Chapter 51

The Plant *Salvia divinorum* (Lamiaceae)—Chemistry and Pharmacology

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Abbreviations

ADMET Absorption, distribution, metabolism, excretion, and toxicity
CD Circular dichroism
CNS Central nervous system
CPP Conditioned place preference
DMAPP Dimethylallyl diphosphate
EL Extracellular loop
GPCR G-protein coupled receptors
i.p. Intraperitoneal
IPP Isopentenyl diphosphate
i.v. Intravenous
K_i Inhibitory (affinity) constant
LSD Lysergic acid diethylamide
NIDA National Institute on Drug Abuse
NIMH National Institute of Mental Health
NMR Nuclear magnetic resonance
PDSP Psychoactive Drug Screening Program
PET Positron emission tomography

INTRODUCTION

The plant *Salvia divinorum* (Epling & Játiva-M.; Figure 1) is a member of the mint family (Lamiaceae) endemic to the Sierra Mazateca region of the Sierra Madre de Oaxaca of southern Mexico. It has a history of known ethnobotanical use by the Mazatec Indians extending several centuries both in medicinal and spiritual practices (Valdes, Diaz, & Paul, 1983). Initially, it was reports of the perceptiotropic effects that accompanied use of this material and its use as an alternative to psilocybin containing mushrooms that generated interest in the chemistry and pharmacology of this plant (Schultes & Hofmann, 1980). However, the effects of *S. divinorum* are distinct from those produced by classical hallucinogens such as psilocybin containing mushrooms or mescaline containing cacti. Traditional practices utilized fresh leaves of *S. divinorum* consumed by either chewing a rolled quid or by drinking an aqueous infusion. Approximately 50–100 leaves would be consumed to produce a short-acting (15–30 min) mild hallucinogenic state to aid divination ceremonies (Siebert, 1994; Valdes et al., 1983).

In 1982, Ortega et al. isolated a new neoclerodane diterpenoid from the leaves of *S. divinorum* that they named salvinorin A. In 1984, Valdes, Butler, Hatfield, Paul, and Koreeda separately isolated salvinorin A and reported behavioral activity in a mouse model that resembled effects seen in traditional human consumption of the plant. In 1994, Daniel J. Siebert reported the results of a human trial administering pure salvinorin A. This study revealed that vaporized salvinorin A inhaled at a dose range of 200–500 μg/human subject produced perceptiotropic effects similar to that of the whole herb—but with a much faster onset (approximately 30 s), far greater intensity (mixed hallucinogenic and dissociative effects), and shorter duration (approximately 5–10 min).

CHEMISTRY

The major secondary metabolites isolated from *S. divinorum* have largely been diterpenoids, which are biosynthesized from four isoprene building blocks through condensation of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Kutrzeba et al., 2007). Since the first isolation of salvinorin A in 1982 additional diterpenoids have been reported (Figure 2) including divinatorins (A–F), salvidivins (A–D), salvinicins (A and B), and nine additional salvinorins (B–J) (Casselman, Nock, Wohlmuth, Weatherby, & Heinrich, 2014). Salvinorin A is a representative member of the neoclerodane structural class, which is a subclass of the diterpenes which has a core carbon skeleton possessing the same configuration as the clerodin isolated from *Clerodendron infortunatum* (Sim, Hamor, Paul, & Robertson, 1961). The neoclerodane skeleton is a regularly encountered carbon structure in natural products and has been isolated from a wide range of plant families including Asteraceae (Compositae), Euphorbiaceae, Lamiaceae, and Verbenaceae (Rogers et al., 1979). However, due to the unique and extremely potent perceptiotropic activity that salvinorin A displays it has been the focus of extensive psychopharmacological research.

Complementing initial nuclear magnetic resonance (NMR)-facilitated structure assignment of salvinorin A, the absolute configuration was determined by single-crystal X-ray crystallography (Ortega, Blout, & Manchand, 1982) and was corroborated by circular dichroism (CD) spectra analysis by Koreeda, Brown, and Valdes (1990). The first total synthesis of salvinorin A, reported in 2007, consisted of 29 steps with a 0.8% total yield (Scheerer, Lawrence,

Wang, & Evans, 2007), with later improvements resulting in a reduction to 13 steps with a 2.8% overall yield (Hagiwara, Suka, Nojima, Hoshi, & Suzuki, 2009). Notwithstanding the continued improvements in the total synthesis of the salvinorin A, this process is not competitive with the effective and low-cost isolation from the leaves of the host plant *S. divinorum*. The isolation approach continues to serve as the primary source of salvinorin A used in the semi-synthesis of a vast array of analogues.

FIGURE 1 ***Salvia divinorum*** **plant in its natural habitat.** (Oaxaca region in Mexico, 2008, J. Zjawiony collection).

In 2002, Roth et al. screened salvinorin A against the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) battery of cloned human G-protein coupled receptors (GPCR), ligand-gated ion channels, and transporters to identify potential targets. Surprisingly, they found that salvinorin A was selective for the κ-opioid receptor (KOR) and did not possess significant activity against any of the other assessed molecular targets. What made this so surprising is the extremely high degree of receptor subtype-selectivity toward the KOR that salvinorin A exhibited and that it displayed no appreciable activity toward the serotonin receptors, specifically 5-HT_{2A}, which is the primary site of classic hallucinogens such as lysergic acid diethylamide (LSD), mescaline, psilocybin, etc. (Roth et al., 2002).

Salvinorin A represents the first known nonnitrogenous KOR agonist. Until its discovery, the presence of a nitrogen atom was considered a structural requirement for high-affinity opioid receptor agonist interaction. The lack of a cationic nitrogen suggested that hydrogen bonding likely played a major role in

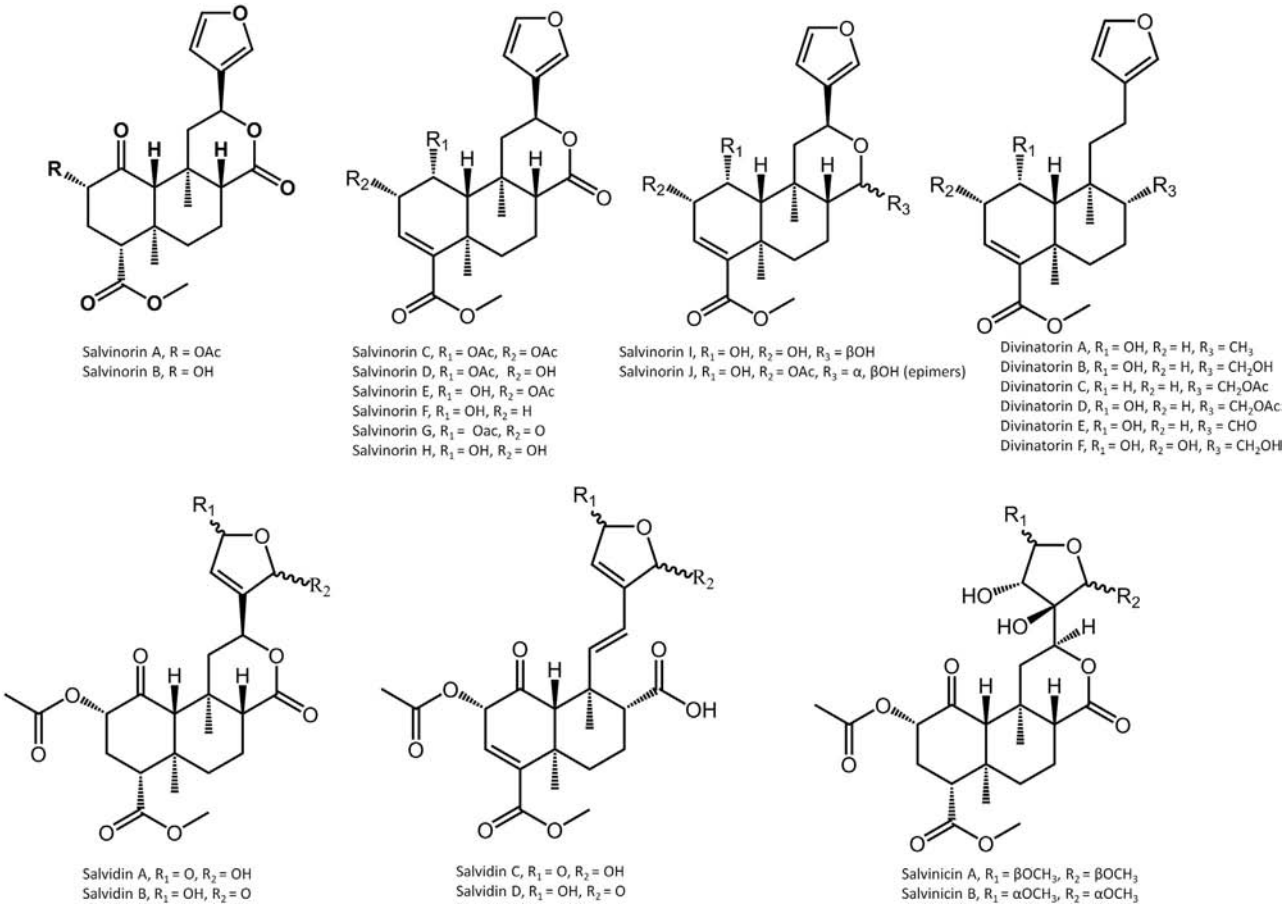

FIGURE 2 **Neoclerodane diterpenoids isolated from** ***Salvia divinorum*****.** Since the first isolation of salvinorin A in 1982 additional neoclerodane diterpenoids have been isolated including divinatorins (A–F), salvidivins (A–D), salvinicins (A and B), and nine additional salvinorins (B–J). *Adapted from Zjawiony, J. K. (2015) with permission from CRC Press, Boca Raton, FL, USA.*

receptor binding. To determine the importance of the hydrogen bond accepting groups (Figure 3), salvinorin A structure–activity relationship studies focused analogue design on the roles the C(1)-carbonyl, C(2)-acetoxy, C(4)-carbomethoxy, C(12)-furanyl, and the C(17)-carbonyl groups played in KOR binding/activation (Prisinzano, 2013).

Early work quickly established the importance of having substituents at the C(2)-position capable of making specific acceptor/donor interactions at KORs. This was readily apparent from the minor structural difference between salvinorin A and salvinorin B,

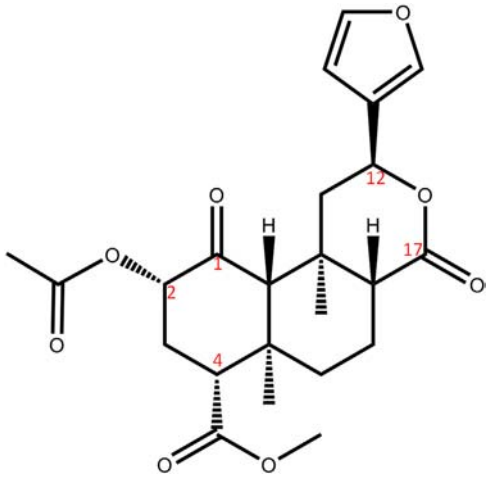

FIGURE 3 **Salvinorin A.** Salvinorin A pharmacophore. Numbered in red are key structural positions capable of hydrogen bond interactions. C(1)-carbonyl, C(2)-acetoxy, C(4)-carbomethoxy, C(12)-furanyl, and the C(17)-carbonyl groups.

the loss of the hydrogen bond accepting acetoxy group in salvinorin A results in the biologically inactive salvinorin B compound in regards to δ-, κ-, and μ-opioid receptors' binding affinity. This was initially modeled in silico where the acetoxy group was required for high affinity receptor docking (Roth et al., 2002). Subsequent metabolic studies (Schmidt et al., 2005) and structure–activity relationship studies (Chavkin et al., 2004) verified the importance of this position for KOR activity.

There have been more than 200 salvinorin A analogues created as of 2015 of which only a small portion possess KOR binding affinity (K_i) less than 10 nM. Most of the salvinorin analogues display decreased κ-opioid affinity or even a complete loss of significant binding affinity at the opioid receptors (Yan et al., 2009). Of the high-affinity analogues the majorities are based upon C(2)-position modifications, further supporting the importance of this position toward opioid receptor activity. The synthesis design focus has been to probe the physiochemical and steric tolerances of the opioid receptors for this region of the salvinorin structure, as well as, to minimize metabolic lability of the resulting analogues. It has been shown that analogues whose functional group substitution at the C(2)-position is able to mimic carbonyl oxygen characteristics are capable of producing high binding affinity toward the KOR (Riley et al., 2014). Of particular interest has been the discovery that introducing aromatic moieties in conjunction with ester-mimetic linkages at the C(2)-position result in a significant shift in the pharmacological profile of the resulting analogue from KOR selective agonists to dual-affinity κ/μ-opioid receptor agonists (Cunningham, Rothman, & Prisinzano, 2011; Harding et al., 2005; Polepally et al., 2014).

In general, structural modifications (Figure 4) to the C(1)-carbonyl, C(4)-carbomethoxy, C(12)-furanyl, and the C(17)-carbonyl groups tend to produce reduced or KOR affinity compared with

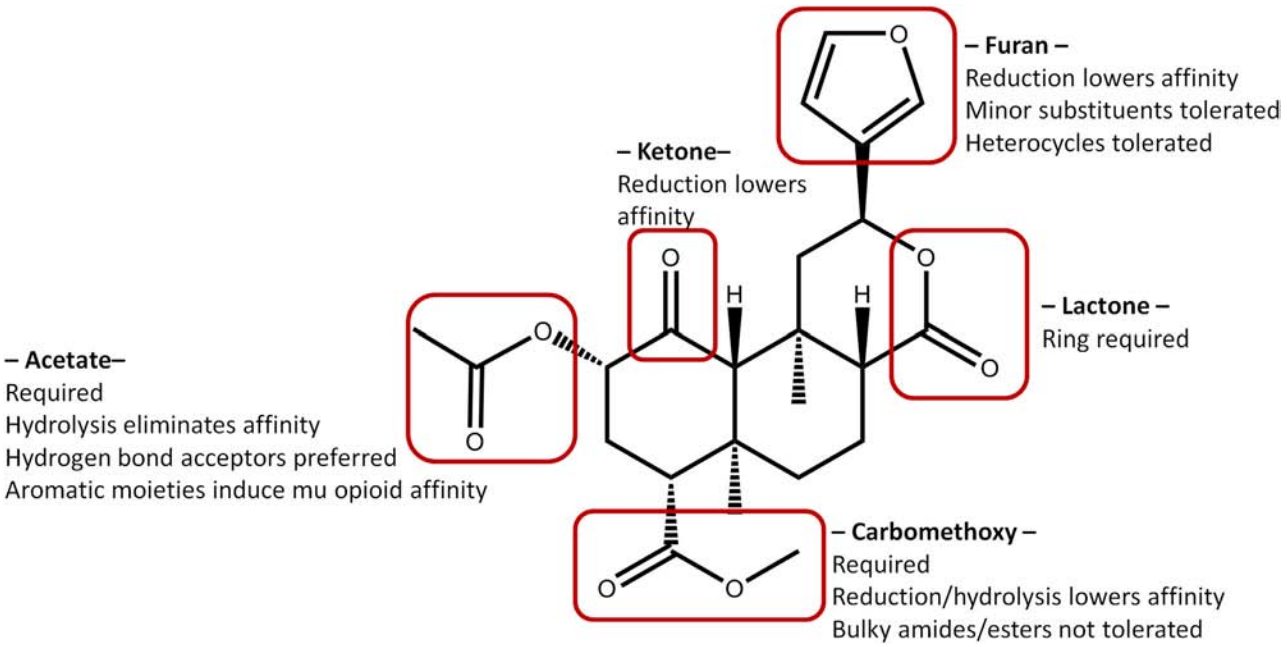

FIGURE 4 **Effect of structural modifications to salvinorin A.** Structural modifications to the salvinorin A pharmacophore at the C(1)- carbonyl, C(4)-carbomethoxy, C(12)-furanyl, and the C(17)-carbonyl groups tend to produce reduced or abolished KOR affinity compared with the salvinorin A parent compound. To date only modifications to the C(2)-acetoxy have surpassed the binding affinity of the lead compound salvinorin A. *Adapted from Prisinzano and Rothman (2008) and Cunningham, Rothman and Prisinzano (2011) with permission from American Chemical Society and American Society of Pharmacology.*

the salvinorin A parent compound (recommended reviews: Cunningham et al., 2011; Prisinzano & Rothman, 2008).

PHARMACOLOGY

The opioid receptors are a family of GPCR divided into three main subtypes: δ-, κ-, and μ-opioid receptors, with a fourth member (nociception receptor) that shares structural similarity but limited affinity for classic opioid ligands. Activation of opioid receptors is often clinically targeted for their ability to produce analgesia; however, each subtype can also produce concomitant effects in addition to their ability to relieve pain. δ-Opioid receptor agonists are known to produce respiratory depression and convulsions (Clapp et al., 1998; Jutkiewicz, Baladi, Folk, Rice, & Woods, 2006). KOR agonists are known to produce dysphoria and pronounced perceptiotropic effects such as hallucinations and dissociations (Land et al., 2008; Roth et al., 2002). μ-Opioid receptor agonists, which account for the majority of clinically used opioids, typically possess potent analgesic activity but also are known to induce euphoria. This induction of euphoria is often correlated to subsequent addiction.

These adverse secondary effects related to individual subtypes represent prominent therapeutic liabilities for which ongoing research attempts to address through multiple approaches. Functional activation approaches seek to activate the opioid receptors in a selective manner to achieve analgesia but avoid adverse effects (respiratory depression, hallucinations, euphoria, etc.). Peripheral localization attempts to minimize central nervous system (CNS)-related effects by restricting chemotherapeutics (e.g., induce peripheral analgesia while avoiding CNS induced euphoria). Dual-affinity approaches seek to moderate the adverse effects of a single opioid subtype by co-activation of a second type (e.g., activation of κ and μ can both induce analgesic effects, but κ-induced dysphoria can moderate mu induced euphoria to yield a neutral pain reliever).

Due to the pronounced perceptiotropic effects of salvinorin A that are resultant from its highly selective binding affinity for the KORs, it is the most widely researched neoclerodane diterpenoid from *S. divinorum*. However, additional neoclerodane diterpenoids isolated from *S. divinorum* have exhibited appreciable activity toward the KOR. In particular, divinatorin D was determined to possess a $K_i = 230$ nM, salvidivin A had a reported $K_i = 440$ nM (and exhibited a dual-affinity at μ-opioid receptors of $K_i = 760$ nM), salvinicin A was reported at $K_i = 390$ nM, and salvinorin G possessed a $K_i = 418$ nM. Nevertheless, the activities of the preceding diterpenoids are significantly less than that of salvinorin A which is highly selective toward KORs with measured binding affinity as high as $K_i = 1$ nM (Lee et al., 2005; Simpson et al., 2007).

Binding Mode Studies of Salvinorin A

A number of studies focused on elucidating the binding mode of salvinorin A at the KORs have been undertaken. These include the development of both computational models, as well as, biochemical approaches such as point-mutations alterations and chimeral receptor design (Kane, McCurdy, & Ferguson, 2008; Kane, Nieto, McCurdy, & Ferguson, 2006; Polepally et al., 2014; Yan et al., 2005). The first reported in silico model was based on the previous docking of a KOR-selective agonist U69593 (Roth et al., 2002). This base model was developed from a general model of the seven α-helical domains for rhodopsin-like GPCRs using hydrogen bonding constraints that are central to salvinorin A binding (Pogozheva, Lomize, & Mosberg, 1998). This allowed for the binding orientation within the KOR binding pocket to be proposed with the C(12)-furanyl being oriented toward the transmembrane (TM) I and II α-helices and the C(4)-carbomethoxy group toward the TM V and VI α-helices (Pogozheva et al., 1998).

Subsequent biochemical investigations generating a series of point mutations began to elucidate key regions within the transmembrane helices. In particular, point mutations along the TM II, III, and VII α-helices, that are characterized by a number of lipophilic tyrosine residues, revealed that loss of tyrosine residues: Y119 on TM II; Y139 on TM III; and Y312, Y313, and Y320 on TM VII negatively affected the ability of salvinorin A to bind to the KOR (Yan et al., 2005). These results indicated that the binding epitope for salvinorin A is unique from classical opioid agonists. Additionally, due to the specific residue interactions it was proposed that the salvinorin A binding epitope vertically spans transmembrane α-helices II and VI (Figure 5), with involvement at extracellular loop (EL) 2. This suggests that residues of the TM II helix, in their binding with salvinorin A, rotate to optimize receptor–ligand interactions. This conformational shift potentially represents a unique mechanism of binding.

Additional point-mutations studies determined that residue Q115 on TM II; and residues I316 and Y320 on TM VII are required for salvinorin A binding (Kane et al., 2008). This study also corroborated the importance of Y119 on TM II and Y313 on TM VII, which interact with the C(4)-carbomethoxy and C(2)-acetoxy, respectively. This supports the proposed binding epitope orientation that salvinorin A vertically spans transmembrane α-helices II and VI. Lastly, Kane et al. (2008) concluded that none of the amino acid residues frequently associated with classic

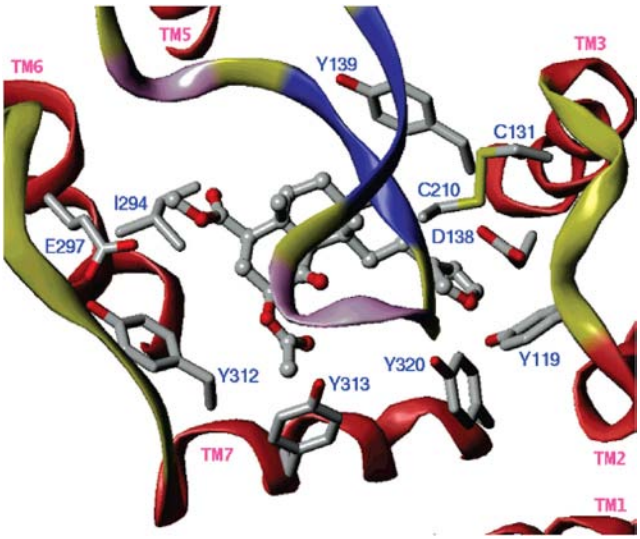

FIGURE 5 Model of salvinorin A docked within the κ-opioid receptor. The docked view is from the extracellular side of the κ-opioid receptor. Salvinorin A and important numbered residues are rendered as ball and stick (red = oxygen atom and yellow = sulfur atom), the rest of the receptor are color coded (blue = β-sheet, red = α-helix, violet = turn, yellow = coil). *Taken from Yan et al. (2005) with permission of American Chemical Society.*

opioid binding, commonly observed on TM III and VI, appear to be involved with the binding of salvinorin A.

Utilizing this amassed in vitro data Wu et al. (2012) developed improved in silico molecular model to explore the putative binding mode of salvinorin A at the KOR (Figure 6). In their model the diterpenoid tricyclic core is vertically oriented toward TM II and delineated by the side chains of amino acid residues: D138, Q115, T111, V108, V118, V134, and V135. The C(12)-furanyl was calculated to interact with residues: $C210^{EL2}$, V118, $W124^{EL1}$, Y313. Residue Y313 has previously been shown in point mutation studies to be critical for salvinorin A binding (Yan et al., 2005) and the current molecular model indicated that Y313 likely forms a key hydrogen bond with the C(12)-furanyl. The C(4)-carbomethoxy was oriented into a binding pocket defined by residues: T111, V108, W287, and Y320. Amino acid residues T111 and Y320 in the current molecular model are suggested to engage in hydrogen bonding with the C(4)-carbomethoxy moiety. Previous point mutations studies have determined that Y320 is required for salvinorin A binding (Kane et al., 2008), however the significance of T111 has yet to be explored in vitro. Lastly, their molecular model positioned the C(2)-acetoxy into a binding pocket defined by residues: D138, M142, and W139. However, continued research into elucidating the unique binding mode of the salvinorin A pharmacophore at the KOR is still needed, with special focus on validating in silico approaches with in vitro point-mutations studies.

Absorption, Distribution, Metabolism, Excretion, and Toxicity of Salvinorin A

The traditional methods of administration consist of consuming fresh leaves of *S. divinorum* by either chewing a rolled quid or by drinking an aqueous infusion. Approximately 50–100 leaves would be consumed to produce a short-acting (15–30 min) mild hallucinogenic state to aid divination ceremonies (Siebert, 1994; Valdes et al., 1983). However, clinical trials have showed that both of these routes of administration are largely inefficient as sublingual doses of up to 4 mg of isolated salvinorin A failed to produce perceptiotropic effects and that salvinorin A is largely deactivated in the gastrointestinal tract when consumed as an aqueous infusion (Mendelson et al., 2011; Siebert, 1994). These results likely accounts for the mild activity found in traditional practices. However, in 1994, Daniel J. Siebert reported the results of a clinical trial administering pure salvinorin A which revealed that vaporized salvinorin A inhaled at a dose range of 200–500 µg/human subject produced perceptiotropic effects similar to that of the whole herb—but with a much faster onset (approximately 30 s), far greater intensity (mixed hallucinogenic and dissociative effects), and shorter duration (approximately 5–10 min). This method, vaporization, is currently the prevalent mode of administration in nonclinical settings, though the previously discussed traditional methods are still widely employed.

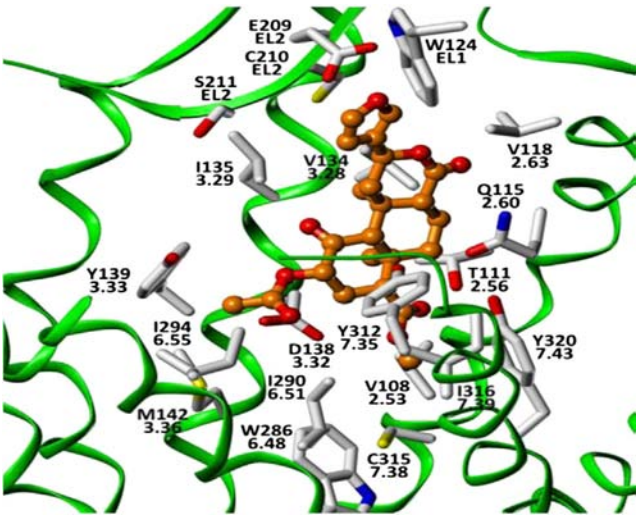

FIGURE 6 **Improved model of salvinorin A docking within the κ-opioid receptor.** The docked view is from the extracellular side of the KOR. Salvinorin A and important numbered residues are rendered as ball and stick (blue = nitrogen atom, red = oxygen atom, yellow = sulfur), the remaining transmembrane α-helices are colored green. *Taken from Polepally et al. (2014) with permission of Elsevier Masson SAS.*

Positron emission tomography (PET) studies of intravenous (i.v.) administered radiolabeled salvinorin A performed in nonhuman primates (baboons) revealed an extremely fast CNS uptake in approximately 40 s with a half-life of 8 min (Hooker et al., 2008). This study corroborates the extremely short duration of activity that salvinorin A has been reported to produce in both controlled clinical trials and from ethnobotanical studies. Hooker et al. (2008) also determined that while salvinorin A was distributed throughout the brain, the highest concentrations were in the cerebellum and visual cortex. In following the distribution of radiolabeled salvinorin A they discovered that initial uptake was highest in the kidneys, however the liver and gallbladder began to accumulate the radiolabel (Figure 7). The gallbladder eventually had the highest uptake of any organ for the radiolabelled ligand. Whole-body scans indicated that approximately equal amounts of the radiolabel were concentrated in the gallbladder (and biliary tract) and the urinary bladder. They suggested that this likely indicates that there are, at a minimum, two routes of metabolism and excretion for salvinorin A: collection through the gallbladder (likely as lipophilic metabolites) and the second through renal filtration (likely as hydrophilic metabolites).

Salvinorin A has been assessed for toxicological effects in a number of model organisms (rodent, primate, etc.) and even in human trials (Table 1), it has to date yielded results that indicate a safe physiological profile under a range of doses. In mice an acute physiologic and chronic study of salvinorin A at a high dose range of at 0.4–6.4 mg/kg failed to elicit significant effects on either body temperature, cardiac conduction, galvanic skin response, or pulse pressure (Mowry, Mosher, & Briner, 2003). Histologic studies of the blood, bone marrow, brain, kidney, liver, and spleen failed to find any significant histopathological changes. In human clinical trials dose ranges of 0.375–21 µg/kg have been assessed and did not produce significant adverse physiological effects (i.e., no dose-related change to blood pressure, heart rate, or resting/kinetic tremors was measured) (Johnson et al., 2011). Overall there is a substantial body of research to indicate that the potential toxicity of salvinorin A is quite low.

Current Use and Misuse of *Salvia divinorum*

Due to the perceptiotropic effects of *S. divinorum* and possible recreational use thereof, it can be argued that *S. divinorum* represents a potential drug of abuse. Moreover, modern use typically

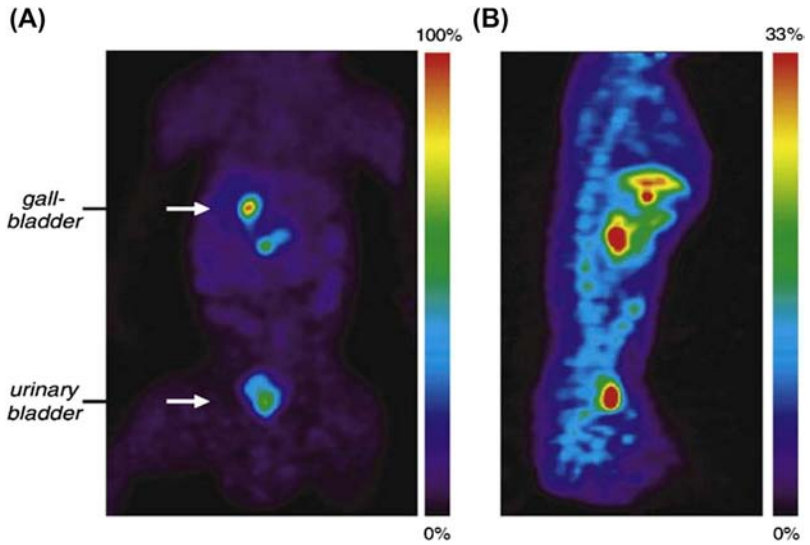

FIGURE 7 Whole-body PET images of radiolabeled salvinorin A in nonhuman primates. Whole-body PET images of baboon administered i.v. radiolabeled salvinorin A. Images collected from 65–110 min. (A) Coronal slice through gallbladder and urinary bladder (scaled to 100% of maximum pixel value). (B) Midline sagittal slice visualizing the liver, gallbladder, urinary bladder, as well as the intestinal tract and spine (scaled to 33% of maximum pixel value). These images show the cumulative distribution of administered radiolabeled salvinorin A. *Taken from Hooker et al. (2008) with permission from Elsevier Masson SAS.*

TABLE 1 Clinical Trials with *Salvia divinorum* and Salvinorin A

Test Material	Route of Administration	Dose Range	*N*	Physiological Effects	References
Salvinorin A	Vaporization/ inhalation	0.375–21 µg/kg	8	No significant change to blood pressure or heart rate. No resting or kinetic tremors were observed.	MacLean, Johnson, Reissign, Prisinzano, and Griffiths (2013)
Fortified leaf material	Vaporization/ inhalation	100–1017 µg/kg	30	No significant change to body temperature or systolic blood pressure.	Addy (2012)
Salvinorin A	Vaporization/ inhalation	0–12 mg	10	No significant change to blood pressure or heart rate.	Ranganathan et al. (2012)
Salvinorin A	Vaporization/ inhalation	0.375–21 µg/kg	4	No significant change to heart rate or blood pressure.	Johnson, MacLean, Reissig, Prisinzano, and Griffiths (2011)
Salvinorin A	Sublingual	1–4 mg	8	No effects, poor bioavailability by sublingual administration.	Mendelson et al. (2011)
Fresh leaves	Sublingual	30 g (of leaves)	6	No negative effects reported.	Siebert (1994)
Salvinorin A	Vaporization/ inhalation	200–500 µg	6	No negative effects reported.	Siebert (1994)

Brief summary of key human trials administering salvinorin A (or *Salvia divinorum*). N = number of human participants. Lack of observed adverse physiological or toxicological effects from these studies corroborate preclinical studies concluding that *S. divinorum* and salvinorin A possess absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles suggesting an extremely low potential for toxicity.
Adapted from Casselman et al (2014). Data compiled from referenced articles.

differs from traditional routes of administration by utilizing fortified leaf material that is smoked: this produces a much faster onset (approximately 30 s), far greater intensity (mixed hallucinogenic and dissociative effects), and shorter duration (approximately 5–10 min) than by traditional routes. The potential for disorientation and/or experiencing negative psychological effects resulting from this rapid onset and increased intensity of the experience is a potential risk for unprepared users, especially those acting outside of any unified practice or those expecting marijuana-like effects.

Numerous studies have assessed the effects of modern vaporization/inhalation administration of fortified leaf material (Addy, 2012), as well as, pure salvinorin A (Johnson et al., 2011; Ranganathan et al., 2012; Siebert, 1994) in humans. Additional studies have employed

traditional methods of administration and unprocessed *S. divinorum* plant material (Mendelson et al., 2011; Siebert, 1994). However, to date, no clinical study has reported adverse physiological or toxicological effects in humans, further corroborating numerous preclinical studies that indicated the potential toxicity as being extremely low (i.e., no statistically significant adverse effects measured) (Johnson et al., 2011; Mowry et al., 2003).

In terms of psychological effects, while the clinical studies have noted measureable differences between the perceptiotropic effects of administered salvinorin A (or use of fortified leaf material) and those of classic hallucinogens such as LSD, mescaline, psilocybin, etc., clinical studies have not reported adverse persisting psychological effects afterward (MacLean et al., 2013). The acute perceptiotropic effects of vaporizes/inhaled fortified leaf material is largely identical to that of pure salvinorin A. These effects are often characterized by hallucinogenic and dissociative activity which include altered perception of the passage of time, altered perceptions of bodily form (i.e., body merging with objects/environment), and perception of vivid colors, patterns, scenes, etc. (Zawilska & Wojcieszak, 2013).

A number of large epidemiological studies have assessed the prevalence of *S. divinorum* use. Analysis of United States National Surveys on Drug Use and Health data sets (2006–2008, n = 166,453) showed that 1.3% of those surveyed had used *S. divinorum* in their lifetime (Wu, Woody, Yang, Li, & Blazer, 2011). The National Institute on Drug Abuse (NIDA), examining more than 390 private and public schools (2010), reported that approximately 5.5% of high school students (n = 46,482) had used *S. divinorum* (Lin, Li, Chen, Chang, & McKetin, 2014). These numbers correspond very well with those from a Canadian study that reported 6.2% of adolescents (age 12–17 years) had used *S. divinorum* (Currie, 2013). A study of 1516 university students reported that 4.4% had used *S. divinorum* in their lifetime (Lange, Reed, Croff, & Clapp, 2008). A separate time-course study of 825 undergraduate students (from a different university) reported a 6.7% rate of lifetime use of *S. divinorum*, but this drops to 3% within the last year, and 0.5% with the past month during the course of their study, with the authors concluding that the data suggests a likely low rate of continuance for this substance (Khey, Miller, & Griffin, 2008).

Applications Toward Addiction and Substance Misuse

In nearly every model assessed (mouse, rat, nonhuman primates, human, etc.) *S. divinorum* and its major constituent, salvinorin A, are not reported to induce addictive behavior or produce euphoria. Two studies by Braida et al. report conditioned place preference (CPP; a possible indicator for potential reinforcing activities of a test compound) at low doses in rats and zebrafish (Braida et al., 2008, 2007). Their tested CPP dose range of 0.1–40 μg/kg was reinforcing in rats, with higher doses producing aversive effects. This same study reported that for self-administration assays in rats 1 μg/i.v. infusion was aversive (Braida et al., 2008). However, the aggregate data indicates that in humans this substance is unlikely to be used in a compulsive/repetitive manner or persistently. More importantly, salvinorin A and a number of salvinorin A analogues have been showed to exhibit antiaddictive properties (Kivell, Ewald, & Prisinzano, 2014).

Representative studies include: Morani, Kivell, Prisinzano, and Schenk (2009) reporting that salvinorin A was able to attenuate cocaine self-administration in rats at doses of 0.3 and 1 mg/kg via intraperitoneal (i.p.) injection. Prevatt-Smith et al. (2011) described the assessment of a series of Salvinorin A analogues that attenuate drug-seeking behavior in rats utilizing a self-administration assay. Sufka et al. (2014) reported that whole extracts of *S. divinorum* and salvinorin A administered i.p. produced conditioned place aversion in rats, extracts at 10 and 100 mg/kg and salvinorin A at 0.3 and 1.0 mg/kg. Corroborating reports in nonhuman primates studies have shown that i.v. administration of salvinorin A attenuated self-administration of both cocaine and remifentanil (a μ-opioid agonist) (Freeman, Naylor, Prisinzano, & Woolverton, 2014). Lastly, some countries like Finland, Iceland, Norway, and Estonia provide for physician prescribed use of *S. divinorum* in the treatment of cocaine and heroin addiction in humans (Listos, Merska, & Fidecka, 2011).

CONCLUSION

To date, there is an overwhelming amount of preclinical and clinical research that indicates *S. divinorum* and its major constituent, salvinorin A, exhibit a relatively safe physiological profile (i.e., no reports of statistically significant adverse physiological or toxicological effects in humans). Epidemiological studies also indicate that lifetime-incident use of this material is extremely minor (1.3–6.7% rate) with the data suggesting use to largely be self-limiting resulting in a low rate of continuance. Lastly, both *S. divinorum* and salvinorin A (as well as a growing number of analogues) have been shown to exhibit antiaddictive effects in relation to both cocaine and heroin.

DEFINITION OF TERMS

Dissociative A psychoactive compound that produces pronounced perceptual alterations resulting in feelings of detachment/dissociation from self and/or environment.

Diterpenoid It is a chemical structure composed of at least four isoprene units and in which oxygen atoms have been incorporated.

Fortified leaf It is a substance in which material has been extracted from one set of leaves and deposited onto another to enrich the phytochemical content (e.g., the fortified leaf material has two times the amount of phytochemicals present in unprocessed leaves).

Hallucinogen It is a psychoactive compound that produces pronounced alterations in perceptions and thought processes, such as inducing hallucinations (i.e., subjective phenomena becomes indistinguishable from objective phenomena).

Lysergic acid diethylamide It is an ergoline derivative that produces pronounced hallucinogenic effects at a dose range of 100–400 μg with duration of approximately 10 h.

Mescaline It is a phenethylamine class natural product that is biosynthesized in a number of cacti. At dose range of 200–400 mg will produce hallucinogenic effects with duration of approximately 8 h.

Neoclerodane It is a chemical structure in which the carbon skeleton possesses the same configuration as the natural product clerodin.

Perceptiotropic It is a substance or combination of substances that produces an alteration in perception, used as a general term to encompass the range of effects such as dissociative, empathogenic,

hallucinogenic, etc. and especially complex mixed states (e.g., dissociative–hallucinogenic).

Pharmacophore It is the essential molecular features that are required for a chemical structure to possess a targeted biological activity (e.g., recognition at a specific receptor).

Psilocybin It is a tryptamine class natural product that is biosynthesized by some mushrooms. A dose range of 10–25 mg will produce hallucinogenic effects with a duration of approximately 6 h.

KEY FACTS OF THE KOR

- KOR is one of three opioid receptor subtypes.
- Opioid receptors are a family of transmembrane GPCRs.
- KORs have system wide distribution.
- KOR activation can induce analgesic effects.
- KOR activation is also known to induce dysphoria which is often viewed as a clinical liability.
- KOR ligands have been shown to exhibit antiaddictive effects.
- KOR is a clinical target for antiaddiction therapeutics.

SUMMARY POINTS

- This chapter focuses on the perceptiotropic plant *S. divinorum* (Epling & Játiva-M.).
- Endemic to the Sierra Mazateca region of the Sierra Madre de Oaxaca of southern Mexico.
- Has an established history of ethnobotanical use extending several centuries both in medicinal and spiritual practices.
- Traditional practices utilize fresh leaves of *S. divinorum* in the form of either an aqueous infusion or a chewed quid.
- The natural product salvinorin A, isolated from *S. divinorum*, binds with extremely high selectivity and affinity to the KOR in a functionally unique manner.
- Extensive studies have reported that both *S. divinorum* and its major constituent, salvinorin A, exhibit a relatively safe physiological profile.
- Inhaled salvinorin A at a dose range of 200–500 μg produces perceptiotropic effects similar to that of the whole herb—but with a much faster onset (30 s), far greater intensity (mixed hallucinogenic and dissociative effects), and shorter duration (5–10 min).
- Epidemiological studies indicate that lifetime-incident use of this material is extremely minor with the data suggesting use to largely be self-limiting resulting in a low rate of abuse.
- Both *S. divinorum* and salvinorin A (as well as a growing number of analogues) have been shown to exhibit antiaddictive effects in relation to both cocaine and heroin.
- Potential for *S. divinorum* to serve as the source of novel antiaddiction therapeutics.

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