Analysis of the Psychoactive Terpenoid Salvinorin A Content in Five *Salvia divinorum* Herbal Products

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Study Objective. To determine the content of the hallucinogen salvinorin A in a variety of *Salvia divinorum* herbal products and to compare the content with the label claims of potency and purity.

Design. Laboratory analysis.

Setting. University-affiliated laboratory.

Samples. Five herbal products containing *Salvia divinorum*.

Measurements and Main Results. The samples were purchased from the Internet and local drug paraphernalia shops ("head shops"). High-performance liquid chromatography and thin-layer chromatography–gas chromatography–mass spectroscopy were used for the analysis. All five samples contained salvinorin A, a psychoactive compound found in *Salvia divinorum*; however, the salvinorin A concentrations we measured were much lower than those claimed on the product label. Vitamin E was also found in two samples and caffeine in one sample.

Conclusion. The five salvinorin A herbal products were found to be subpotent, and three products contained adulterants. Any discrepancy between the advertised salvinorin A concentration and their actual concentration may pose a potential risk of both misuse and overdose. These concerns, and the recently reported teenage suicide that could have been related to salvia consumption, underscore the need for practitioners to become familiar with the signs and symptoms of salvia use.

Key Words: *Salvia divinorum*, salvia, salvinorin A, psychoactive, psychotropic terpenoid, adolescent suicide, diterpene, hallucinogen, drugs of abuse.

(Pharmacotherapy 2006;26(9):1268–1272)

Salvia divinorum (also known as diviner's sage, magic mint, and Maria Pastora), a plant belonging to the Lamiaceae (mint) family, has been used for centuries by indigenous people of the Sierra Mazateca region of Oaxaca, Mexico, for ceremonial healing and divination rituals.[1] Salvia was first described by Jean Basset Johnston in 1939, who was studying psilocybin mushroom use of the Mazatec people when he encountered this entheogen.[2] An entheogen is defined as "that which causes god (or godly inspiration) to be within a person."[2] The first botanical collections of *Salvia divinorum* in the United States, established in 1962, were considered a new species of salvia.[3]

The plant's active compound was identified as a *trans*-neoclerodane diterpene and named salvinorin A.[4] It is a psychotropic terpenoid; other psychoactive plants containing terpenoid essential oils are *Artemisia absinthium* (wormwood) and *Cannabis sativa*.

Ethnobotanical plants that can induce hallucinations or changes in perception have attracted the interest of young adults and adolescents. Salvia is advertised to this consumer group

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Presented in part as a poster at the North American Congress of Clinical Toxicology, Seattle, Washington, September 9–14, 2004.

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through online botanical companies and drug promotional sites as a legal alternative to illegal substances such as cannabis or mescaline. For example, the following statement appears on a Web site: "Outside Mexico Salvia became famous as one of the best legal highs (hallucinogens, herbal smoke, psychoactives) ever discovered."[5] The problem with statements like this one is that the experience from salvia is not euphoric and can be overwhelming to a naïve person.

Initial pharmacology studies of salvinorin A found no affinity for serotonin or other receptors commonly associated with hallucinogenic effects; this caused investigators to investigate the family of opiate receptors.[6] Salvinorin A demonstrated potent binding and activation of the κ-opioid receptor, resulting in psychomimetic actions.[7] It became known as the first naturally occurring nonnitrogenous κ-opioid-receptor selective agonist.[8] Opioid receptors are subdivided into μ, Δ, and κ types, each of which has subtypes. When stimulated, all opiate receptor subtypes elicit analgesic effects. The κ subtype also elicits psychomimetic effects and, in humans, modulates perception, cognition, and the neurobiology of mood.[9, 10] Common experiences with salvinorin A are altered perceptions, hallucinations, ataxia, depersonalization, hysterical laughter, incoherent speech, and unconsciousness.[6]

Some Internet sources classify the hallucinogenics into three subsets: psychedelics, dissociatives, and deliriants.[11] Lysergic acid diethylamide (LSD) and mescaline are psychedelics, and anticholinergic drugs such as hyoscyamine or atropine are deliriants. Salvinorin A has been classified with the dissociatives, along with phencyclidine (PCP, angel dust), ketamine, dextromethorphan, ibogaine, and nitrous oxide.

A comparison of the structures of salvinorin A and morphine indicates that salvinorin A lacks both the amino functionality and the phenolic moiety common to all opiate-based ligands (Figure 1). Moreover, the absence of the amino group (nonnitrogenous) places salvinorin A in a new class of opioid ligand with unknown potential regarding opioid-mediated analgesia. Further research using structural homologues of salvinorin A is continuing.[12]

Salvia is available as natural dried-plant material, fortified-plant material, and liquid extracts. Salvia leaves sell for $15–120/ounce, plants for $20–45, and liquid extract for $110–300/ounce.[5] Onset and intensity of the effects of salvinorin A are related to the route of salvia administration. Routes that avoid the hepatic first-pass effect (sublingual, inhalation by smoking or vaporization) are the quickest and most intense. Other routes are the oral "quid" method (slowly chewing a rolled cylinder of leaves), infusions of the herb, or drinking tea containing the herb. Once absorbed through the oral mucosa, the effects of salvia are detected in 5–10 minutes and peak at 1 hour; they subside after 2 hours. Inhaled vapors take effect after 30 seconds, peak at 5–10 minutes, and subside after 20–30 minutes.

The purveyors of salvia use nomenclature intended to imply standardization; 1x is the potency of the natural product. An Internet users forum claimed that 1x is equivalent to a salvinorin A content of 2.5 mg/g.[13] A salvia users guide implies that 10x means 10 times the potency of 1x.[14] The concentrated preparation of the salvia leaf is called salvia extract, with relative strengths designated as 5x, 10x, and 20x. The extract is smoked in place of natural-strength leaves, thus reducing the amount of smoke inhaled and facilitating more powerful experiences.

Psychomimetic effects of the compound are detected at doses as low as 200–500 μg after vaporization and inhalation; at doses higher than 1 mg, out-of-body experiences are commonly reported.[15] By comparison, a typical dose of the synthetic hallucinogen LSD is 50–250 μg.[16] Doses of the naturally occurring hallucinogens mescaline and psilocybin are 100 mg and 5 mg, respectively.[17, 18] Therefore, salvinorin A is one of the most potent naturally occurring hallucinogens.

To date, no specific federal regulations exist for salvinorin A; however, the Drug Enforcement Agency (DEA) Office of Diversion Control has placed the drug on its list of drugs and chemicals of concern.[19] Other drugs on this list are 3,4 methylenedioxymethamphetamine (MDMA,

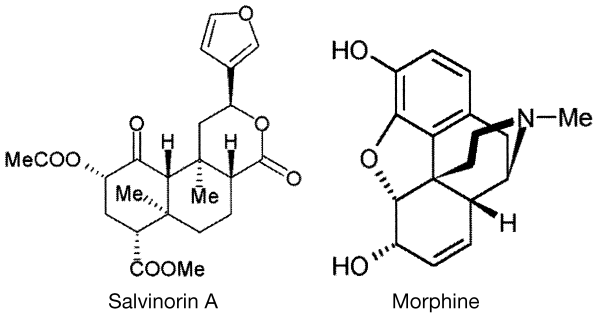

Figure 1. Structural comparison of salvinorin A and morphine. Salvinorin A is the only known nonnitrogenous opioid ligand.

Table 1. Salvinorin A Content and Adulterants Identified in Five Salvia Samples

		Salvinorin A Content				
Sample Type	Source	Labeled Potency	Label Claim (mg/g)	Analysis Result (mg/g)	Analysis Result (% of label claim)	Adulterants Identified
Leaves	Internet	20x	50.0	0.461	1	Vitamin E
Leaves	Internet	5x	12.5	0.126	1	Vitamin E
Leaves	Internet	5x	12.5	1.137	9	None
Leaves	"Head shop"	1x	2.5	0.408	16	None
Extract	"Head shop"	10x	25.0	0.951	4	Caffeine

Ecstasy), cocaine, dextromethorphan, LSD, fentanyl, γ-hydroxybutyrate (GHB, "date rape" drug), and oxycodone.

We therefore sought to determine the content of salvinorin A in a variety of salvia products and compare it with the label claims of potency and purity.

Methods

The study was approved by the local human subjects research office. We obtained samples from Web sites on the Internet and from local drug paraphernalia shops ("head shops") in spring 2004. Five different salvia products were purchased, with labeled potencies of 1x–20x. Samples were extracted and analyzed for salvinorin A content using a previously described method.[20]

To validate the assay in our laboratory and quantify (weight in weight) the amount of salvinorin A in the samples, a standard curve was prepared using an authentic sample of purified salvinorin A (Biosearch Technologies, Novato, CA). We dissolved 4.9 mg of salvinorin A in 10 ml of methyl alcohol–acetone (4:1) and serially diluted it. This provided nine solutions with a salvinorin A concentration of 1.9–490 µg/ml. We then used the following equation describing the standard curve to inversely predict the mass of salvinorin A in the five samples: peak area = 6700515 • (mass injected [µg]) + 22655. The coefficient of determination for the linear regression analysis was 0.9998.

We also analyzed the salvia samples for adulterants using thin-layer chromatography–gas chromatography–mass spectroscopy (Controlled Substances and Pharmaceuticals Screen; National Medical Services, Willow Grove, PA).

Results

The salvinorin A concentration and other compounds identified in the five salvia samples are shown in Table 1. Salvinorin A content ranged from 0.126–1.137 mg/g, or from 1–16% of the label claim. The adulterant screen revealed the presence of vitamin E in two samples and caffeine in one sample.

Discussion

The objective of this study was to analyze for comparison a variety of salvia products that are easily available to the public and are advertised to be pure and to contain a specific concentration of salvia's active ingredient, salvinorin A. Among the five samples obtained, the salvinorin A concentration ranged from 0.126–1.137 mg/g. This was comparable to previous research using the same extraction and analytical methods to examine salvia botanical samples in which the salvinorin A content ranged from 0.63–3.70 mg/g.[20] The actual concentration found in each sample did not coincide with the advertised 1x concentration. An average 1x potency claimed in a users group discussion blog is equivalent to 2.5 mg/g.[13,14]

In our study, the sample labeled 1x contained a higher concentration than one of the samples falsely labeled 5x. The 1x sample contained 0.4 mg/g, which is 16% of the average 2.5 mg/g. The 20x sample contained only 1% of the claimed concentration. A screen for controlled substances and pharmaceuticals revealed that two samples of crushed leaves obtained on the Internet contained vitamin E, and the 10x extract obtained from a head shop was adulterated with caffeine.

The general public has become increasingly aware of salvia since June 1, 2002, when Australia became the first country to ban salvia and salvinorin A. In late 2002, a California Congressman unsuccessfully introduced a bill in the House of Representatives to schedule salvia as a controlled substance. The DEA has indicated on its Web site that salvia is a drug of concern and is evaluating the plant for possible scheduling. Under Louisiana Act 159, a total of 40 plants,

including *Salvia divinorum*, are illegal if sold for human consumption; *Salvia divinorum* was outlawed in Missouri in the fall of 2005. New York is considering a bill that would place heavy civil penalties on the sale of the drug; Illinois also is considering regulating the drug's use. In January 2006, the Swedish government declared its intention to make salvinorin A and all plants containing the substance illegal, and in March 2006 the law was enacted.[2]

The popularity of salvia is growing, as gauged by hits from search engines on Internet sites. A Yahoo search for *Salvia divinorum* in 2003 yielded 100 hits; an identical Yahoo search in March 2006 yielded 881,000 hits.

Practitioners need to be aware of this compound when treating individuals with unusual intoxication, and especially Internet-savvy teenagers. The human toxidrome associated with salvia is expected to be similar to that seen with other hallucinogens, except that the duration of the effects is much shorter. In fact, the duration of action is so short that a patient who sought medical attention would probably be lucid by the time help arrived. The intensity of the psychological effect is dose dependent, however, and high doses can produce extreme effects, such as depersonalization, with loss of reality intense enough that users have unintentionally harmed themselves.[15]

In one study, investigators intending to study the human pharmacokinetics of salvinorin A asked volunteers—all of whom had experience with hallucinogens—to smoke salvia.[21] The volunteers became so intoxicated 30 seconds after inhaling that drawing blood was considered hazardous. After regaining lucidity 20 minutes later, they refused to have blood drawn and, presumably, refused any further participation in the experiment.

In a pharmacokinetic study involving nonhuman primates, two-compartment behavior was exhibited after the animals were administered an intravenous 0.032-mg/kg bolus of salvinorin A, which should result in approximately the same disposition as smoking salvia.[22] The rapid distribution phase was essentially complete 5 minutes after administration of the bolus. The overall elimination half-life was 37.9 and 80.0 minutes in male and female primates, respectively. The rapid onset and short duration of effect reported in humans make it likely that the pharmacokinetics are similar in humans. Interactions between salvinorin A and other agents have not been reported. For a prolonged effect, salvinorin A has been used in combination with other recreational drugs such as cannabis.

To our knowledge, no studies of human toxicity with salvia have been published. A placebo-controlled study of acute and long-term toxicity in rats examined the effect of salvinorin A by intraperitoneal injection at doses of 400, 800, 1600, 3200, and 6400 µg/kg/day for 14 days.[23] No histologic evidence of liver, spleen, kidney, bone marrow, or brain tissue damage was found. The doses used in this study were 100–1000 times the dose range of 200–500 µg found hallucinogenic in humans. The authors concluded that salvinorin A has relatively low toxicity compared with other hallucinogens, especially amphetamine derivatives such as MDMA. In addition, the authors warned that psychological effects are not assessed in a rat model, and in humans, these effects could be the stimulus for an episode of panic that could cause myocardial ischemia.

A rat model used to screen for efficacy of antidepressant drugs also was used to investigate salvinorin A.[10] Results of the forced swim test, intracranial self-stimulation, and locomotor activity suggested that salvinorin A produced depressant effects. National Public Radio recently reported the case of a salvia user who committed suicide.[24] An expert interviewed expressed concern that salvia is being marketed to teenagers and young adults as producing a marijuana-like high. The expert also stated that salvia should be regulated like alcohol and should be kept strictly off-limits to teenagers, as suicide rates are high among adolescents and teenagers.[25] The potential for depression caused by salvia consumption must also be considered and needs further investigation.

Conclusion

Five samples of *Salvia divinorum* herbal products were easily obtained from several Web sites on the Internet and from local head shops. Although the products contained the active compound salvinorin A, the concentrations we measured were much lower than those claimed on the product label. Vitamin E was also found in two samples and caffeine in one sample.

Our study demonstrates that the variability in the samples and the inconsistency of the product labeling precluded reliable determination of the salvinorin A concentration ingested. As carefully pointed out in the salvia users guide, due to the recognized potency of this hallucinogen, it is

imperative that the dose content claimed on the label is accurate. For example, if a salvia user becomes familiar with the effects from a mislabeled product and then ingests a more potent product that is correctly labeled, it may result in an unfamiliar and dangerous state of intoxication. Therefore, any discrepancy, including the subpotency of the products analyzed in this study, between the advertised salvinorin A concentration in products and their actual concentration may pose a potential risk of both misuse and overdose. These concerns, and the recently reported teenage suicide that could have been related to salvia consumption, indicate that practitioners must become familiar with the signs and symptoms of salvia use.

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