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Salvinorin A

Pharmacology, therapeutic potential and structural considerations of a unique non-nitrogenous selective k-opioid receptor agonist, and active component of the sage *Salvia divinorum*.

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Summary

Salvia divinorum is a plant indigenous of Oaxaca, Mexico. Traditionally, the plant is used for healing and divinatory purposes. At present, *S. divinorum* is also used recreationally by teenagers and young adults around the world. The main active component is salvinorin A, a unique non-nitrogenous kappa-opioid receptor agonist with hallucinogenic properties. Scientific interest is high, due to two facts: 1) salvinorin A was the first non-nitrogenous opioid-receptor ligand, 2) it elicits hallucinogenic effects without binding at serotonin receptors, as classical hallucinogens (LSD, psilocin, mescaline) do. Structural modifications of salvinorin A led to the discovery of herkinorin and other non-nitrogenous opioid receptors ligands, which are a powerful tool for elucidating the complex biological mechanisms of opioid receptors and for drug discovery of new therapeutic agents for pain treatment, drug dependence and mental disorders. The pharmacological profile of salvinorin A suggests several clinical applications related to the regulation of gastrointestinal functions, mood and drug-seeking behavior. The fast metabolism and pharmacokinetics of salvinorin A hinder clinical development, however it has been shown that some analogs have improved metabolic and pharmacokinetic profile. The first psychopharmacological studies on humans reported intense and unique psychedelic effects and positive after-effects on mood, well-being and awareness which may outweigh negative effects. Moreover, the drug exhibits low toxicity, few reported adverse effects and low abuse potential, making it suitable for further clinical studies. Taking in account the traditional use of the plant, the overall safe pharmacological profile, and the positive results on mood and general well-being obtained so far, it would be interesting and potentially beneficial to investigate further on the psychopharmacology of this unique molecule in respect of drug-assisted psychotherapy and treatment of depression, besides the clinical applications of salvinorin A and analogs for gastrointestinal disorders, pain treatment, drug dependence and mental problems.

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Introduction

Salvia divinorum is a very interesting plant among almost 1000 species of *Salvia* in the world. It is a perennial herb of the Labiatae family, endemic to a small region of Oaxaca, Mexico. *Salvia divinorum* does not produce flowers on a regular seasonal basis (Valdés *et al.* 1987; Reisfield 1993) and its pollination and sexual reproduction are still mostly unknown, even though it has been suggested that the plant could be ornithophilous (Reisfield 1993). The usual method of propagation is clonal, both naturally and by humans (Reisfield 1993). The name *Salvia divinorum* means "Salvia of the seers".

Ethnopharmacology

Traditionally, *Salvia divinorum* has been used by the Mazatecs, an ancient indigenous Mexican group located in northeast Oaxaca (Figure 1) (Valdés *et al.* 1983). The Mazatecs employ three main psychoactive substances for their spiritual-healing rituals, which are mushrooms (*Psylocibe* spp.), morning glory seeds (*Rivea corymbosa, Ipomoea purpurea)* and *Salvia divinorum* leaves (Valdés *et al.* 1983). Among the three, *Salvia divinorum* was reported as the best "teacher" for healing, the most delicate one, and the first to be employed in shamanic training (Valdés *et al.* 1983).

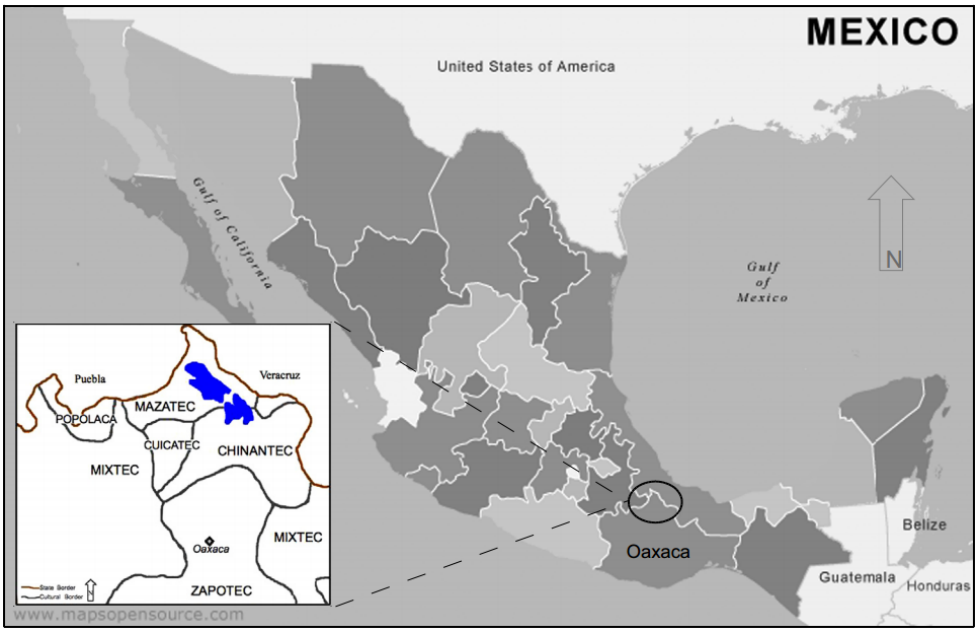


Figure 1. Mazatec traditional territory (in blue). (Casselman *et al.* 2014)

Figure 2. *Salvia divinorum* (Epling & Jàtiva-M)

Salvia divinorum has several names among the Mazatecs, and many are related to the Virgin Mary. The association with the Virgin Mary is due to Dominicans and Jesuits who converted indigenous people to Catholicism after the Spanish colonization in the 16th century (Mooney 1911). Traditional Mazatecs names are *ska Maria* or *ska Pastora,* spanish names are *hojas de Maria* ("leaves of the Virgin Mary")*, hojas de la Pastora* ("leaves of the shepherdess")*, hojas de Maria Pastora* ("leaves of Virgin Mary the shepherdess")*,* and *hierba Maria* ("Mary herb") (Wasson 1962; Valdés *et al.* 1983). In Christian tradition the Virgin Mary is not a shepherdess, and Wasson suggested that the attribution of the role of shepherdess could be heritage of the pre-Christian figure "dueno de los animales" ("the lord of the animals"), an important figure in the folk tradition of Central American Indians. Wasson also suggested that the pagan name would have been sanctified by the addition of the Virgin's name (Wasson 1962).

S. divinorum is used by the Mazatecs for curing at least four illnesses. First, diarrhea and other eliminatory dysfunctions are often treated with the plant. Second, *S. divinorum* is used in small doses against headache and rheumatisms. Third, an infusion of the plant's juice is given to people who are near death, as palliative care. Fourth, traditionally a semi-magical illness known as the *panzón de barrego* (panzón="swollen belly"), caused by a brujo, an evil shaman, can be cured with *S. divinorum* (Johnson 1939; Valdés *et al.* 1983; Ott 1996). Other than physical illnesses, *Salvia divinorum* is traditionally used for divination practices, spiritual rituals, and training of medical practitioners (Johnson 1939; Ott 1996; Valdés *et al.* 1983). Valdés reported that the plant was used by a *curandero* (traditional healer) as a divination tool for investigating diseases that the *curandero* could not recognize: after treatment with

Figure 3. Natural habitat of *S. divinorum,* very humid and shady, in Oaxaca, Mexico. Photography from 1973. (Diaz 2013)

the plant, “the sick person begins to describe the type of illness they are suffering from” (Valdés 2001). Traditionally, fresh leaves are chewed or a juice is made by crushing the leaves and adding water. The leaves are always counted in pairs, and while for medical purposes only 4-5 pairs of leaves are used, usually 20-80 pairs of leaves are used for divination practices (Valdés *et al.* 1983).

Current use

Far from Oaxaca, Mexico, *S. divinorum* was mentioned first in the literature in 1939 (Johnson 1939), and described botanically in 1962 (Epling & Jàtiva-M. 1962). Siebert identified its active principle salvinorin A in 1994 (Siebert 1994). From the identification of its active principle the scientific interest grew progressively and at present there is a substantial interest for the plant, mainly due to the unique molecular characteristics of salvinorin A and to its pharmacology of clinical interest (Casselman *et al.* 2014; Prisinzano 2005; Jenks *et al.* 2011; Cunningham *et al.* 2011).

Besides the scientific interest, *Salvia divinorum* started gaining popularity as a recreational drug in the 1990s, especially among teenagers and young adults (Wu *et al.* 2011; Perron *et al.* 2012; Zawilska & Wojcieszak 2013). The reasons of *S. divinorum*’s popularity lie in its strong hallucinogenic effects, the easy access via online shops and “smartshops”, its legality in many countries, the lack of detectability with common drug screening tests and the perception of safety and lack of toxicity of the plant (Perron *et al.* 2012; Miller *et al.* 2009; Lange *et al.* 2008; Kelly 2011; Ford *et al.* 2011). Contrary to traditional routes of administration, modern consumption is usually performed via vaporization of the leaves/extracts (Baggott *et al.* 2010; Kelly 2011).

Due to the increasing recreational use and public concerns regarding health and safety, the use of *Salvia divinorum* is currently regulated in several countries (Siebert 2014). Australia was the first country to make possession of the plant illegal (January 1st, 2002). At present, *Salvia divinorum* is illegal to possess or sell in Australia, Belgium, Croatia, Czech Republic, Denmark, Germany, Hong Kong, Italy, Japan, Latvia, Lithuania, Poland, Republic of Ireland, Romania, South Korea, Sweden, Switzerland and in 27 U.S.A. states; it is illegal to sell in Chile, France, Spain and Russia and it is regulated in 9 U.S.A. states. Interestingly, in Estonia, Finland, Iceland and Norway the plant

Figure 4. *S. divinorum* extract, commercially available. © Zamnesia

is legal only for medical purposes, considered a medicinal herb that requires a doctor's prescription (Siebert 2014). However, *Salvia divinorum* is still legal in many european countries, including the Netherlands, where it can be easily purchased in the form of dried leaves, extracts of various potencies (Figure 4) and small living plants from online vendors and "smartshops".

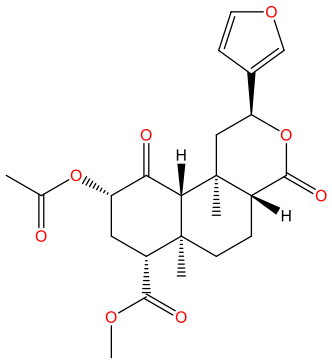
Constituents of *Salvia divinorum*

Figure 5. *Salvia divinorum*

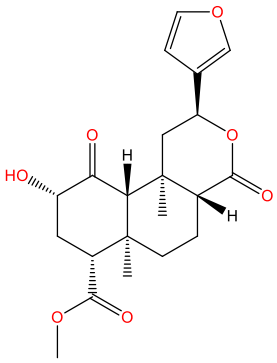
Many compounds have been isolated from *Salvia divinorum.* The active component is the neoclerodane diterpene salvinorin A, discovered independently by Ortega *et al.* in 1982 along with its deacetylated derivative salvinorin B (Figure 6) (Ortega *et al.* 1982) and by Valdés *et al.*, which called them divinorins A and B, in 1984 (Valdés *et al.* 1984). Few years later, Siebert (1994) identified salvinorin A as the main active component of the plant. Subsequently, several other components of *S. divinorum* have been identified, being mostly diterpenes.

The neoclerodane diterpenes isolated from *S. divinorum* are: salvinorins C to J (Valdés *et al.* 2001; Munro & Rizzacasa 2003; Lee, Ma, *et al.* 2005; Shirota *et al.* 2006; Kutrzeba *et al.* 2009), divinatorins A to F (Bigham *et al.* 2003; Lee, Ma, *et al.* 2005; Shirota *et al.* 2006), salvinicins A and B (Harding, Tidgewell, Schmidt, *et al.* 2005), and salvidivins A to D (Shirota *et al.* 2006), as shown in Figure 7.

Further, other compounds have been isolated from the plant (not shown). Four triterpenes have been identified: presqualene alcohol (Bigham *et al.* 2003), peplusol (Bigham *et al.* 2003), oleanolic acid (Munro 2006) and stigmasterol (Munro 2006). Also, several miscellaneous constituents have been reported: hardwickiic acid (Misra *et al.* 1968), (E)-phytol (Bigham *et al.* 2003; Rajab *et al.* 1998), neophytadiene (Munro 2006), loliolide (Hanson 2010; Valdés 1986), dehydrovomifoliol (Hanson 2010), nepetoidin B (Grayer *et al.* 2003; Hanson 2010), 5-hydroxy-7-4'-dimethoxyflavone (Valdés *et al.* 2002).

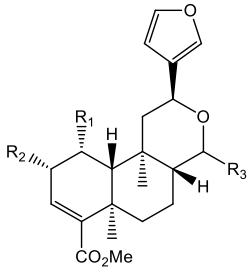


salvinorin A

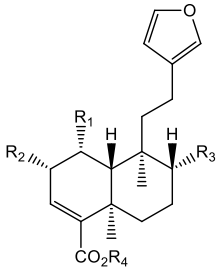


salvinorin B

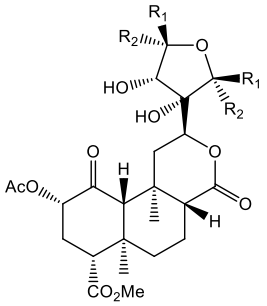
Figure 6. Salvinorin A and salvinorin B.



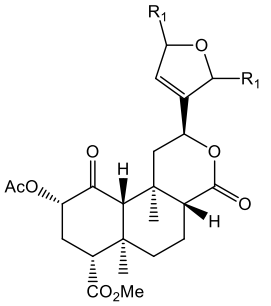
	R_1	R_2	R_3
salvinorin C	OAc	OAc	O
salvinorin D	OAc	OH	O
salvinorin E	OH	OAc	O
salvinorin F	OH	OH	O
salvinorin G	OAc	O	O
salvinorin H	OH	OH	O
salvinorins I	OH	OH	OH
salvinorins J	OH	OAc	OH



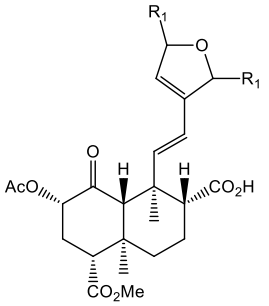
	R_1	R_2	R_3	R_4
divinatorin A	OH	H	CH_3	H
divinatorin B	OH	H	CH_2OH	CH_3
divinatorin C	H	H	CH_2OAc	H
divinatorin D	OH	H	CH_2OAc	CH_3
divinatorin E	OH	H	CHO	CH_3
divinatorin F	OH	OH	CH_2OH	CH_3



	R_1	R_2
salvinicin A	OCH_3	H
salvinicin B	H	OCH_3



	R_1	R_2
salvidivin A	O	OH
salvidivin B	OH	O



	R_1	R_2
salvidivin C	O	OH
salvidivin D	OH	O

Figure 7. Chemical structures of neoclerodane diterpenes isolated from *Salvia divinorum.*

Salvinorin A

Among the neoclerodane diterpenes isolated from *S. divinorum*, salvinorin A is predominant, and the only with reported psychoactive properties (Hanson 2010). When smoked, a dose of 200-500 µg of salvinorin A results in strong and brief (5-10 minutes) hallucinogenic effects and change of perception (Siebert 1994).

Salvinorin A is a unique molecule. In fact, it is the first reported non-nitrogenous hallucinogen, and first diterpene with psychoactive properties (Valdés 1994). Another peculiar characteristic, discovered by Roth *et al.*, is that contrary to the "classic" hallucinogens such as lysergic acid diethylamide (LSD), mescaline and psilocin (Figure 8), which exert their activity mainly by binding to the 5-HT_{2A} receptor (Glennon *et al.* 1984; Roth *et al.* 1998), salvinorin A binds with high selectivity to the κ-opioid receptor (KOR), with full agonistic activity (Roth *et al.* 2002). This finding is very interesting, considering that the structure of salvinorin A is far different from other known KOR agonists such as dynorphin A or U-60,593 (Figure 8) (Vardy *et al.* 2013). The findings of Roth *et al.* are also remarkable for the fact that a basic amino group, missing in salvinorin A, had long been considered necessary for opioid receptor binding and efficacy (Rees & Hunter 1990). Considering the intriguing characteristics of salvinorin A, and the ethnopharmacology of *Salvia divinorum*, many efforts have been made to further understand the binding mode, the pharmacokinetics and the pharmacology of this unique compound.

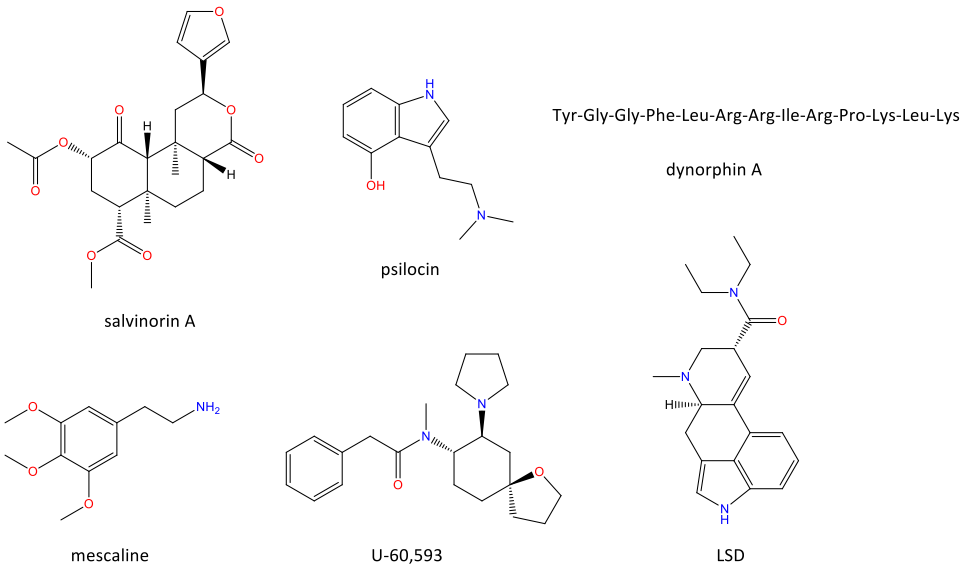


Figure 8. Chemical structures of salvinorin A and ligands with activity at 5-HT (mescaline, psilocin and LSD) or at KOR (U-60,593 and dynorphin A).

Structural considerations

Much effort has been directed towards understanding the structure activity relationships (SARs) of salvinorin A. One distinctive characteristic of salvinorin A is the absence of a basic amino substituent that would be positively charged at physiological pH, a substituent which was commonly considered a necessary requirement for activity at opioid receptors (Rees & Hunter 1990). Many synthetic and natural derivatives of salvinorin A have been tested for their activity at KOR and other opioid receptors, to investigate the binding mode of this unique ligand. Also several studies aimed at understanding the enigmatic ligand-receptor interactions of salvinorin A with KOR have been conducted, using computational models and receptor-based binding and activity studies, as reviewed by Cunningham *et al.* (2011).

Despite the numerous amount of synthetic derivatives, few have resulted in increased potency or selectivity for KOR in respect of salvinorin A (Cunningham *et al.* 2011). Other modifications resulted in similar or lowered affinity and/or potency, different activity for κ-, μ- or δ-opioid receptors, and different efficacy (agonist, partial agonist, antagonist), leading to a better understanding of SARs at opioid receptors (Cunningham *et al.* 2011). Salvinorin A synthetic derivatives of particular interest (**1-4**) are described below and shown in Figure 9, while an overview of SARs of salvinorin A is shown in Figure 10.

Structural derivatization of the C-2 position

The C-2 position is extremely important for the action of salvinorin A at KOR. Modifications in this position are not well tolerated, and have a clear effect on affinity and activity (Cunningham *et al.* 2011). Interesting derivatives have been synthesized replacing the C-2 acetyl group. Replacement of the C-2 ester moiety with a methoxymethyl ether (compound **1**) increased potency and affinity (Lee, Karnati, *et al.* 2005). When the ester moiety on the C-2 position is replaced by an ethoxymethyl ether (**2**), potency and affinity are increased, affording the most potent neoclerodane at KOR to date (Munro *et al.* 2008). It has been shown that addition of an aromatic group in the C-2 position decreases affinity for KOR, while increases affinity for μ-opioid receptor (Harding, Tidgewell, Byrd, *et al.* 2005; Tidgewell *et al.* 2008). Herkinorin (**3**) was identified as first non-nitrogenous μ-opioid receptor agonist (Harding, Tidgewell, Byrd, *et al.* 2005). Inversion of the C-2 acetate of salvinorin A (**4**) resulted in the first neoclerodane diterpene with antagonistic activity at δ-opioid receptor (Harding *et al.* 2006).

Other structural modifications

Modifications of the C-12 furan ring have been investigated (Cunningham *et al.* 2011). The tetrahydro derivative was reported to have a fortyfold decrease in affinity in one study (Munro *et al.* 2005), and only a threefold decrease in activity in another study (Simpson *et al.* 2007). A furan ring at C-12 is not considered a requirement for biological activity (Cunningham *et al.* 2011), but removal of the furan moiety resulted in a 1700-fold decrease in affinity for KOR, compared with salvinorin A (Simpson *et al.* 2007). Several studies suggest that the methyl ester at C-4 position is an important component of the pharmacophore, while C-17 lactone and C-1 ketone are not as stringently required (Vortherms & Roth 2006; Cunningham *et al.* 2011; Lee, Karnati, *et al.* 2005).

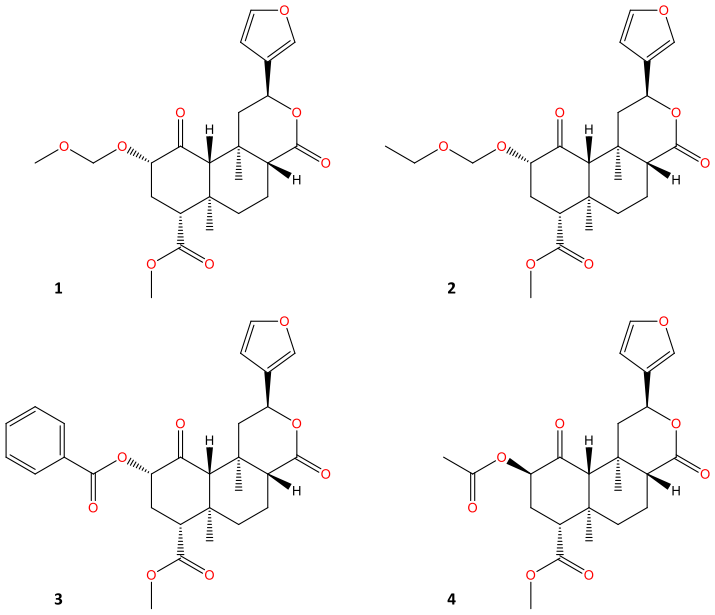


Figure 9. Synthetic analogs of salvinorin A.

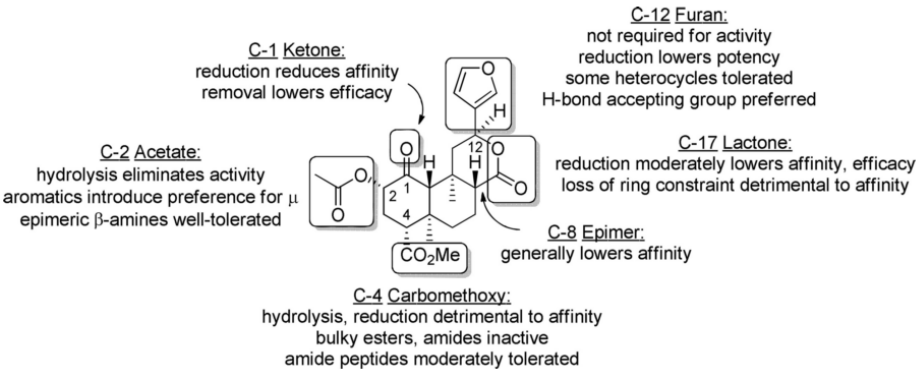


Figure 10. General SARs for salvinorin A activity at KOR. (Cunningham *et al.* 2011)

Physico-chemical properties

Chemical Formula	$C_{23}H_{28}O_8$
Exact Mass°	432.178417872 Da
Molecular Weight°	432.4636 Da
#H-bond donors	0
#H-bond acceptors	8
Polar surface area°	109.11 Å^2
Molar refractivity°	105.995 $m^3\,mol^{-1}$
logD at pH 7.4*	2.34 ± 0.09
Melting point§	238-240 °C

Table 1. Physico-chemical properties of salvinorin A.
° = calculated by ChemAxon (chemicalize.org)
* = Hooker *et al.* (2008)
§ = Merk Index (O'Neil 2006)

Figure 11. Salvinorin A crystals (purity unknown).
© Sphere (sagewisdom.org)

Salvinorin A takes the form of colorless crystals when obtained from methanol (Figure 11) (O'Neil 2006). It obeys the Lipinski's rule of 5 (Lipinski *et al.* 2001), having a molecular weight below 500 Da, less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, and an octanol-water partition coefficient (logP) below 5. In the case of salvinorin A, the partition coefficient is equal to the distribution coefficient (logD), because the molecule is not ionized in the pH range 1-14. Further, salvinorin A also meets the criteria for drug-like molecules set by Ghose *et al.* (1999). Therefore, it presents a strong drug-like character, even though it is not orally active (Siebert 1994).

Pharmacokinetics

The most efficient route of administration for humans is inhalation of the smoke or vapors of salvinorin A. When smoked, salvinorin A is effective at 200-500 µg (Valdés 1994), and the duration of drug action is very short, with effects peaking at 2 minutes and disappearing after approximately 20 minutes (Johnson *et al.* 2011; MacLean *et al.* 2013). When administered via buccal absorption, like traditional use, effects start within 10 minutes, lasting for approximately 1 hour (Siebert 1994). However, a recent laboratory experiment reported no activity after buccal administration of 4 mg salvinorin A (Mendelson *et al.*

2011). Oral administration results in small absorption through the mucosa, and degradation of most of the dose in the gastrointestinal tract (Siebert 1994).

Pharmacokinetics of salvinorin A have been investigated in animals. In one study, in which salvinorin A was intravenously administered to rhesus monkeys, rapid distribution and elimination rates were reported, next to a high variability of half-life (mean 56.6 minutes) among the four subjects of the experiment (Schmidt *et al.* 2005). In a more recent study, the distribution of [^{11}C]salvinorin A was monitored with positron emission tomography in brains of baboons, and it was found that the maximum concentration occurred 40 seconds after administration. The clearance was also fast, with a half-life time of 8 minutes. The maximum central concentration was 0.0175% injected dose per cm^3, and the highest concentration was found in the cerebellum (0.016 ± 0.002 injected dose/cm^3) (Hooker *et al.* 2008). From the results of another study in which salvinorin A was administered to rats, Hooker *et al.* suggested that metabolism is not entirely responsible for the fast clearance of salvinorin A from the brain (Hooker *et al.* 2009). Teksin *et al.* assessed the pharmacokinetics properties of a single dose of salvinorin A (10 mg/kg, intraperitoneal injection) in rats (Teksin *et al.* 2009). Similarly to previous studies, plasma uptake was fast (t_{max} 15 min), and elimination $t_{1/2}$ was relatively fast (75.4 min). Elimination from the brain was faster, with t_{max} of 10 minutes and elimination $t_{1/2}$ of 36.1 minutes. Distribution was extensive (Vd of 47.1 L/kg), even though the brain to plasma ratio was very low, ranging from 0.092 to 0.074 over a 60 minutes period (Teksin *et al.* 2009).

Taken together, pharmacokinetic studies highlight the fast kinetics of salvinorin A in the body, consistent with the rapid onset and the briefness of the effects of salvinorin A.

Metabolism

Ester hydrolysis of C-2 acetate of salvinorin A results in the C-2 hydroxyl derivative salvinorin B. The suggestion that salvinorin B is an inactive metabolite of salvinorin A (Valdés *et al.* 2001; Chavkin *et al.* 2004) has been confirmed by Schmidt *et al.*, who demonstrated salvinorin B to be the major metabolite in non-human primates (Schmidt *et al.* 2005). Results from Hooker *et al.* experiment on baboons suggest that at least two pathways are responsible for metabolization of salvinorin A in non-human primates: renal filtration for hydrophilic metabolites and biliary excretion for lipophilic ones (Hooker *et al.* 2008).

Experiments *in vitro* performed by Teksin *et al.* suggest that salvinorin A may be a substrate for P-glycoprotein, UDP-glucuronosyltransferase-2B7 (UGT2B7), cytochrome P (CYP) 2D6, CYP1A1, CYP2E1 and CYP2C18 (Teksin *et al.* 2009). Another *in vitro* study performed by Tsujikawa *et al.* reported that

degradation of salvinorin A in rat plasma was inhibited by esterase inhibitor sodium fluoride, carboxylesterase-selective inhibitor *bis-p*-nitrophenyl phosphate and serine esterase inhibitor phenylmethylsulfonyl fluoride. Also, other inhibitors specific to acetylcholinesterase, butyrylcholinesterase, and arylesterase did not influence salvinorin A degradation, suggesting lack of involvement of these enzymes in the metabolism of salvinorin A (Tsujikawa *et al.* 2009). Further, Tsujikawa *et al.* estimated that the degradation products of salvinorin A by liquid chromatography-mass spectrometry are salvinorin B (the deacetylated form of salvinorin A) and the lactone-ring-open forms of salvinorins A and B (Tsujikawa *et al.* 2009). Another *in vitro* study investigated on potential metabolism routes using 30 fungal species as a model for mammalian metabolism (Kutrzeba *et al.* 2009). The only metabolite found was salvinorin B, suggesting a large degree of metabolic stability inherent to the tricyclic trans-decalin core of salvinorin A (Kutrzeba *et al.* 2009). A study on human volunteers reported that only approximately 0.8% of an administered dose of salvinorin A was extracted from urine, supporting the idea that salvinorin A is rapidly metabolized *in vivo* (Pichini *et al.* 2005).

Toxicity

Salvinorin A presents little physiological toxicity, as reported from *in vivo* studies. Experiments on rodents performed by Mowry *et al.* (2003) suggested that salvinorin A presents relatively low toxicity, even at doses far exceeding the ones human are exposed to. Also studies on non-human primates suggest low toxicity for salvinorin A (Butelman *et al.* 2007). In several human laboratory studies, pharmacologically active doses of salvinorin A did not significantly affect blood pressure or heart rate (Johnson *et al.* 2011; Ranganathan *et al.* 2012; MacLean *et al.* 2013; Addy 2012). Also, Ranganathan *et al.* (2012) reported no changes in cognition after administration of the drug, and no resting or kinetic tremors were observed by MacLean *et al.* (2013).

Pharmacology

Salvinorin A is a potent and highly selective κ-opioid receptor full agonist (K_i = 18.74 ± 3.38 nM, EC_{50} = 7 nM, from Chavkin *et al.* 2004). Other than the agonistic activity at KOR, negligible affinity for many other receptors has been measured, including μ-, δ-, and ORL-opioid receptors, σ1- and σ2-receptors, CB_1 and CB_2 cannabinoid receptors, muscarinic and nicotinic cholinergic receptors, serotonin receptors and

several ionotropic and metabotropic glutamate receptors (Roth *et al.* 2002; Chavkin *et al.* 2004). The κ-opioid receptor is involved in pain perception, mood and motor control, and it is found in the brain, spinal cord and pain neurons (Fine & Portenoy 2004; Van't Veer & Carlezon 2013). Other than activity on KOR, recent studies showed interactions of salvinorin A with several other biological systems, specifically the endo-cannabinoid system (Braida *et al.* 2008; Braida *et al.* 2009; Capasso, Borrelli, Zjawiony, *et al.* 2008; Jakub Fichna *et al.* 2009).

Several *in vitro* and *in vivo* studies elucidated the pharmacological activity of salvinorin A, reviewed by Cunningham *et al.* (2011) and Casselman *et al.* (2014). Overall, salvinorin A presents a pharmacological profile consistent with known KOR agonists, including effects on mood and reward behavior, drug-seeking behavior, antinociception, analgesia, gastrointestinal transit, conditioned place aversion, sedation (Cunningham *et al.* 2011; Casselman *et al.* 2014). In particular, some pharmacological effects of clinical interest and aspects of the human psychopharmacology of salvinorin A are described below.

Gastrointestinal effects

In Mazatec tradition, *Salvia divinorum* was also used as a remedy for diarrhea and other eliminatory dysfunctions (Valdés *et al.* 1983). Several studies support the traditional use. Capasso *et al.* (2006) found that salvinorin A can inhibit myenteric cholinergic transmission in guinea pig ileum. Also, Capasso *et al.* reported that salvinorin A inhibited gastrointestinal motility in mice with gut inflammation (Capasso, Borrelli, Cascio, *et al.* 2008; Capasso, Borrelli, Zjawiony, *et al.* 2008). Fichna *et al.* (2009) studied the gastrointestinal effects of salvinorin A in mice, and reported that salvinorin A slows colonic motility *in vitro* and *in vivo*.

Further evidence of the effects of *S. divinorum* on gastrointestinal functions is shown in a case-report of a 51-years-old woman (Travis *et al.* 2012). She was using *S. divinorum* consistently (3-5 cigarettes per day, for 3-4 months) and developed gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal discomfort) after *S. divinorum* withdrawal.

Antidepressant and anti-addiction effects

An increasing body of literature supports a role of the endogenous dynorphin/KOR system in mood disorders, stress, anxiety, psychosis and brain reward mechanisms (Kreek 1996; Rothman *et al.* 2000; Shippenberg *et al.* 2007; Mysels & Sullivan 2009; Knoll & Carlezon 2010). Several experiments have been

performed to assess the pharmacological properties of salvinorin A and analogs in relation to mood and brain reward mechanisms.

In animals, salvinorin A showed interesting results. In one study, anxiolytic-like effects were assessed in rats using the elevated plus maze model, while antidepressant-like effects were assessed with the forced swim test in rats and tails suspension test in mice (Braida *et al.* 2009). Furthermore, salvinorin A showed antidepressant effects in rats when chronically administered (Harden *et al.* 2012). Rats were exposed to chronic mild stress to model anhedonia which is common in depression, and administration of salvinorin A (1 mg/kg body weight (BW)) successfully reversed this anhedonia, indicating the effectiveness of salvinorin A as an antidepressant when chronically administered to rats showing depressive symptoms similar to humans (Harden *et al.* 2012). However, a study by Carlezon *et al.* (2006) reported that administration of salvinorin A to rats increased immobility in the forced swim test, while standard antidepressant drugs produce the opposite effect, but it did not affect locomotor activity in an open field. Also, salvinorin A increased intracranial self-stimulation thresholds, similarly to treatments that have depressive effects in humans (Carlezon *et al.* 2006). Increased intracranial self-stimulation thresholds in rats after administration of salvinorin A were also reported by Ebner *et al.* (2010).

Interestingly, there is one case report of antidepressant effects of *S. divinorum* (Hanes 2001). A 26-years-old woman suffering from chronic depression used to self-administer small doses of *S. divinorum* (2-3 leaves, chewed for 15-30 minutes, three times per week). After some months of continuous self-administration, complete remission of depressive symptoms was measured with the Hamilton Depression Scale (Hamilton 1960). The subject also claimed that she benefited from occasional use of larger doses (8-16 leaves), which led her to a kind of "psycho-spiritual" awakening (Hanes 2001). Therefore, the objective remission of depressive symptoms can hardly be attributed only to the continuous use of small doses, while also the psychoactive larger doses may be considered as beneficial for treating her depression. Subsequently, the same author has briefly reported that several other individuals had beneficial effects from the use of *S. divinorum*, including relief from depression (Hanes 2003).

The involvement of dynorphin/KOR system in drug addiction has been documented (Shippenberg *et al.* 2007; Mysels & Sullivan 2009). The anti-addiction potential of salvinorin A and analogs is being investigated (Kivell *et al.* 2014), and the first results indicate that salvinorin A and analogs hold potential for the future of anti-addiction treatments. In a study from Chartoff *et al.* (2008), it was shown that acute administration of salvinorin A (2 mg/kg BW, intraperitoneal) blocked the locomotor-stimulant

effects of cocaine. In the same study, it was reported that acute administration of salvinorin A attenuated cocaine-induced c-Fos expression induced by cocaine in the dorsal striatum (Chartoff *et al.* 2008). Morani *et al.* (2009) reported that cocaine-induced drug seeking behavior in rats was attenuated by salvinorin A administration, and Potter *et al.* (2011) reported that salvinorin A reduced the reward-potentiating effects of cocaine. A more recent study showed a decrease in cocaine-induced behavioral sensitization after administration of salvinorin A to rats (Morani *et al.* 2012).

A promising analog of salvinorin A with anti-addiction properties is the 2-methoxy methyl analog of salvinorin A (compound **1**, MOM Sal B, Figure 9). MOM Sal B presents higher potency and longer half-life time *in vivo* compared to salvinorin A, and it was shown that it attenuates cocaine-induced drug seeking or taking and sucrose reinforcements in rats without casing sedation, thus suggesting an improved side effects profile compared to salvinorin A (Morani *et al.* 2013; Simonson *et al.* 2014).

Human psychopharmacology

To date, only four studies aimed at investigating the effects of salvinorin A on humans have been accomplished, using healthy subjects having previous experience with common hallucinogens and/or *S. divinorum* (Johnson *et al.* 2011; Addy 2012; Ranganathan *et al.* 2012; MacLean *et al.* 2013). Another similar study failed at producing physiological and subjective effects with sublingual administration of salvinorin A (Mendelson *et al.* 2011). It is noteworthy that, even though in the four accomplished human studies the drug was administered via inhalation, the volatilization of salvinorin A was performed with different methods, potentially resulting in incomplete volatilization and/or partial combustion of salvinorin A. Therefore, comparison of different studies should take this differences into account.

Johnson *et al.* (2011) tested different doses of salvinorin A (0.375 µg/kg BW to 21 µg/kg BW, inhaled) on 4 human subjects. Salvinorin A was reported as physiologically safe and psychologically well tolerated at the given doses, with no adverse effects. Time- and dose-related effects were observed. Mainly positive effects were reported, with relative lack of dysphoric effects, in contrast with previous findings. The subjective effects reported present similarities to classical psychedelics, including mystical-type effects. The participants reported changes in spatial orientations, feelings of pressure or energy in parts of the body, and psychedelic effects such as recalling childhood memories and contact with entities.

Addy (2012) analyzed the acute effects of salvinorin A (1,017 µg, inhaled) and long-lasting after-effects on 30 human subjects. Salvinorin A significantly increased laughing, movement while sitting, physical contact, paranoia and talking. Effects lasting less than 24 hours were reported by 87% of the

participants and were overall positive: reflectiveness and curiosity occurred in 22% of the participants, enhanced emotional sensitivity/empathy (22%) and general positive after-effects (17%). A smaller number of participants reported headache (13%), fatigue (13%), difficulty concentrating (13%), but also enhanced intuition (9%), feelings of floating or lightness (9%) and enhanced awareness of beauty (9%). Also long-lasting effects (assessed by an interview 8 weeks after drug administration) were overall positive, and reported by the 70% of the subjects: positive changes in relationships with family members (22%) or with others (9%), general positive changes in themselves (17%), increased empathy or sensitivity (13%) and negative effects (*e.g.* headache, unsureness, mood instability; 13%).

Ranganathan *et al.* (2012) assessed the effects of salvinorin A (8 and 12 mg, inhaled) on 10 young individuals. Soma-esthetic changes, dissociative effects and perceptual alterations were reported. Salvinorin A did not produce euphoria nor cognitive deficits.

MacLean *et al.* (2013) performed a study on humans with ascending doses of salvinorin A (0.375 µg/kg BW to 21 µg/kg BW, inhaled) on 8 subjects. Qualitative subjective effects were assessed after each session and after 1 month of the last session with questionnaires. From the questionnaires collected after each session, five recurrent themes were identified: disruptions in vestibular and interoceptive signals, contact with entities, revisiting childhood memories, cartoon-like visuals and recurring content through different sessions. Surprisingly, all participants not only experienced alterations of their body in space, but also reported meeting entities or beings. Here is shown a verbatim passage from an user who encountered beings: "*They are incredibly encouraging, playful, and fairy-like trickster sprites, though their personalities ranged infinitely."* No persisting adverse effects were reported at 1-month follow-up. During the follow-up assessment, subjects rated the salvinorin A experiences as personally meaningful (mean=4.9, range 4-6, where 5="similar to meaningful experiences that occur on average once every 5 years) and spiritually significant (mean=3.6, range 1-5, where 4="very much"). Four participants reported positive changes (*e.g.* increased self-confidence, enhanced physical comfort and calm, improvements in interpersonal relationships, renewed interest in daily duties) which they attributed to their experiences with salvinorin A occurred during the study.

An early case report supports the evidence of beneficial effects of *Salvia divinorum* (Hanes 2001). Ms. G., a 26-years-old woman who suffered from depression since adolescence, presented complete remission of depressive symptoms (Hamilton Depression Rating Scale (Hamilton 1960)) after continuous use of small doses of the herb. Furthermore, she claimed that occasional assumption of larger doses of the herb triggered "*a kind of psycho-spiritual awakening*", improving her sense of self, her self-confidence, her intuition and her relationship with nature (Hanes 2001).

Early reports present similar effects when fresh leaves of the plants are chewed (Valdés *et al.* 1983; Ott 1995). Physical effects such as sensations of flying, floating and traveling through space, twisting and spinning, heaviness and lightness of the body, dizziness, lack of coordination, slurred speech were reported by Valdés *et al.* (1983). Valdés *et al.* noticed that the physical dizziness and lack of coordination did not correspond to a similar mental state, like intoxication from alcohol. In fact, subjects claimed their mind to be in a state of acute awareness and sensitivity. It is noteworthy that Valdés *et al.* also reported that a dark and quiet setting could considerably enhance the effects of the herb, and that traditionally the Mazatecs used the herb in quiet and dark places (Valdés *et al.* 1983). It would be interesting to apply such conditions of quietness and darkness to modern human clinical studies, in order to see whether an enhanced setting could improve the outcome and maximize the potential of studies investigating the psychopharmacology of salvinorin A in humans.

Besides the information obtained by clinical human studies and early subjective reports, a growing body of data is being collected through internet based surveys (Baggott *et al.* 2010; Nyi *et al.* 2010), analysis of audiovisual information present on YouTube™ (Lange *et al.* 2010; Casselman & Heinrich 2011) and questionnaires or interviews addressed to *S. divinorum* users (González *et al.* 2006; Kelly 2011; Sumnall *et al.* 2011). Baggott *et al.* (2010) analyzed a sample of 500 *S. divinorum* and salvinorin A users. The findings of this study on the effects of salvinorin A are similar to studies conducted on humans in a laboratory setting (Johnson *et al.* 2011; Addy 2012; MacLean *et al.* 2013), principally presenting positive after-effects. After-effects occurring in the first 24 hours after administration of the drug include increased insight (for 47% of the sample), improved mood (44.8%), calmness (42.2%), increased connection with universe or nature (39.8%), but also weird thoughts (36.4%) and things seeming unreal (32.4%). Adverse effects were reported by a smaller number of subjects, like difficulty concentrating (12.0%), anxiety (9.4%), and/or worsened mood (4.0%). Interestingly, 25.8% of participants also reported positive effects lasting 24 hours or more after use, the majority of which reported an improved mood and "antidepressant-like effects" (46.5%). It was calculated that people who expressed high possibility of using *S. divinorum* again and people who had used the plant for auto-psychotherapy were more likely to report positive after-effects lasting more than 24 hours. Adverse effects were rare, only 4.4% of the 500 subjects sample reported negative effects (usually anxiety) lasting 24 hours or more after use of *S. divinorum*.

As a result of *S. divinorum* use among teenagers and young adults, thousands of videos showing users during acute intoxication have been uploaded on the popular video sharing website YouTube™. Two studies analyzed some of these videos with a rigorous approach. One study reported that this type

of approach is valuable for further behavioral observation research (Lange *et al.* 2010), and the other one reported that 65% of the analyzed experiences were classified as positive, while only 12% were classified as negative (Casselman & Heinrich 2011).

Similarly to the unique chemical character of salvinorin A, being the first non-nitrogenous opioid receptor agonist and hallucinogen, its psychedelic effects are reported as unique as well. Despite similarities with other hallucinogens, different studies and reports agree on the unicity of the effects of *S. divinorum* or salvinorin A (Siebert 1994; González *et al.* 2006; Baggott *et al.* 2010; MacLean *et al.* 2013). Interestingly, Addy (2012) reported that 43% of the participants of its study found their experience with salvinorin A similar to dreaming, while only 13% and 10% reported similarities to LSD or psilocybin, respectively.

Combined, findings from controlled human studies and data obtained from surveys and YouTube™ observations are consistent with a benign psychopharmacological profile of salvinorin A, producing more positive after-effects such as increased mood, sense of well-being, and (self-)awareness than negative after-effects such as persistent anxiety, paranoia or physical problems. However, the positive effects showed in those studies were probably influenced by the personal background and expectations of the subjects, who had previously experienced psychedelic drugs and/or *S. divinorum*, also as a therapeutic tool. Also, the higher incidence of positive experiences on YouTube™ reported by Casselman & Heinrich (2011) could have been heavily influenced by the attitude of sharing "good" or "positive" videos more than "bad" and embarrassing ones. Controlled experiments on a more heterogeneous sample, for instance including subjects with no prior use of psychedelics and from different socio-cultural backgrounds, could produce more accurate results and minimize bias. It is noteworthy that some of these human studies reported the feasibility of further human research with salvinorin A without appreciable risk, also on subjects who never had any experience with psychedelics (Johnson *et al.* 2011; MacLean *et al.* 2013).

Abuse Liability

Little evidence supports an abuse potential for salvinorin A. Braida *et al.* (2008) reported intracerebroventricular salvinorin A self-administration and conditioned place preference in mice. The conditioned place preference paradigm is useful for studying the rewarding and aversive effects of drugs. Two compartments of a closed space are associated with administration of drug and absence of drug, respectively. When an animal spends significantly more time in the drug-paired compartment, the drug is said to produce conditioned place preference. When it spends significantly more time in the

drug-free compartment, the drug is said to produce conditioned place aversion. Usually, drugs of abuse, such as cocaine, produce conditioned place preference. Besides experiments on mice, a recent study on humans suggest abuse liability of salvinorin A (MacLean *et al.* 2013). The study reported an increase in "good effects and drug liking" with higher doses of salvinorin A, while "bad effects and disliking" effects remained low for all the administered doses.

More evidence supports lack of abuse liability, both on animals and on humans. It was shown that salvinorin A produces conditioned place aversion in mice (Zhang *et al.* 2005), and that it elevates intracranial self-stimulation thresholds and decreases extracellular dopamine concentrations in the nucleus accumbens in rats (Carlezon *et al.* 2006). More recently, Serra *et al.* (2014) showed that salvinorin A does not produce stable intravenous self-administration behavior in rats. Further evidence is brought by human studies, both in clinical settings or based on surveys, which report low abuse liability, and also considering the very intense psychological effects, the perceptual distortions and the lack of euphoric effects (Baggott *et al.* 2010; Ranganathan *et al.* 2012; Sumnall *et al.* 2011; MacLean *et al.* 2013).

Conclusions

The origins of *Salvia divinorum* are found in Oaxaca, a small region of Mexico. From serving the indigenous population of the Mazatecs for healing and divinatory purposes, this fascinating plant gained worldwide recognition thanks to the work of early pioneers such as Jean Bassett Johnson (Johnson 1939), Gordon Wasson (Wasson 1962) and Albert Hofmann (Hofmann 1980). Its main active component salvinorin A was isolated independently by Ortega *et al.* and Valdés *et al.,* and was identified by Siebert few years later. Scientific interest grew quickly when Roth *et al.* identified salvinorin A as a potent and selective κ-opioid receptor full agonist. In fact, salvinorin A is the first known non-nitrogenous opioid receptor agonist, and the first known non-nitrogenous hallucinogen. Moreover, it elicits its hallucinogenic effects by binding at KOR, instead of binding at serotonin receptors as classical hallucinogens such as LSD, psilocin and mescaline do.

The peculiar chemical and pharmacological profile of salvinorin A interested many scientists around the world, but also teenagers and young adults who use *S. divinorum* recreationally. Structural

modifications led to the discovery of herkinorin, a promising μ-opioid selective ligand useful for treatment of pain (Prisinzano 2013). Also, by modifying the salvinorin A scaffold, the first neoclerodane with activity at δ-opioid receptor and the most potent neoclerodane at κ-opioid receptor were discovered. These findings highlight the potential of salvinorin A and its analogs for investigating biological mechanisms related to opioid receptors, and for facilitating the discovery of new therapeutic agents for pain treatment, drug dependence and mental disorders.

The unique salvinorin A is being investigated thoroughly, and it showed activity in humans already at the very small dose of 200-500 μg, when inhaled. It is also active with buccal administration, however oral administration is not effective because the drug is rapidly degraded in the gastrointestinal tract. Salvinorin A presents fast pharmacokinetics, that means fast uptake and elimination, with effects peaking at 2 minutes after inhalation and lasting approximately 20 minutes when inhaled. The short duration of action is due to the rapid metabolism. The C-2 ester is rapidly hydrolyzed, yielding the inactive metabolite salvinorin B. There is consistent evidence of a low toxicity profile for salvinorin A.

Pharmacologically, salvinorin A presents similarities to other KOR agonists, such as anti-nociception, effects on mood and reward behavior, drug-seeking behavior, effects on gastrointestinal tract, and sedation. In particular, several experiments and a case report suggest clinical potential for regulation of gastrointestinal transit and dysfunctions, a potential which could be explored with further studies. The effects of salvinorin A on mood are more complex. While usually KOR agonists present dysphoric effects, also produced by salvinorin A, it has been shown that salvinorin A has also antidepressant-like effects in animals. Unfortunately there are few reports of antidepressant effects on humans. The antidepressant-like effects of salvinorin A can be compared to the findings of the first studies on human subjects, which experienced an increased sense of well-being and other positive effects lasting more than 24 hours after administration of the drug, with a higher occurrence than long-lasting negative effects. However, despite the fact that the positive effects on mood seem clear, and also considering the traditional use, more research is needed for producing solid evidence of the antidepressant effects of salvinorin A.

Another interesting field of research on salvinorin A is related to its ability to lower drug-seeking behavior, consistent with other KOR agonists. The 2-methoxymethyl ether of salvinorin B showed an improved metabolic profile and fewer side effects compared to salvinorin A in attenuating cocaine-induced drug seeking behavior.

Studies on human psychopharmacology of salvinorin A are at an early phase, with only four studies being successfully accomplished so far, all on hallucinogen-experienced subjects. The main findings

show a distinctive and strong psychedelic effect, in contrast with other KOR agonists. Subjects reported encounters with beings or entities when under the influence of salvinorin A, and also showed increased awareness and intuition. Negative effects are reported with a lower occurrence than positive ones. Salvinorin A presents psychedelic effects of a unique character, yet similar to classical hallucinogens. No severe adverse effects have been reported, and the feasibility of further human research also on hallucinogen-naïve users has been suggested. Studies that analyzed self-reports and interviews of occasional *S. divinorum* users reported similar findings, such as strong psychedelic effects, relative safety of use and lack of long-lasting adverse effects. Most of the studies showed that several users reported improvements in their daily life lasting longer than the acute effect of the drug, such as an increased sense of well-being, increased sensitivity and awareness. Despite the concerns of many countries that banned *S. divinorum,* and in addition to low toxicity and few adverse effects, low abuse liability has been reported in several studies.

Taken together, the information reported in this manuscript suggest the high potential of salvinorin A for investigating the neurobiology of opioid receptor systems and for producing new therapeutic agents based on the neoclerodane scaffold.

Discussion

The name *Salvia divinorum* suggests the beneficial character of this plant. The genus name "*Salvia*" derives from Latin *salvare*, "to save". The latin verb *salvare* is related to *salus*, which means "health", "well-being" or "safety". The common English name for *Salvia* is sage, which also mean very wise. *Divinorum* means "of the seers", and the seers are the ones that see, the ones that predict the future, or people credited with notable spiritual insight. Also the traditional Mazatecs names "ska Maria" and "ska pastora" associate the plant to the Virgin Mary, certainly a positive figure, and with a shepherdess, which could be heritage of the pre-Christian figure "dueno de los animales" ("the lord of the animals"), an important magical figure in the folk tradition of Central American Indians (Wasson 1962).

Other plants from the *Salvia* genus have an established history of medicinal use, for example the common sage *Salvia officinalis* (*officinalis* = "used in medicine"), Clary sage, *Salvia sclarea* (Grieve 1971), and the Red sage, *Salvia miltiorrhiza*, which is one of the five astral remedies in Chinese medicine (Smith

& Stuart 1973). Also, far from Oaxaca, *Salvia divinorum* is currently regulated in Estonia, Finland, Iceland and Norway as a medicinal herb that requires a doctor's prescription.

Considering the name, the genus, the recognized medicinal use in four European countries, and most importantly the traditional use among the Mazatecs*,* it is clear that *Salvia divinorum* holds great healing potential not yet unraveled by modern scientists, which are studying this fascinating plant and its active principle with curiosity and wonder, while starting to assess its properties.

Other than the physiological benefits already discussed, obtained with salvinorin A or analogs, the psychological effects and potential benefits on humans still need to be understood. Only few human clinical studies have been performed so far, and subjective psychological effects are way more difficult to assess than objective animal behavior or *in vitro* effects. However, there is some evidence suggesting the antidepressant effects of salvinorin A, and human clinical trials would probably produce valuable outcomes in this respect, also considering that other plants have a very long history in herbal medicine as antidepressant agents, such as St. John's Wort (Linde *et al.* 1996; Linde *et al.* 2008). Alternative treatments for depression are needed, since in the Western countries major depression is a leading disease, and the majority of the patients do not respond significantly to current treatments or discontinue treatments due to side effects. Sadly, the illegality of *S. divinorum* in many countries hinders further clinical research with the plant or with its active component salvinorin A.

Furthermore than a potential aid against depression and mood disorders, *S. divinorum* may help us understand the complex mechanisms of human consciousness. The plant's active component salvinorin A distorts or alters the consciousness of the users and has strong psychedelic effects, in contrast with other KOR agonists, suggesting that agonistic activity at KOR is not the only requisite necessary to alter consciousness and produce psychedelic effects. Further investigations about the mechanism of action of salvinorin A will hopefully help to elucidate the mechanisms of human consciousness and its alterations. In a recent work, based on the theory of Crick and Koch that the claustrum is a "*conductor of consciousness*" (Crick & Koch 2005), Stiefel *et al.* (2014) support the theory including salvinorin A in the discussion. In fact, the high density of KOR in the claustrum, which is a thin layer of neurons attached to the neocortex, and the modifications of consciousness produced by salvinorin A, would suggest that the claustrum has indeed a role in regulating human consciousness. However, the authors do not address the fact that other KOR agonists do not produce such intense alterations of consciousness. Another interesting insight in the relationship between the KOR system and human consciousness is brought by two independent reports of post-mortem studies of Alzheimer's disease (Barg *et al.* 1993; Mathieu-Kia *et al.* 2001). The two studies reported upregulation of KOR expression in the amygdala, putamen and

cerebellar cortex. Overall, little evidence has been produced so far, and the mechanisms responsible for human consciousness remain largely unknown.

Probably as mysterious as human consciousness is the divinatory use of *Salvia divinorum* among the Mazatecs. In traditional divinatory rituals *S. divinorum* is used to see in the future, find causes and cures of illnesses and answers to questions about important subjects (Valdés *et al.* 1983). The knowledge of the Mazatecs will most likely not be shared with the Western men, who can only try to benefit from this plant as much as the Mazatecs do. Our modern society is eager of spirituality, and seems benefiting more and more from certain psychoactive plants and drugs such as LSD, ibogaine, *Psilocibe* spp., ayahuasca, *Cannabis* spp., 3,4-methylenedioxy-N-methylamphetamine (MDMA), especially due to the renewed interest in psychedelic therapies for end-of-life anxiety, post-traumatic stress disorder, cancer and treatment of addictions (Bravo & Grob 1989; Baker 2005; Sessa 2014; Smith *et al.* 2014; Emerson *et al.* 2014).

In this respect, *S. divinorum* may contribute positively to psychedelic-assisted psychotherapy. In fact, the herb seems to enhance the descriptive abilities of the users, as reported by Valdés (2001) speaking of an ill person when the doctor cannot understand their disease: "[…] *the sick person begins to describe the type of illness they are suffering from. The sick one finds themselves in a semi-delirious state, they speak as if in a trance and the others listen attentively to what they say* […]". Valdés *et al.* (1983) also reported that when a person is intoxicated their mind is in a more receptive state. In a session with a local *curandero*, both Valdés and Díaz were speaking continuously during their session with the herb. Enhanced descriptive abilities could be a valuable aid for psychotherapy, for the patients being able to describe better their problems and emotions.

Furthermore, studies on humans suggest an interesting beneficial spiritual profile of *S. divinorum* use. Users reported recalling childhood memories and contact with entities during the peak of the experience, which may argued to be a reflection of the user's self. Also after-effects such as enhanced reflectiveness, intuition, sensitivity, awareness, empathy, calmness, connection with nature, and positive changes in relationships with themselves and with others have been reported. With a minor occurrence, also negative after-effects were described, such as mood instability, headaches, unsureness of things, and difficulty in concentrating. Further, it is reported that a population older than 21 years started using *S. divinorum* mostly for its spiritual effects (Nyi *et al.* 2010), and that, in contrast to the first use of the plant driven by curiosity, fun or boredom, the most recent uses of the plant were driven by spiritual purposes, desire to get closer to nature, and auto-psychotherapy (Sumnall *et al.* 2011). It is important to stress out the low toxicity and low abuse potential of salvinorin A and of *S. divinorum,* and

the lack of serious adverse effects reported during human experiences, which make this herb or its psychoactive constituent salvinorin A suitable for clinical use. The beneficial effects reported by many users could possibly be enhanced and the adverse effects reduced if the drug would be administered in a controlled setting, with the supervision and guidance of professional personal.

While many cultures around the world developed traditional use of psychoactive substances for both individually and socially beneficial purposes, our modern society is left with alcohol and cigarettes. The natural search for spirituality stimulates many people to use psychedelic drugs, even though these substances are strictly regulated in the majority of the countries. The illegality of psychedelic drugs, that is the deny of spiritual tools, together with lack of knowledge, traditions and rituals necessary to guide spiritual experiences, produced an underground population of “recreational drug abusers”, as they are indistinctively labelled, which fatigue to integrate and interpret their experiences, ultimately lowering the therapeutic potential of such powerful tools and exponentially increasing the risks of traumatic experiences, psychotic reactions and health issues. For the common benefit of the recreational psychedelic users and the society as a whole, psychiatrists, scientists and governments should recognize, study and validate the therapeutic potential of such powerful compounds.

Ultimately, the traditions of shamanic healing should be considered for the invaluable knowledge they hold, which could significantly improve the therapeutic applications and the challenging process of integration of certain psychedelic substances in our modern society.

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