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Original Article

Quantitative determination of salvinorin A, a natural hallucinogen with abuse liability, in Internet-available *Salvia divinorum* and endemic species of *Salvia* in Taiwan

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ABSTRACT

In recent years, recreational use of *Salvia divinorum* (Lamiaceae), a herbal drug that contains a hallucinogenic ingredient, salvinorin A, has become a new phenomenon among young drug users. In Taiwan, as in many other countries, dry leaves of *S. divinorum* and its related concentrated extract products are available via the Internet. Besides *S. divinorum*, there are many endemic *Salvia* species whose salvinorin A content is yet unknown. To understand the abuse liability of these products, the aim of this study was to assess the concentration of salvinorin A in endemic *Salvia* species and Internet-available salvinorin A-related products. Samples of *S. divinorum* were purchased via the Internet and samples of eight endemic species of *Salvia* were collected in Taiwan, including *S. arisanensis* Hayata, *S. coccinea* Juss. ex Murr, *S. hayatana* Makino ex Hayata, *S. japonica* Thumb. ex Murr, *S. nipponica* Miq. Var. formosana (Hayata) Kudo, *S. scapiformis* Hance, *S. tashiroi* Hayata. Icon. PI. Formosan, and *S. keitaoensis* Hayata. The content of salvinorin A was determined by high performance liquid chromatography (HPLC). Salvinorin A was extracted from the dry leaves of *S. divinorum* and endemic species of *Salvia* with methanol and analyzed on a C-18 column by isocratic elution with a mobile phase of acetonitrile–water. Salvinorin A was detected in *S. divinorum*, but not in the endemic *Salvia* species of Taiwan. Therefore, endemic species of *Salvia* in Taiwan may not possess hallucinogenic potential. However, the potential harm from *S. divinorum* available via the Internet should be thoroughly assessed in Taiwan, and control measures similar to those implemented in many other countries should be considered.

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1. Introduction

Salvia divinorum Epl. & Játiva-M. (Lamiaceae), which is endemic to the northeastern Sierra Mazateca mountain region of Mexico and traditionally used in spiritual rituals by the Mazatec Indians to produce hallucinatory effects, is used for traditional medicine purposes, including the treatment of diarrhea, headache, anemia, and rheumatism [1]. *S. divinorum* is ingested by chewing the fresh leaves, smoking the dry leaves, or drinking the extraction solution of fresh leaves to induce hallucinatory effects such as "entering another reality", "dissociative sensations", and "spatiotemporal dislocation" [2,3]. Salvinorin A, a potent hallucinogenic ingredient isolated from *S. divinorum,* is the primary non-nitrogenous neoclerodane diterpene selective agonist of naturally-occurring κ-opioid receptors [4]. The hallucinogenic mechanism of salvinorin A is different from those of classical hallucinogens, such as lysergic acid diethylamide (LSD), $\triangle^9$-tetrahydrocannabinol, and ketamine, because it does not interact with 5-hydroxytryptamine (5-HT) receptor (serotonin receptor), cannabinoid (CB) receptor, or N-methyl=D-aspartate (NMDA) receptor [5,6]. Previous studies have estimated that smoking approximately 200–500 μg of salvinorin A would be sufficient to cause intense hallucinogenic and psychotomimetic effects [7,8]. Salvinorin A is rapidly absorbed by inhalation, whether in dry leaves or from a "concentrated extract" product; the hallucinogenic effect can occur within about 30 seconds and can last up to 20–30 minutes [7]. Oral administration causes hallucination after about 5–10 minutes, and can last up to 1 hour [7]. Salvinorin A is rapidly degraded by blood esterase and several cytochrome P450 isoenzymes, including CYP2E1, CYP2C18, CYP1A1, and CYP2D6 [9,10]. The short psychoactive effects of salvinorin A are due to rapid hydrolysis to the inactive metabolite salvinorin B [9]. One study reported that the elimination half-life of salvinorin A was short, at 56.6 ± 24.8 minutes after intravenous administration [10]. In a previous study, salvinorin A was not detected in urine samples collected after 1.5 hours from two human volunteers who had smoked *S. divinorum* dry leaves [11].

In recent years, *S. divinorum* has become increasingly popular among adolescents and young adults. Babu et al [12] indicated that *S. divinorum* has several features attractive to young drug users and is a desirable hallucinogen substance: (1) owing to the legality of *S. divinorum*, its related products are easily purchased from various sources, including smart shops, head shops, and online vendors; (2) sellers always declare that evidence indicates that *S. divinorum* is safe and not addictive; (3) salvinorin A may not be detected in urine because it has a very short half-life [11].

According to the Substance Abuse and Mental Health Services Administration (SAMHSA) publication, the 2006 National Survey on Drug Use and Health (NSDUH) database, it is estimated that 1.8 million adolescents or young adults have used *S. divinorum* in their lifetime and 756,000 people have used *S. divinorum* in the past year [13]. A previous study, analyzing the 2006–2008 NSDUH public-use data ($N = 166{,}453$), indicated that the lifetime prevalence of *S. divinorum* use has increased by about 83% among individuals aged 12 years or older [14]. In 2010, the National Institute on Drug Abuse (NIDA) investigated 46,482 students in the 8th, 10th, and 12th grades from 396 public and private schools and 5.5% reported having used *S. divinorum*, which is greater than other recreational drugs, including heroin (0.9%), cocaine (2.9%), LSD (2.6%), methamphetamines (1.5%), ecstasy (4.5%), γ-hydroxybutyric acid (GHB) (1.4%), ketamine (1.6%), and oxycodone (5.1%) [15,16].

S. divinorum has not been placed on the list of the United Nations Drug Conventions, although it has become increasingly popular in recent years. In 2002, Australia became the first country to ban the possession and sale of *S. divinorum* [17]. In the USA, Missouri was the first state to restrict *S. divinorum* use in 2003. Two years later, Louisiana became the first state to pass a law regulating *S. divinorum*. In 2006, a Delaware teenager named Brett Chidester used *S. divinorum*, which led to suicide, and *S. divinorum* and salvinorin A were then placed on Schedule I of Delaware's Controlled Substances Act. In 2007, the Drug Enforcement Administration (DEA) placed *S. divinorum* on the list of drugs of concern and into the preliminary stages of drug regulation [18]. In 2008, the DEA reported that nine states had passed a law controlling *S. divinorum*, four states banned its use and sale, and seven states proposed legislative bills, suggesting a tendency towards regulatory control in the USA [19]. In Europe, Denmark, Germany, Latvia, Italy, Sweden, Croatia, Romania, Lithuania, and Belgium have placed bans on under-the-table sale of *S. divinorum* and salvinorin A; Poland has banned the possession and sale of *S. divinorum* and its derivatives; Russia and Spain have prohibited the possession and sale of *S. divinorum* plants. However, in Norway, Iceland, Finland, and Estonia *S. divinorum* is legal for medical purposes that include treatment of cocaine and heroin addiction. In Asia, Japan and South Korea have also placed bans on *S. divinorum* and salvinorin A trafficking [17]. In 2012, in Hong Kong, *S. divinorum* was the subject of a proposed legislative bill that suggested regulatory control [20].

Fig. 1 – Dried leaves and related products of *Salvia divinorum* purchased from the Internet in Taiwan. (A) Dry leaves of *S. divinorum*; (B) *S. divinorum* 100*fx*; (C) *S. divinorum* 30*fx*.