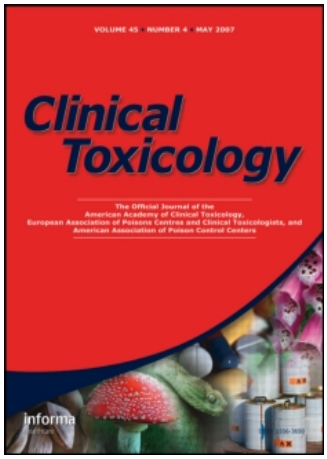

Clinical Toxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597279

Opioid receptors and legal highs: **Salvia divinorum** and Kratom

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Online Publication Date: 01 February 2008
To cite this Article: Babu, Kavita M., McCurdy, Christopher R. and Boyer, Edward W. (2008) 'Opioid receptors and legal highs: **Salvia divinorum** and Kratom', Clinical Toxicology, 46:2, 146 - 152
To link to this article: DOI: 10.1080/15563650701241795
URL: http://dx.doi.org/10.1080/15563650701241795

Clinical Toxicology (2008) **46**, 146–152

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650701241795

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ARTICLE

Opioid receptors and legal highs: *Salvia divinorum* and Kratom

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Salvia divinorum and *Mitragyna speciosa* ("Kratom"), two unscheduled dietary supplements whose active agents are opioid receptor agonists, have discrete psychoactive effects that have contributed to their increasing popularity. *Salvia divinorum* contains the highly selective kappa- opioid receptor agonist salvinorin A; this compound produces visual hallucinations and synesthesia. Mitragynine, the major alkaloid identified from Kratom, has been reported as a partial opioid agonist producing similar effects to morphine. An interesting minor alkaloid of Kratom, 7-hydroxymitragynine, has been reported to be more potent than morphine. Both Kratom alkaloids are reported to activate supraspinal mu- and delta- opioid receptors, explaining their use by chronic narcotics users to ameliorate opioid withdrawal symptoms. Despite their widespread Internet availability, use of *Salvia divinorum* and Kratom represents an emerging trend that escapes traditional methods of toxicologic monitoring. The purpose of this article is to familiarize toxicologists and poison control specialists with these emerging psychoactive dietary supplements.

Keywords *Salvia divinorum*; Salvinorin A; Kratom; Mitragynine; Dietary supplements

Introduction

Toxicologists and poison control specialists play an important role in the identification of emerging trends in substance abuse. However, the traditional methods of toxicologic monitoring may fail or lag in detection of substances of abuse that do not typically provoke calls to a poison control center or visits to the emergency department. The Internet has long been recognized as a source of drug information, and monitoring of widely accessed sites can provide insight into emerging substance abuse trends that escape conventional methods of observation. *Salvia divinorum* and *Mitragyna speciosa* ("Kratom") are two unscheduled psychoactive dietary supplements whose popularity has grown significantly in the past few years. The purpose of this article is to familiarize toxicologists and specialists in poison information with *Salvia divinorum* and Kratom, and to illustrate the need for novel methods of observation to predict emergent trends of substance use.

Received 11 October 2006; accepted 22 January 2007.
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Salvia divinorum

Salvia divinorum is a perennial herb classified as a member of the mint family (see Figure 1). Other names for *Salvia divinorum* include "Diviner's Sage," "Mystic Sage," and "Magic Mint." While more than 500 species of *Salvia* exist, *S. divinorum* has been recognized for its hallucinogenic properties for centuries. Some users ingest *Salvia divinorum* for shamanistic purposes, replicating its original use by Mazatec Indians to create religious visions.

Salvia divinorum is one of the most widely marketed recreational botanicals available via the Internet (1). Many websites advertise it as a "legal" hallucinogen, while others seem to encourage experimentation, advertising a combination of dried leaves and extracts of salvinorin A as "the freshman selection" or the "starter pack" (2–4) . *Salvia divinorum* is being used recreationally by both adults and adolescents internationally. In a recent study of innovative adolescent drug users, 25% of the surveyed adolescents stated that they had used the Internet to obtain information about *Salvia divinorum* (5).

Several features make *Salvia divinorum* attractive to young drug users. First, plant material or extracts of salvinorin A may be purchased from "head" shops, record stores, online vendors, and even university campus stores (6). Whole plants, seeds, and tips for successful cultivation are available via the Internet (4, 7–9). While several vendors state that they will not sell *Salvia divinorum* or other psychoactive natural

Fig. 1. *Salvia divinorum*. Image courtesy of Dr. Christopher McCurdy.

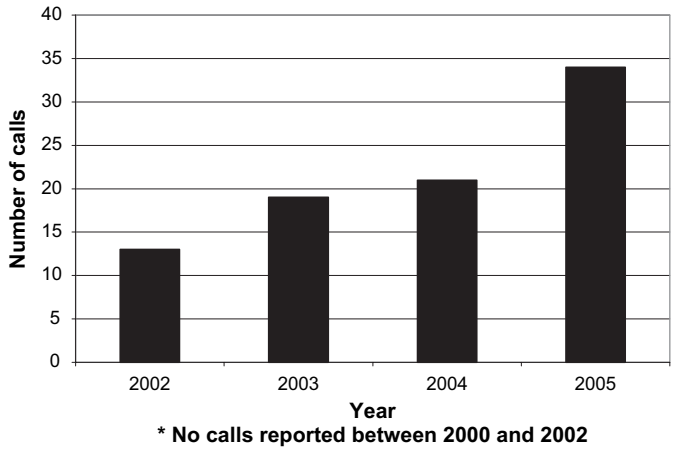

Fig. 2. AAPCC call data: Salvia divinorum (2000–2005)*.

products to minors, many websites lack clear mechanisms to prevent sales to persons younger than 18. Second, online drug encyclopedias, such as www.erowid.org, correctly report that *Salvia divinorum* does not trigger any positive results on qualitative urine drug screens (10–12). Third, potential adolescent users may be influenced by the availability of anecdotal Internet instructions that suggest evidence supporting *Salvia divinorum's* safety (13). Ease of access, legality, safety, and lack of detectability combine to make *Salvia divinorum* a desirable hallucinogen to adolescents and young adults who wish to experiment with drugs yet avoid discovery of their substance use.

Concern regarding *Salvia divinorum* use by adolescents has prompted legislation to criminalize *Salvia divinorum*. Possession and cultivation of *Salvia divinorum* and salvinorin A is therefore illegal for human consumption in Delaware, Louisiana, and Missouri (14). *Salvia divinorum* was listed as a "Drug or Chemical of Concern" in 2004 by the National Drug Intelligence Center and Drug Enforcement Administration (15).

Little formal epidemiologic data are available for *Salvia divinorum* use, however, ethnographic investigations suggest a marked increase in the use of Salvia divinorum (16). Additional information was obtained from the Americal Association of Poison Control Centers. A search of the AAPCC data set from 2000 to 2005 using keywords "Salvia divinorum" and "Maria Pastora" revealed a total of 90 exposures (see Figure 2) (17). The average age among intentional users was 21.5 years, with a 30:1 female predominance. Ten percent of these patients were subsequently admitted for observation. In contrast, data from www.erowid.org described 463 and 424 daily visits to the Erowid *Salvia divinorum* index on 3/1/2000 and 9/1/2000, respectively. By 2005, there were 2,212 and 1,628 daily visits to the *Salvia divinorum* index on 3/1 and 9/1 (F. Erowid and E. Erowid, founders of www.Erowid.org, personal communication, 12 October 2006). While some of this increase may reflect the growth of the Internet, hits to the *Salvia divinorum* index grew disproportionately relative to other substances indexed on the website. These preliminary data indicate the inability of clinicians and epidemiologists to rely solely upon poison control center data in recognizing trends in emerging recreational substances.

Potential factors contributing to the disproportionately low number of contacts with the AAPCC regarding *Salvia divinorum* include failure of clinicians to recognize use of this substance, incorrect coding by specialists in poison information, lack of significant acute toxicity and lack of user contact with the health care system. Further limitations of AAPCC data as described by the AAPCC follow: "The American Association of Poison Control Centers (AAPCC; http://www.aapcc.org) maintains the national database of information logged by the country's 61 Poison Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s)" (16).

Pharmacology

The active component of *Salvia divinorum* is salvinorin A, a psychotropic diterpene that produces hallucinations (see Figure 3) (18). However, salvinorin A demonstrates no apparent binding affinity for the 5-HT_{2A} receptor, thus differing sharply from other hallucinogens with related neuropsychiatric effects (18). Instead, salvinorin A is a highly selective, naturally-occurring agonist of the kappa opioid receptor (KOR). The kappa- receptor exists in both the spinal

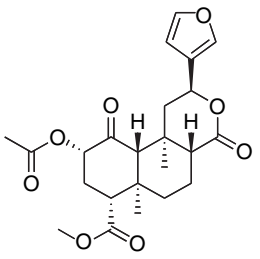

Fig. 3. Structure of salvinorin A.

cord and brain. Stimulation of the kappa- receptor produces psychotomimesis, diuresis and spinal analgesia, but does not result in respiratory depression. Salvinorin A has been demonstrated to have pharmacological activity consistent with known KOR agonists including analgesia, sedation, inhibition of GI transit, aversion, and depressant effects (19–24).

The mechanism by which the KOR produces hallucinations is unknown, but its role in diseases of perception, including schizophrenia and depression, has been postulated (25). The selectivity of salvinorin A for the KOR suggests that this natural product could be used as a probe to ascertain the molecular basis of a number of psychiatric conditions (26). Additionally, there is interest in the therapeutic potential of salvinorin A as a novel antidepressant, or antipsychotic agent (26).

Salvia divinorum and salvinorin A may be administered via buccal or pulmonary routes and the onset and duration of effect varies with route of administration. Salvinorin A is rapidly absorbed through the buccal mucosa, whether in extract or leaf form, and psychoactive effects can occur within seconds to minutes, and persist for up to one hour (27). Inhalation (of either vaporized salvinorin A extract or smoked dried leaves) produces psychoactive effects within seconds, which last up to 20 to 30 minutes (27). Threshold doses of *Salvia divinorum* required to produce hallucinations depend on route of administration. Two hundred micrograms of salvinorin A has been described as the threshold dose for hallucinations after inhalation, while doses of 10 mg failed to produce hallucinations after ingestion (27). The intravenous administration of salvinorin A is not described in humans, although it has been performed in an animal model (28).

Ingestion of salvinorin A produces no psychoactive effects, suggesting enzymatic deactivation or significant first-pass metabolism (27). The exact mechanism of salvinorin A metabolism is unknown, as are pathways of elimination. One ex vivo study demonstrated that salvinorin A is converted to salvinorin B via ester hydrolysis by blood esterases (29). However, an animal model demonstrated that salvinorin B never reached detectable levels after intravenous injection of salvinorin A, and may be rapidly cleared in vivo (28). After intravenous administration of salvinorin A to four primates, the elimination half-life was 56.6 ± 24.8 minutes. The elimination half-life was significantly longer in the females, suggesting that elimination kinetics may vary with gender (28).

Clinical effects and toxicity

Hallucinations occur rapidly after administration and are typically very vivid (27). *Salvia divinorum* produces synesthesia as its characteristic psychotropic effect; many users report a confusion of the senses, like hearing colors or smelling sounds (27). Hallucinogenic effects are typically brief, lasting only one to two hours. Side effects are not described, but individuals may be susceptible to trauma through lack of insight (30). The absence of reports describing acute or chronic *Salvia divinorum* toxicity implies either its relative safety or failure of clinicians to recognize *Salvia divinorum* use by patients. Additionally, users have described aversive effects with *Salvia divinorum* exposure, perhaps limiting long term, frequent use.

Routine drug screens do not detect the presence of salvinorin A (10,12). High Performance Liquid Chromatography (HPLC) and Liquid Chromatography Mass Spectrometry (LC-MS) protocols have been applied to the quantitative analysis of salvinorin A and B in plant matter and in *ex vivo* animal studies (12). One study demonstrated the feasibility of quantifying salvinorin A added to samples of primate blood, urine, and CSF. Gas chromatography/ mass spectrometry identified salvinorin A in urine and saliva obtained from two human volunteers who had smoked *Salvia divinorum* (31). To date, no studies have validated a method for the detection of salvinorin A or B in human blood after use.

Management

In comparison to other hallucinogens, the physiological and neuropsychiatric effects produced by *Salvia divinorum* are relatively mild, but agitated delirium and confusion are reported (30,31). Sweating, chills, and diuresis have been also attributed to *Salvia divinorum* (13). Symptoms severe enough to require treatment in the emergency department are thought to be uncommon, and the greatest risk may be trauma in the context of complex activity, like driving (30). To date, no cases of *Salvia divinorum* toxicity or deaths from overdose have been reported (30). Theoretically, naloxone (a non-specific opioid receptor antagonist) may reverse the physiological and psychiatric effects of salvinorin A at the kappa opioid receptor. Indeed, the selective kappa opioid receptor antagonist, norbinaltorphine, demonstrated complete reversal of the analgesic effects of salvinorin A in mice (19).

Abuse liability

Addiction to *Salvia divinorum* has not been described. One study demonstrated a weak aversive effect of salvinorin A in animals, suggesting that the compound would not be addictive (23). However, no reports currently exist in the literature on tolerance or withdrawal to the effects of salvinorin A.

Kratom (*Mitragyna speciosa*)

Kratom, or *Mitragyna speciosa Korth*, is a tree native to swampy regions of Asia and Africa (32) (see Figures 4 and 5). Kratom has long been considered unusual in its dual properties as a stimulant and sedative. Kratom was used in Thailand and Malaysia by manual laborers to enhance productivity, and for its euphoric (also called "coca-like") effect at low doses (33). At higher doses, Kratom has opioid-like effects, and its use to treat pain and opium withdrawal was described as early as the nineteenth century (32). In Thailand, the use of Kratom was historically associated with working class men, while its use by women was considered unusual (34). Kratom has been illegal in Thailand since 1946, and was criminalized in Australia in 2005. Kratom is not currently scheduled in the United States.

The wide availability of Kratom on the Internet reflects extensive demand for this product, however, no national drug abuse survey currently monitors Kratom use in the United States (35). A search of the AAPCC data set for Kratom revealed a total of two reported exposures between 2000 and 2005, using the keyword "Mitragyna speciosa." The patients were aged 17 and 20 (36). In contrast, there were less than 50 hits to the Kratom index on www.erowid.org on both 3/1/2000 and 9/1/2000. By 2005, there were 219 hits to the Kratom index on 3/1, and 189 hits on 9/1 (F. Erowid and E. Erowid, founders of www.erowid.org, personal communication, 12 October 2006). While this increase may simply reflect the growth of the Internet, reports of the use of Kratom to modulate opioid withdrawal symptoms increasingly appeared on an Internet bulletin board that offers advice to individuals regarding the purchase of online pharmaceuticals in 2005 (37,38).

Fig. 4. *Mitragyna speciosa*. Image courtesy of Dr. Christopher McCurdy.

Fig. 5. *Mitragyna speciosa*. Image courtesy of Dr. Christopher McCurdy.

Many abusers of opioid analgesics develop withdrawal symptoms during periods of intentional opioid abstinence. Kratom is widely used by this online community to mitigate opioid withdrawal symptoms, and is available through more than fifty online vendors (38). At $10 to $40 per ounce of plant material, Kratom is an economical alternative to other opioid-replacement medications (such as buprenorphine), and can be obtained without a prescription (9,39).

Pharmacology

Mitragynine is the most prevalent of the more than twenty alkaloids that have been isolated from Kratom, and is responsible for the substance's opioid effects (see Figure 6) (40,41). An indole alkaloid, mitragynine is structurally similar to yohimbine. Mitragynine displays *in vitro* activity at both supraspinal opioid mu- and delta- receptors (42). The

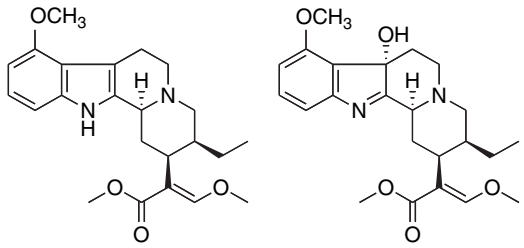

Fig. 6. Structures of Mitragynine and 7-Hydroxymitragynine.

mu- receptor mediates analgesia, euphoria, and respiratory depression, which accounts for the analgesia activity of mitragynine, as well as its amelioration of opiate withdrawal symptoms. Mitragynine has also been postulated to be involved in the activation of descending noradrenergic and serotonergic pathways in the spinal cord (43). However, there are no reports of mitragynine being screened for affinity at these specific receptors. The chemical similarity between the Kratom alkaloids and other biologically active compounds suggests that mitragynine and its congeners may be involved in activation or inhibition of other receptor systems.

Additional alkaloids isolated from Kratom, including 7-hydroxymitragynine, possess antinociceptive effects in animal models and a high affinity for opioid receptors (44). Studies on 7-hydroxymitragynine have demonstrated that this alkaloid may be more potent than morphine, even after oral administration (45). Animal studies suggest that mitragynine may stimulate post-synaptic alpha-2 adrenergic receptors, and/or block stimulation of 5-HT_{2A} receptors (44).

Kratom leaves, which are very bitter, can be chewed, smoked or brewed into tea (46). Kratom leaves contain approximately 0.2% mitragynine by weight, and twenty leaves of Kratom contain approximately 17 mg of mitragynine (33,34). Chewing of leaves produces greater effect at lower mitragynine doses; this may be in part due to the presence of other alkaloids in the leaves themselves (33). The mitragynine content of Kratom leaves is variable and may be dependent on geographic origin of trees, as well as season (40). Dose-dependent neuropsychiatric effects may occur within five to ten minutes after consumption, and last for up to one hour (33,34). In the mouse model, mitragynine doses as high as 920 mg/kg have been delivered without apparent clinical effect (47).

Clinical effects and toxicity

The clinical effects of Kratom are dose-dependent; consistent descriptions exist of stimulant effects at lower doses, and opiate effects predominating at higher doses in humans (33,34). This effect has also been witnessed in animal models (47). However, the doses required to produce stimulation, analgesia and toxicity in human remain poorly defined.

The antitussive, antinociceptive and antidiarrheal properties of mitragynine have been described as clinically similar to codeine; tolerance has also been described (34, 46). Nausea, vomiting, and diarrhea have been commonly described among Kratom users, with occasional reports of nystagmus and tremor (33). Anorexia, weight loss, hyperpgimentation and psychosis have been described in chronic users (34).

Diagnosis

No diagnostic testing for the presence of mitragynine or its metabolites has been reported. The diagnosis is established by obtaining an accurate history.

Management

Reports of toxicity secondary to mitragynine are rare (33,34,48). In animal models, mitragynine has been shown to cause less respiratory depression than other narcotics (46). Animal literature provides conflicting results regarding the efficacy of opioid receptor antagonists in reversing Kratom effects (49). Given the safety profile and potential benefits of naloxone use in the emergency department setting, this antidote should be considered for patients who present with respiratory depression after Kratom use, in addition to supportive care. No cases of death due to Kratom have been reported in the United States.

Abuse liability

Addiction to Kratom has been described in older reports (48). Additionally, an opioid abstinence syndrome has been reported after chronic Kratom use. The symptoms include irritability, yawning, rhinorrhea, myalgias, diarrhea and arthralgias (34). Also, the development of hyperpigmentation over the cheeks has been described in long-term Kratom addicts (34,48).

Conclusions

Salvia divinorum and Kratom are both widely available over the Internet, and their use is increasing in the United States. These products escape traditional methods of toxicological monitoring, as use of *Salvia divinorum* or Kratom are unlikely to prompt a call to the poison control center, or a visit to the Emergency Department. Little is known about the clinical effects, potential toxicity and abuse potential of these products. Further study of the pharmacokinetics, toxicokinetics, clinical effects, toxicity and long-term effects of *Salvia divinorum* and Kratom is required.

Acknowledgments

The authors gratefully acknowledge the contribution of Fire Erowid and Earth Erowid of www.erowid.org, and Drs. Melisa W. Lai and Robert S. Hoffman to the generation of this article. Dr. Boyer is supported by NIH grant R21 DA14929.

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