, D.J. Siebert, A.H. Der Marderosian, R.S. Hock, High performance liquid chromatographic quantification of salvinorin A from tissues of *Salvia divinorum* Epling & Játiva-M, Phytochem. Anal. 10 (1999) 22–25.

[17] W.R. Wolowich, A.M. Perkins, J.J. Cienki, Analysis of the psychoactive terpenoid salvinorin A content in five *Salvia divinorum* herbal products, Pharmacotherapy 26 (2006) 1268–1272.

[18] K. Tidgewell, W.W. Harding, M. Schmidt, K.G. Holden, D.J. Murry, T.E. Prisinzano, A facile method for the preparation of deuterium labeled salvinorin A: synthesis of [2,2,2-$^2$H$_3$]-salvinorin A, Bioorg. Med. Chem. Lett. 14 (2004) 5099–5102.

[19] D.J. Siebert, *Salvia divinorum* and salvinorin A: new pharmacologic findings, J. Ethnopharmacol. 43 (1994) 53–56.