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Review

From local to global—Fifty years of research on *Salvia divinorum*

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ABSTRACT

Ethnopharmacological relevance: In 1962 ethnopharmacologists, Hofmann and Wasson, undertook an expedition to Oaxaca, Mexico. These two researchers were the first scientists to collect a flowering specimen of *Salvia divinorum* allowing the identification of this species. While the species' traditional use is confined to a very small region of Mexico, since Hofmann and Wasson's expedition 50 years ago, *Salvia divinorum* has become globally recognized for its main active constituent, the diterpene salvinorin A, which has a unique effect on human physiology. Salvinorin A is a kappa-opioid agonist and the first reported psychoactive diterpene.

Methods: This review concentrates on the investigation of *Salvia divinorum* over the last 50 years including ethnobotany, ethnopharmacology, taxonomy, systematics, genetics, chemistry and pharmacodynamic and pharmacokinetic research. For the purpose of this review, online search engines were used to find relevant research. Searches were conducted between October 2011 and September 2013 using the search term "*Salvia divinorum*". Papers were excluded if they described synthetic chemical synthesis of salvinorin A or analogues.

Results: Ethnobotanically there is a comprehensive body of research describing the traditional Mazatec use of the plant, however, the modern ethnobotanical use of this plant is not well documented. There are a limited number of botanical investigations into this plant and there are still several aspects of the botany of *Salvia divinorum* which need further investigation. One study has investigated the phylogenetic relationship of *Salvia divinorum* to other species in the genus. To date the main focus of chemistry research on *Salvia divinorum* has been salvinorin A, the main active compound in *Salvia divinorum*, and other related diterpenoids. Finally, the effects of salvinorin A, a KOR agonist, have primarily been investigated using animal models.

Conclusions: As *Salvia divinorum* use increases worldwide, the emerging cultural use patterns will warrant more research. More botanical information is also needed to better understand this species, including germination, pollination vector and a better understanding of the endemic environment of *Salvia divinorum*. As well there is a gap in the genetic knowledge of this species and very little is known about its intra-species genetics. The terpenes in *Salvia divinorum* are very well documented, however, other classes of constituents in this species warrant further investigation and identification. To date, the majority of the pharmacology research on *Salvia divinorum* has focused on the effects of salvinorin A using animal models. Published human studies have not reported any harmful effects when salvinorin A is administered within the dose range of 0.375–21 μg/kg but what are the implications when applied to a larger population? More data on the toxicology and safety of *Salvia divinorum* are needed before larger scale clinical trials of the potential therapeutic effects of *Salvia divinorum* and salvinorin A are undertaken.

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1. Introduction

In 1962 ethnopharmacologists, Hofmann (1980) and Wasson (1962), undertook an expedition to Oaxaca, Mexico . On this trip they recorded several different plants and their use by Mazatec healers. As well as recording the cultural uses, these men attended ceremonies, which incorporated the use of *Salvia divinorum* (Epling & Jativa), a member of the family Lamiaceae (Labiatae). This expedition contributed much to the understanding of the historical cultural use of this species. Wasson and Hofmann were also able to obtain a flowering specimen of this plant, making possible the scientific description (Epling and Jativa, 1962) of *Salvia divinorum*.

After its scientific description, Ortega et al. (1982) isolated and identified the main active compound in *Salvia divinorum*, salvinorin A. In the early 1990s the psychoactive properties of salvinorin A were elucidated (Siebert, 1994). With the confirmation of its psychoactivity, the cultural adoption of *Salvia divinorum* as a "new" psychoactive, outside Mexico, gained considerable momentum. In reviewing these studies, it is apparent that whilst much has been learned about this plant over the last 50 years there are still research avenues to pursue.

This review concentrates on five general categories of the use and scientific investigation which *Salvia divinorum* has undergone over the last 50 years. First the ethnobotany and ethnopharmacological data will be outlined. Next botany, taxonomy, systematics and genetics will be discussed. The chemical constituents will then be reviewed. The paper will finish with an outline of the pharmacodynamic and pharmacokinetic research to date.

2. Methods

For the purpose of this review the following databases were searched without time restrictions up to September 2013 using the search term "*Salvia divinorum*": Scopus, Google Scholar and relevant databases as accessed through EBSCO (*e.g.* Medline) were used for this search. In addition other articles were included from specifically targeted non-electronic hand searches to ensure full coverage of the subject. Papers describing the chemical synthesis of salvinorin A, its analogues or other *Salvia divinorum* compounds were excluded.

3. Ethnobotany

Until 1964, the use of *Salvia divinorum* appears to have been confined to the Mazatecs, an indigenous Mexican group located in northeast Oaxaca (Fig. 1). This group's population occurs mainly in the districts of Cuicatlan and Teotitlan, with villages in the upland valleys and mountains (Mooney, 1911; Valdés et al., 1983). According to the CDI web site there are 305,836 Mazatec residing in a 2400 km^2 area in Oaxaca (Comisión Nacional para el Desarrollo de los Pueblos Indígenas. México, 2013). The name Mazatec or Mazateca is said to mean 'Lords of the Deer,' and was the name given to this group by the Aztec (Mooney, 1911). After Spanish colonization in the 1500s, the Dominicans and Jesuits began to convert indigenous peoples to Catholicism (Mooney, 1911). Although Spanish attempts at conversion were largely successful, the Mazatecs also maintained their traditional beliefs, which are still practised today (Hofmann, 1990, 1980; Mooney, 1911; Ott,

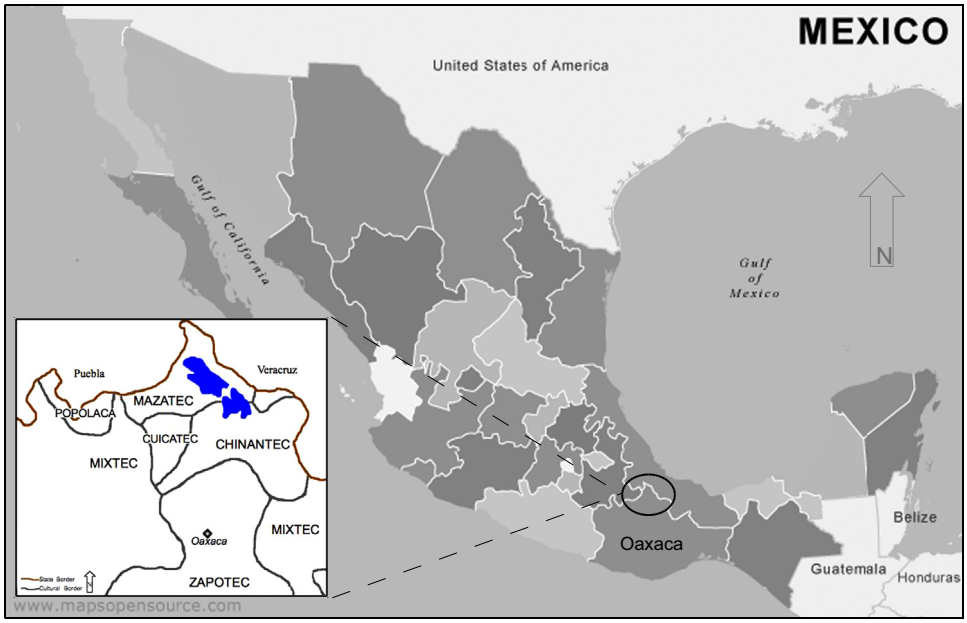


Fig. 1. Mazatec traditional territory (Mexico Map, n.d.).

1996). The Mazatec employ three main plants with psychoactive properties as part of their spiritual practices. These include *Psilocybe* spp. mushrooms, the seeds from *Ipomoea violacea* L. (morning glory) and the leaves of *Salvia divinorum* (Schultes, 1969; Foster, 1984; Allen, 1997, 1994). Mazatec use of *Salvia divinorum* takes place primarily during healing and divination ceremonies, as well as in the training of medical practitioners (Giovannini and Heinrich, 2009).

There are four illnesses for which Mazatecs are known to have used *Salvia divinorum* (Johnson, 1939; Valdés et al., 1983; Ott, 1996; Prisinzano, 2005). First, this plant is often employed to cure eliminatory dysfunction such as diarrhoea. Second, people who are near death can be given an infusion of the plant's juices as a palliative, after which it is reported that the patient often recuperates for a short time. Third, *Salvia divinorum*, in small doses, is used to cure headaches and rheumatism. Finally, it is given to cure a Mazatec illness known as *panzón de arrego* or swollen belly. This Mazatec illness is caused by a curse from a brujo, someone who practises black or evil magic (Johnson, 1939; Ott, 1996; Valdés et al., 1983; Prisinzano, 2005).

Salvia divinorum is tended in secret groves deep within the forest by medicinal practitioners known as curandero (male) or curandera (female) (Reisfield, 1993). It is planted in rich, black soil at the bottom of a gully, usually in close proximity to a stream (Diaz, 2013). Cuttings can be taken from the mother plant and planted directly into the moist soil, however, this plant will also root itself if a branch breaks off and falls on the ground (Beifuss, 1997). Although these *Salvia divinorum* groves may be natural, it is difficult to determine the extent of human influence (Reisfield, 1993; Ott, 1996). The locations are well protected by each individual curandero or curandera to avoid theft, and more importantly, contamination by malicious magic (Johnson, 1939). The large mature leaves of *Salvia divinorum* are harvested by pinching the petiole of the leaves close to the main stem of the plant. The leaves can be kept fresh for up to a week when wrapped in the leaves of *Xanthosoma robustum* Schott (Ott, 1995), as fresh leaves are required for Mazatec ceremonies. The leaves are either eaten or crushed into a fine pulp using a mortar and pestle, and subsequently infused in water (Campbell, 1997; Valdés, 2001).

Mazatec curandero and curandera are trained through an informal apprenticeship, during which time they are led through a series of progressive visions by an experienced teacher (Diaz, 1979; Valdés et al., 1983). These visions are initiated by the three psychoactive plants mentioned previously, and are an integral part of training. Over a period of two years, curanderos and curanderas ingest these plants at regular intervals to integrate the knowledge from their experiences into their practice (Valdés et al., 1983). Initially, trainees ingest increasingly large doses of *Salvia divinorum* leaves which show them the way to heaven, where the initiated learn from the tree of knowledge (Valdés et al., 1983).

During consumption of *Salvia divinorum*, either the leaves are chewed or the juice from crushed leaves is infused in water and ingested as a liquid (Diaz, 2013, 1979; Valdés, 2001). These ceremonies are led by a curandero or curandera, and last approximately two to three hours during which time the participants who ingested the plant are guided through different states of consciousness (Schultes, 1976; Estrada, 1977; Valdés et al., 1983; Hofmann, 1990, 1980; Ott, 1996; Schultes et al., 2001). These ceremonies take place at night in a dark and remote location to prevent disruptions (Diaz, 1979; Valdés et al., 1983; Valdés, 2001), as absolute quiet is considered essential to the success of the ceremony. Several leaves are rolled into cigar-shaped tubes, chewed and swallowed. If the participant is unable to chew the leaves or manage the bitter taste, he or she is permitted to drink juice-infused water instead (Estrada, 1977). During each ceremony there is one person present who has not ingested *Salvia divinorum*, and it is the job of this person to watch over the ceremony and prevent any harm to participants (Diaz, 1979; Valdés et al., 1983). After the effects of *Salvia divinorum* have worn off, the curandero or curandera will often bathe the participant in the juice of the leaves (Valdés, 2001), which is said to end the effects of the experience (Valdés et al., 1983). After the ceremony, participants are debriefed; this dialogue helps to explain the meaning of their visions and ensure the success of the ceremony (Estrada, 1977; Diaz, 1979; Valdés et al., 1983; Hofmann, 1990).

The Spanish chronicled many of the rituals which employed psychoactive plants, but very little about *Salvia divinorum* was recorded. One reason for this could be that the Mazatecs have several names for *Salvia divinorum*; in their native language it is referred to as Ska Maria Pastora, Ska Maria, Ska Pastora, and in Spanish it is called Hojas de Maria Pastora, Hojas de la Pastora, Hoja de adivinación, Hierba Maria or La Maria (Wasson, 1962; Schultes, 1972; Valdés et al., 1983; Valdés, 2001). The Mazatecs associate this plant with the Christian saint, Mary (Valdés et al., 1983), however, the reference to her as a shepherdess is not consistent with Christian mythology (Wasson, 1962). This name may reflect an interpretation of a pre-contact description of the plant that was later incorporated into Christian beliefs (Ott, 1995).

In the scientific literature *Salvia divinorum* has not received as much attention as the other plants used by the Mazatec: the seeds of the morning glory *Ipomoea violacea* and hallucinogenic mushrooms *Psilocybe* spp. (Schultes, 1970; Valdés et al., 1983; Valdés, 2001). *Salvia divinorum* was first mentioned in western academic literature in Johnson (1939). In 1945, B. Reko reported a “magic plant” used by the Mazatecs called “hoja de adivinación” or ‘the leaf of the prophecy,’ indicating that the indigenous people used this plant to produce visions (Schultes, 1967; Diaz, 1979; Valdés et al., 1983). Seven years later in Weitlander (1952) reported “yerba de Maria” used by curanderos in Oaxaca . The first botanical specimen of *Salvia divinorum* was collected by Pompa, a Mexican botanist. Pompa (1957) described this plant as “xka [sic] Pastora,” however, he was unable to collect a flowering specimen at the time and so his collection was only identified to the genus level. The lawyer and ethno-mycologist R. Gordon Wasson was a very important ethnopharmacologist and chronicler of psychoactive plants, especially those used by the Mazatec people. Wasson is best known for his research on the traditional Mexican use of *Psilocybe* spp. mushrooms. In July 1961, during his second expedition to Mexico, Wasson participated in an *Salvia divinorum* ceremony along with Hofmann (1980), known for his discovery of lysergic acid diethylamide or LSD (Wasson, 1962; Reisfield, 1993). In doing so, Wasson and Hoffman were the first western academics to participate in and record this ceremony. In December 1962, Wasson and Hoffman successfully collected a flowering sample of *Salvia divinorum*, which was identified by Epling as a new species (Epling and Jativa, 1962). Contrary to popular belief, the first living *Salvia divinorum* specimen to be propagated outside Mexico was not collected by Wasson and Hoffman but by psychiatrist and ecologist Sterling Bunnell, who in 1962 brought back a living *Salvia divinorum* specimen to UCLA Davis from an expedition to Oaxaca (Siebert, 2003).

Since the 1990s, the distribution and use of *Salvia divinorum* as a psychoactive has increased substantially. Its reputation as a psychoactive plant is evident on (and largely linked with) the World Wide Web (WWW) (Casselman and Heinrich, 2011). Some of the early text-based message boards on the WWW (alt.drugs, aft.drugs.psychedelics and alt.psychoactives) had detailed discussions regarding *Salvia divinorum* as early as the 1990s (Ott, 1995, 1993; Hine, 2008; Casselman and Heinrich, 2011). In contrast to the traditional use of *Salvia divinorum*, usage patterns outside of Mexico are different. Typically, concentrated extracts are smoked

and the use is outside any unified practice (Casselman and Heinrich, 2011). Twenty five urban youth were the subject of a small ethnobotanical study. Findings showed that *Salvia divinorum* was smoked to produce psychoactive a effect. No health issues were reported by the participants (Kelly, 2011) The current use patterns of *Salvia divinorum*, especially those which have developed outside Mexico over the last 50 years, have not been systematically studied. More ethnographic research would certainly add to the overall cultural knowledge of this plant.

4. Botany, systematics and genetics

All recorded native populations of *Salvia divinorum* are in Oaxaca, southern Mexico. This state is bordered by the Pacific Ocean to the west and, in the north, the Sierra Mazateca mountain range. Much of this mountain range is covered by tropical montane cloud forest (Reisfield, 1993; Ott, 1996, 1995), an ecosystem typified by high humidity and persistent cloud cover. Growing in the understory of the forest, *Salvia divinorum* has been found in several locations between 500 and 1500 m altitude (Ott, 1996, 1995). Populations of this plant are mostly found near water courses in partial or full shade and grow in moist, nutrient-rich soil. In these conditions *Salvia divinorum* grows and reproduces primarily vegetatively, flowering sporadically when enough sun penetrates the forest canopy (Reisfield, 1993).

Salvia divinorum grows up to 1.5 m in height and has a hollow, quadrangular stem, which is green, translucent and crisp (Reisfield, 1993; Ott, 1996). The leaves are 10–25 cm long, 5–10 cm wide, and are opposite on the stem, elliptic in shape and have serrated margins (Epling and Jativa, 1962; Reisfield, 1993; Ott, 1996). Numerous glandular and non-glandular trichomes are present on the leaf surface (Siebert, 2004; Kowalczuk et al., 2013). The flowers have white corollas with purple calices. The flowers are three to four centimetres in length and grow on panicles of 20 to 30 flowers. According to reports on wild populations as well as laboratory experiments, *Salvia divinorum* does not produce flowers on a regular, seasonal basis (Valdés et al., 1987; Reisfield, 1993). In Oaxaca this plant is observed to flower between October and June (Reisfield, 1993). Flowering is initiated by set durations of uninterrupted darkness greater than 12 h (Reisfield, 1993). In laboratory experiments, it has been found that if plants are exposed to light during a dark period, flowering is aborted and the plant returns to vegetative growth (Reisfield, 1993).

The pollination vector for *Salvia divinorum* is uncertain. It has been suggested that the pollination may be ornithophilous (Reisfield, 1993). This is corroborated by the dimensions of the corolla as well as the sugar content and the volume of nectar produced (Reisfield, 1993). Recent photos on the WWW also confirm that hummingbirds do take an interest in *Salvia divinorum,* however, these plants were domesticated so this interest could have been opportunistic (www.salviasource.org, 2011).

There is limited information on the sexual reproduction of *Salvia divinorum,* however, it is very adept at clonal propagation both naturally and anthropogenically. On the basis of the reported reproductive behaviour of *Salvia divinorum*, it has been suggested that the more recent evolutionary trajectory of this plant may have been influenced by humans (Reisfield, 1993). It is hypothesised that *Salvia divinorum* may have been translocated from its original environment at some point in history, however, this has not been confirmed nor have other populations of *Salvia divinorum* been discovered in the Americas (Reisfield, 1993). If *Salvia divinorum* is a translocated species, it is possible that the original population became extinct or, as yet, is undiscovered. Further botanical and genomic data is necessary to confirm or refute this hypothesis. There are some ethnographic reports of *Salvia divinorum* grown from seed (Valdés et al., 1987), however, no mature nutlet or consistent pollination activity has been observed in the wild, which suggests propagation is primarily vegetative (Reisfield, 1993). Laboratory experiments confirm that *Salvia divinorum* can set seed but the viability of these seeds is very low. Only 3% of pollinated stigmas developed into mature, viable nutlets (Reisfield, 1993).

Salvia is a globally distributed genus with over 800 recorded species (Mabberley, 2008). According to Bentham, the genus can be divided into four subgenera—*Salvia, Sclarea, Leonia* and *Calosphace* (Bentham, 1876*)*. European and Asian plants in this genus are classified as subgenera *Salvia* and *Sclarea*. North America (excluding Mexico) *Salvia* species are classified as subgenus *Leonia*. In Mexico and South America, the subgenus classification is *Calosphace* (Bentham, 1876; Jenks and Kim, 2013). Using this classification for New World salvias, *Salvia divinorum* falls in the subgenus *Calosphace* (Wood and Harley, 1989). Recent studies suggest the genus *Salvia* is polyphyletic and comprised of at least two, if not three, distinct lineages related to genera in the Mentheae tribe (Reddy, 2009; Walker et al., 2004a). Conversely, both genomic and morphological data shows the subgenus *Calosphace* is monophyletic (Walker et al., 2004b; Walker and Sytsma, 2007; Jenks et al., 2010).

Salvia divinorum is diploid ($2n=22$), which is the most common chromosome number in *Salvia* subg. *Calosphace* (Reisfield, 1993). It is reported that *Salvia concolor* Lamb. ex Benth. forms a nutlet when crossed with *Salvia divinorum*, however, the viability has not been assessed (Wasson, 1962; Ott, 1996). Although *Salvia divinorum* was hypothesised to be an interspecific hybrid (Reisfield, 1993) this is now considered unlikely based on recent molecular data showing concordance between nuclear and chloroplast phylogenetic trees and lack of evidence for sequence additivity in nuclear internal transcribed spacer (ITS) sequences (Jenks et al., 2010). While *Salvia divinorum* is capable of sexual reproduction, anthropogenic translocation and clonal propagation may have limited the occurrence of sexual reproduction in this species (Reisfield, 1993). Recent phylogenetic analysis of *Salvia divinorum* suggests that it does not belong to the section Dusenostachys (Jenks et al., 2010). In both ITS and chloroplast DNA (*trn*L-F and *psb*A-*trn*H) phylogenetic trees, *Salvia divinorum* is most closely related to the Columbian species *Salvia venulosa* (Jenks et al., 2010).

There have been several genetic studies which have included the analysis of *Salvia divinorum*. In total 19 accessions are available on the NCBI website GenBank (http://www.ncbi.nlm.nih.gov). The intergenic spacer region, tnrL-tnrF is represented by three studies (Walker and Sytsma, 2007; Jenks et al., 2011; Murphy and Bola, 2013) and psbA-tnrH is represented by two studies (Walker and Sytsma, 2007; Jenks et al., 2011). Other chloroplast regions include two rbcL accessions (Olmstead et al., 1993; Walker et al., 2004b), one matK accession (Ogata et al., 2012) and one ndhF accession (Wagstaff et al., 1998). Several studies have also looked at ITS1 and ITS2 (Walker et al., 2004b; Jenks et al., 2011; Murphy and Bola, 2013) as well as ribosomal RNA (Walker et al., 2004b; Bertea et al., 2006; Jenks et al., 2011).

The combination of genetic and chemical analysis has been used to identify *Salvia divinorum* found in commercial products. The 5S-rRNA spacer region sequence of *Salvia divinorum* was used in combination with liquid chromatography–mass spectrometry (LC–MS) analysis to identify this species when morphological identification was not possible (Bertea et al., 2006). As well, three chloroplast genome (trnL-trnF, matK and rbcL) and, one nuclear genome (ITS) were used in combination with gas chromatography–mass spectrometry (GC–MS) and LC–MS to identify *Salvia divinorum* in fresh, dried and powdered leaf samples and blended herbal products (Ogata et al., 2012).

Table 1
Diterpenes reported from *Salvia divinorum*.

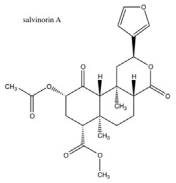
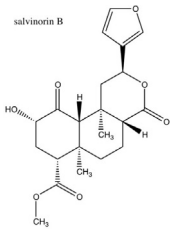
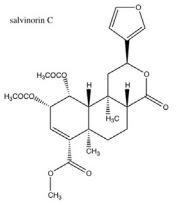
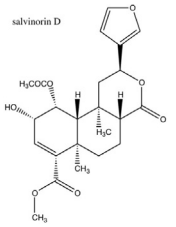
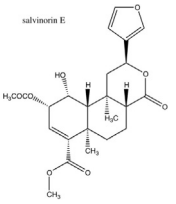
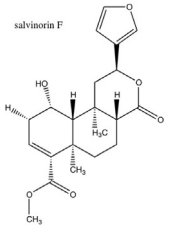
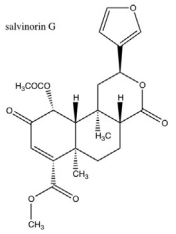
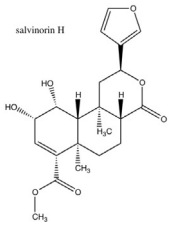
Name	Chemical structure	Reference
Salvinorin A		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Ortega et al. (1982), Shirota et al. (2006), Valdés et al. (1984)
Salvinorin B		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Ortega et al. (1982), Shirota et al. (2006), Valdés et al. (1984)
Salvinorin C		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Shirota et al. (2006), Valdés et al. (1984)
Salvinorin D		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003), Shirota et al. (2006)
Salvinorin E		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003), Shirota et al. (2006)
Salvinorin F		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003), Shirota et al. (2006)
Salvinorin G		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005)
Salvinorin H		Grundmann et al. (2007), Hanson (2010), Shirota et al. (2006)

Table 1 (*continued*)

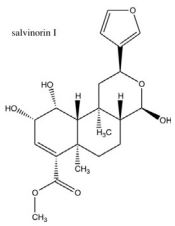
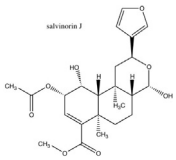
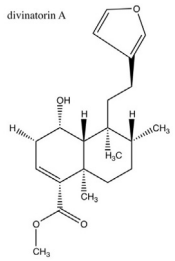
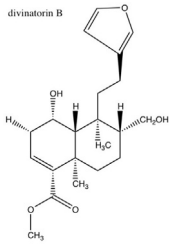
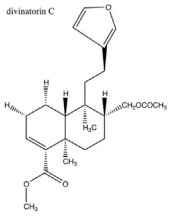
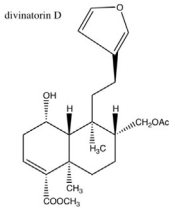
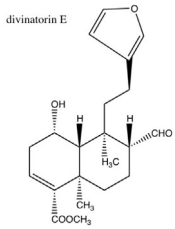
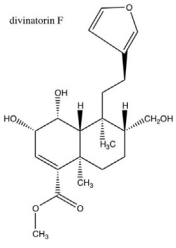
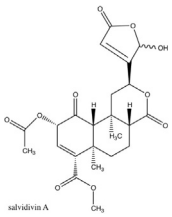
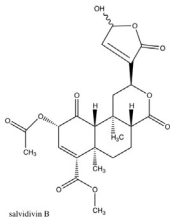
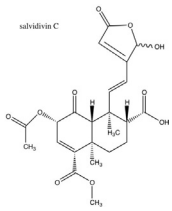
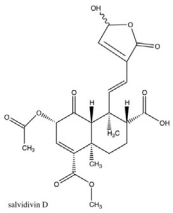
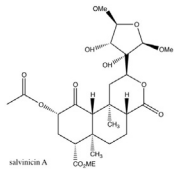
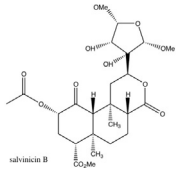
Name	Chemical structure	Reference
Salvinorin I		Grundmann et al. (2007), Hanson (2010), Shirota et al. (2006)
Salvinorin J		Kutrzeba et al. (2009a)
Divinatorin A		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003), Shirota et al. (2006)
Divinatorin B		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003), Shirota et al. (2006)
Divinatorin C		Bigham et al. (2003), Grundmann et al. (2007), Hanson (2010), Lee et al. (2005), Munro and Rizzacasa (2003)
Divinatorin D		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005)
Divinatorin E		Grundmann et al. (2007), Hanson (2010), Lee et al. (2005)
Divinatorin F		Grundmann et al. (2007), Hanson (2010), Shirota et al. (2006)

Table 1 (*continued*)

Name	Chemical structure	Reference
Salvidivin A		Grundmann et al. (2007), Hanson (2010), Prisinzano and Rothman (2008), Shirota et al. (2006)
Salvidivin B		Grundmann et al. (2007), Hanson (2010), Prisinzano and Rothman (2008), Shirota et al. (2006)
Salvidivin C		Hanson (2010), Prisinzano and Rothman (2008), Shirota et al. (2006)
Salvidivin D		Grundmann et al. (2007), Hanson (2010), Prisinzano and Rothman (2008), Shirota et al. (2006)
Salvinicin A		Hanson (2010), Harding et al. (2005), Prisinzano and Rothman (2008)
Salvinicin B		Hanson (2010), Harding et al. (2005), Prisinzano and Rothman (2008)

Intra-specific variability of *Salvia divinorum* has received little research attention to date. A phylogenetic study of the *Salvia* subgenus *Calosphace* found no variation in six individuals of *Salvia divinorum* collected from Sierra Mazateca (Jenks et al., 2010). However, this study included only a small number of samples and may not have included genetic loci that are variable in this species. In terms of populations found outside Mexico, the first reported specimen of *Salvia divinorum* to be propagated outside Oaxaca was deposited at the UCLA Botanical Garden in 1963 by S. Bunnell (Siebert, 2003). It has been suggested that most *Salvia divinorum* plants, at least in the USA, were propagated from this single plant (Valdés et al., 1987). In the past 50 years there have been few recorded live plant collections from Oaxaca, and it appears that the original UCLA plant may be the progenitor of the majority of propagated *Salvia divinorum* outside of Mexico (Siebert, 2003). The ease of vegetative propagation, long-term human use and, the small number of recorded live collections coupled with research suggesting a lack of intraspecific genetic variability, suggest that *Salvia divinorum* propagated outside of Mexico, and perhaps the species in general, has very limited genetic variability.

5. Chemistry

The compounds that have been isolated from *Salvia divinorum* are primarily diterpenes (Table 1). Diterpenoids are derived from the condensation of four isoprene units which, in *Salvia* species, leads to the formation of bicyclic, tricyclic, and tetracyclic compounds (Bonito et al., 2011). It is the diterpene salvinorin A that is responsible for the bioactivity in *Salvia divinorum* and which are also considered to be potential lead compounds in pharmaceutical research.

Clerodanes are a structural class of diterpenes, which contain four contiguous stereo-centers contained in a *cis* or *trans* decalin (Lozama and Prisinzano, 2009). Neoclerodane diterpenes, a term

originally coined in 1979 (Hanson, 2010), are a subtype of clerodanes, which have a carbon skeleton with the same absolute sterochemistry as clerodin, a bitter principle originally extracted from *Clerodendron infortunatum* Bhat. (Paul et al., 1962; Lozama and Prisinzano, 2009). This carbon skeleton is found in several botanical families including Lamiaceae, Verbenaceae, Euphorbiaceae and Compositae (Hanson, 2010).

In Ortega et al. (1982) isolated a novel neoclerodane diterpene from *Salvia divinorum* and named it salvinorin A (Table 1) (Valdés et al., 1984). Salvinorin A, the predominant neoclerodane diterpene found in *Salvia divinorum*, remains the only reported neoclerodane diterpene with psychoactive properties (Hanson, 2010). For this reason research to date has focused on this compound with minor attention given to other diterpenes in this plant.

Salvinorin A is compartmentalized in glandular trichomes located on the abaxial side of *Salvia divinorum* leaves (Siebert, 2004). The mechanisms of salvinorin A synthesis in *Salvia divinorum* were investigated in-vitro using stable isotopes and analysis found that this diterpene is biosynthesised via the deoxyxylulose phosphate (DOXP) pathway (Kutrzeba et al., 2007).

Besides salvinorin A and the other neoclerodane diterpenes found in *Salvia divinorum,* several other interesting groups of chemical constituents have been reported. Loliolide (Table 3) originally extracted from *Fumaria officinalis* L., is a terpene reported to form from the degradation of carotenoids, which are pigments occurring in the chloroplasts of plants as well as other photosynthetic organisms (Schühly et al., 2007). It is also found in *Lolium perenne* L., *Digitalis purpurea* L. and several other species (Valdés et al., 1984; Hanson, 2010). Loliolide treated rye flakes (6.8 mg/g) proved to be an effective ant deterrent (Okunade and Wiemer, 1985).

(−)Hardwickiic acid (Table 3), a furanoid diterpene found in *Salvia divinorum,* has also been extracted from several species including *Kingiodendron pinnatum* DC. Harms, *Solidago juncea* Aiton, *Grangea maderaspatana* L. Desf., *Baccharis macraei* Hook. & Arn., and *Chrozophora oblongifolia* Delile. A. Juss. ex Spreng., (Chaichantipyuth et al., 2004). It has been found to be active against the Cow Pea aphid *Aphis craccivora* Koch. When applied at a concentration of 5 ppm, insect mortality of female aphids was 62% in 24 h (Bandara et al., 1990, 1987). This acid also exhibits antimicrobial activity (McChesney et al., 1991; Chaichantipyuth et al., 2004). In ethanol at 1 mg/ml (−)Hardwickiic acid was found to have antibacterial action against *Bacillus subtilis*, *Staphylococcus aureus* and *Mycobacterium smegmatis* and antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes* and *Helminthosporium sp*. (McChesney et al., 1991).

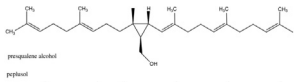
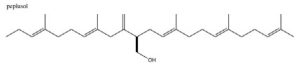
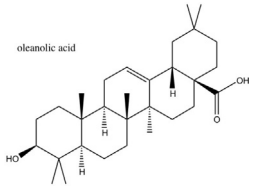
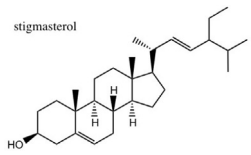
(E)-phytol (Table 3), a diterpene alcohol isolated from *Salvia divinorum*, has also has been shown to exhibit antimicrobial activity with a minimum inhibitory concentration (MIC) of 2 μg/ml (Rajab et al., 1998a). Nepetoidin B (Table 3), also isolated from *Salvia divinorum*, is a caffeic acid ester found predominately in the Lamiaceae sub-family Nepetoideae, was shown to have anti-fungal properties when tested on a TLC plate with *Aspergillus niger* (Grayer et al., 2003; Hanson, 2010).

All the reported compounds from this plant have been isolated primarily from the leaves, and in some cases the stems, while other plant parts, such as flowers and roots have not been studied and may yet yield interesting compounds. Apart from the clerodane diterpenes there are very few reported compounds in *Salvia divinorum*. Chemical compounds such as triterpenes (Table 2), phenolics and flavonoids are ubiquitous in many higher plant families including Lamiaceae (Atanassova et al., 2011) It is likely that these compounds are present in *Salvia divinorum* but have not yet been reported.

6. Pharmacology of salvinorin A

Salvinorin A is the most prevalent diterpene in *Salvia divinorum* and is the only compound from this species which has been studied in detail. This compound is a highly selective kappa-opioid receptor agonist and the first reported diterpene to possess psychoactive properties (Valdés, 1994). The kappa-opioid receptor (KOR) is one of five related receptors in humans that bind opioid-type compounds in the brain and is involved in pain perception, mood and motor control. Encoded by the OPRK1 gene (Butelman et al., 2007), this receptor is found in the brain, spinal cord and pain neurons (Fine and Portenoy, 2004). The primary endogenous agonists of this receptor is the endogenous dynorphin peptide (Schwarzer, 2009). In addition to binding to this endogenous ligand it also binds to naturally occurring alkaloids, synthetic ligands and salvinorin A (James et al., 1982). Initial screening of 50 distinct receptors, transporters and ion channels showed salvinorin A is selective for the kappa-opioid receptor, compared with LSD, which reacted with 22 distinct systems (Roth et al., 2002; Grundmann et al., 2007). The results of *in vitro* (Table 4) and

Table 2
Triterpenes reported from *Salvia divinorum*.

Name	Chemical structure	Reference
Presqualene alcohol		Bigham et al. (2003)
Peplusol		Bigham et al. (2003)
Oleanolic acid		Munro (2006)
Stigmasterol		(Munro (2006)

ex vivo (Table 5) studies also show that salvinorin A has a high affinity for the kappa-opioid receptor, however, recent studies have also shown an interaction with several other biological systems, specifically the endo-cannabinoid system (Braida et al., 2008, 2007; Capasso et al., 2008a; Fichna et al., 2009a).

The endo-cannabinoid system is made up of several cannabinoid binding sites found throughout the body. In humans the CB1 receptor sites are expressed in the brain and the CB2 receptor sites are expressed in the immune system (Pertwee, 2008). The endo-cannabinoid system is primarily known for mitigating the psychoactive effects of cannabis but also is known to modulate appetite, pain, mood and memory (Pertwee, 2008). The interaction between salvinorin A and the endo-cannabinoid receptor CB1 was first investigated in zebrafish (Braida et al., 2007) and further explored and confirmed in rats (Braida et al., 2008). Traditionally *Salvia divinorum* was used to treat gastrointestinal malaise, which

Table 3
Miscellaneous constituents reported from *Salvia divinorum*.

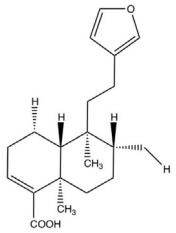
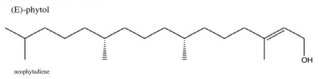
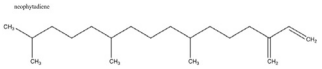
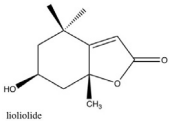
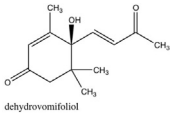
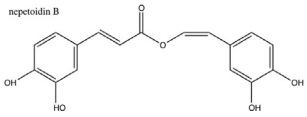
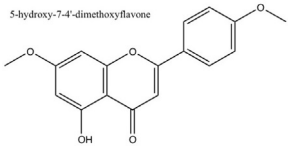
Name	Chemical structure	Reference
Hardwickiic acid	 (-)-Hardwickiic acid	Misra et al. (1968)
(E)-phytol	 (E)-phytol	Bigham et al. (2003), Rajab et al. (1998b)
Neophytadiene	 neophytadiene	Munro (2006)
Loliolide	 lioliolide	Hanson (2010), Valdés (1986)
Dehydrovomifoliol	 dehydrovomifoliol	Hanson (2010)
Nepetoidin B	 nepetoidin B	Grayer et al. (2003), Hanson (2010)
5-Hydroxy-7-4′-dimethoxyflavone	 5-hydroxy-7-4'-dimethoxyflavone	Valdés et al. (2002)

Table 4
In vitro studies with salvinorin A.

Model	Extract	Key outcomes	Reference
Effect of salvinorin A in lipopolysaccharide (LPS)-stimulated macrophages	Salvinorin A (99%)	Potent actions on macrophages	Aviello et al. (2011)
Transport characteristics of salvinorin A using 1. MDCK-MDR1 cell monolayers 2. *P*-glycoprotein APTase assay	Salvinorin A in Cremophor EL and ethanol (70:30)	High secretory transport in the MDCK-MDR1; concentration dependent stimulation of *P*-glycoprotein ATPase activity	Teksin et al. (2009)
Metabolism of salvinorin A using fungal microbial transformation	95% Salvinorin A	Salvinorin A undergoes fast hydrolysis resulting in the formation of salvinorin B	Kutrzeba et al. (2009b)
Binding affinity and agonist efficacy of salvinorin A	Salvinorin A	Salvinorin A uses unique residues within a commonly shared binding pocket to selectively activate KORs	Yan et al. (2005)
Effects of salvinorin A using cloned human kappa-opioid receptors	Salvinorin A	Salvinorin A is a full agonist at the hKOR	Chavkin et al. (2004)
Molecular pharmacological profile of salvinorin A using human cloned G protein-coupled receptors (GPCRs), channels and transporters	Salvinorin A	Salvinorin A is a potent KOR agonist	Roth et al. (2002)

Table 5
Ex vivo studies with salvinorin A.

Model	Extract	Key outcomes	Reference
Analysis of intestinal fluid content in mice	99% Salvinorin A	Inhibited the effects of endotoxin treatment on paracellular permeability in the mouse ileum Inhibitory effect on neurogenic ion transport was reversed by KOR, CB1 and CB_2 receptor-selective antagonists	Fichna et al. (2011)
Effects of salvinorin A as presynaptic modulator of neurotransmitter release	99% Salvinorin A	Salvinorin A facilitates noradrenaline exocytosis from hippocampal terminals and inhibits the K^+-evoked release of 5HT from hippocampal terminals	Grilli et al. (2009)
Stability of salvinorin A in rat blood plasma	Salvinorin A in 2.5% v/v ACN and H_2O	Degradation of salvinorin A and B in rat plasma is catalysed by a carboxylesterase	Tsujikawa et al. (2009)
Effects of salvinorin A on GI motility were assessed using mouse colon, stomach and ileum	99% Salvinorin A	Inhibited twitch contractions from electric shock in mouse stomach, ileum and colon preparations	Fichna et al. (2009a)
Metabolism of salvinorin A in rat liver and brain homogenates	95% Salvinorin A	Salvinorin A is primarily metabolized by hydrolysis to salvinorin B. No difference in metabolism observed between brain and liver	Kutrzeba et al. (2009b)
Effects of a standardized extract of *Salvia divinorum* leaves on the transmission of nerve cells in guinea pig small intestine	1.6% Salvinorin A in DMSO	Extract exerted inhibitory effects on nerve cells in the small intestine of the guinea-pig ileum through activation of prejunctional KORs	Capasso et al. (2006)

links with both *in vitro* data showing that the action of the CB1 receptor inhibits gastrointestinal mobility in the inflamed gut of rats and *ex vivo* research showing that salvinorin A inhibits nerve cells in the small intestine of the guinea-pig (Capasso et al., 2006).

Salvinorin A can be absorbed via two routes. Human studies have confirmed that salvinorin A can be absorbed through the buccal membrane (Siebert, 1994; Ott, 1995) This is consistent with traditional use, as the Mazatec chew or drink a water infusion of *Salvia divinorum* to evoke its psychoactive properties. It was found that sublingual doses up to 4.0 mg were not psychoactive, suggesting the absorption through the buccal membrane requires a minimum concentration to be active (Mendelson et al., 2011). Salvinorin A can also be absorbed by the inhalation of the vaporized compound, which leads to a rapid onset of the psychoactive effects. The effects of salvinorin A are fast acting, yet short in duration (Siebert, 1994). When smoked by humans, the reported psychoactive dose of pure compound is 0.375–21 μg/kg (Johnson et al., 2011; MacLean et al., 2013). When vaporized salvinorin A is inhaled, the effects become manifest within a minute after consumption and last up to 15 min (Valdés, 1994; Johnson et al., 2011). Salvinorin A is deactivated by the gastrointestinal system and is not absorbed through this route (Siebert, 1994).

The distribution of salvinorin A through the body is rapid and less than 10 μg in the brain can account for the psychoactive effect of salvinorin A (Hooker et al., 2008). In non-human primates salvinorin A was found to cross the blood–brain barrier in approximately 40 s and found distributed primarily in the cerebellum and visual cortex (Hooker et al., 2008). When non-human primates were injected with 0.032 ng/kg of salvinorin A, a maximum concentration (Cmax) was reached in the blood at the 2 min time point. The assessed half life of salvinorin A in non-human primates is 8 min (Hooker et al., 2008; Butelman et al., 2009).

Salvinorin A is metabolised by both the liver and gallbladder (Hooker et al., 2008; Fichna et al., 2009b). *In vitro* and non-human primate studies have shown that salvinorin A undergoes hydrolysis, which results in the formation of salvinorin B, which is the main (inactive) metabolite of salvinorin A (Valdés et al., 2001; Chavkin et al., 2004; Schmidt et al., 2005a; Kutrzeba et al., 2009b; Tsujikawa et al., 2009a). The metabolism of salvinorin A is confirmed by findings that only $\pm$0.8% of a 0.5 mg administered dose was recovered from urine in human volunteers (Pichini et al., 2005).

In rats, the elimination half-life ($t_{1/2}$) of salvinorin A was 75.4 min from blood plasma and 36.1 min. from the brain. In non-human primates, the observed elimination of salvinorin A was rapid with a $t_{1/2}$ of 56.6 $\pm$ 24.8 min. Differences in elimination were observed in non-human primates with elimination faster for male primates versus female (Schmidt, et al., 2005b). *In vitro* the glucuronidation pathway is used to eliminate salvinorin A from the body (Teksin et al., 2009). Salvinorin A appears to be removed from the CNS by active transport mechanisms, however, this lipophilic molecule may diffuse through the blood–brain barrier passively (Teksin et al., 2009).

Several animal models have been used to assess the effects of salvinorin A in mice, rats and fish (Fantegrossi et al., 2005; Carlezon et al., 2006; John et al., 2006; Braida et al., 2007). The forced swimming test, inverted screen test, tail flick latency test and conditioned place preference test, have been used to assess the physiological effects of this compound on observed behaviour in animals. The majority of *in vivo* (Table 6) studies report the effects of salvinorin A on rodents, while a small number of studies report the effects of salvinorin A on non-human primates (Table 7) and humans (Table 8).

Studies performed on non-human research subjects, almost exclusively, use injected, pure salvinorin A and fail to report the effect, or lack of effect, of the vehicle used. While the effect of injected salvinorin A on non-human subjects is important to the research on this compound, molecular targets in humans do differ from other animals (Adham et al., 1994). Human studies have only been performed on a very small number of participants, the majority of whom were experienced with psychoactive substances. These results, therefore, may not be applicable to a larger population. At this time, large scale, human, clinical trials are needed to better understand the therapeutic potential of salvinorin A.

7. Toxicology

In published literature *Salvia divinorum*, and its active compound salvinorin A are reported to have low toxicity (Giroud et al., 2000; Prisinzano, 2005; Grundmann et al., 2007; Hoover et al., 2008; Braida et al., 2009; Vohra et al., 2011; Gibbons, 2012). The toxicology of salvinorin A has been assessed in both mice and rats (Mowry et al., 2003) (Table 6). This study assessed the

Table 6
In vivo animal studies (rodents and fish) with salvinorin A and related compounds.

Model	Dose range	Route	Animal	Control	Extract	Key outcomes	Reference
Effects of *Salvia divinorum* and salvinorin A on place aversion and place preference	*Salvia divinorum* 10–100 mg/kg salvinorin A 0.1–1.0 mg/kg	i.p.	Rat	Positive control – amphetamine; Negative control – haloperidol	*Salvia divinorum*/ salvinorin A in 10% DMSO and 10% Tween80 in saline	Both *Salvia divinorum* extract and salvinorin A produce a conditioned place aversion	Sufka et al. (2013)
Antidepressant effects of salvinorin A	1 mg/kg	Not Reported	Rat	Vehicle	Salvinorin A in 75% DMSO and 25% saline	In rats exposed to chronic mild stress, anhedonia was reversed by the administration of salvinorin A	Harden et al. (2012)
Effects of salvinorin A on formalin-induced persistent pain	0.5–2 mg/kg	i.p.	Mouse	No control reported	99% Salvinorin A	Effective in reducing formalin-induced mechanical allodynia and spinal neuronal hyperactivity	Guida et al. (2012)
Effects of salvinorin A on Inflammation		i.p.	Mouse	DMSO and saline	99% Salvinorin A	Showed moderate anti-inflammatory action	Aviello et al. (2011)
Effects of *Salvia divinorum* on G.I. mobility		i.p.	Mouse	Vehicle	99% Salvinorin A in vehicle—DMSO and saline	Inhibited the effects of endotoxin treatment on paracellular permeability in the mouse ileum	Fichna et al. (2011)
Effects of salvinorin A on memory	80–640 μg	s.c.	Rat	Vehicle	Salvinorin A in vehicle—ethanol, tween 80 and saline (1:1:8)	Did not impair short-term spatial working memory	Braida et al. (2011)
Recognition of salvinorin A by rats trained to discriminate LSD and ketamine	Experiment 1 (LSD) 0.125–2.0 mg/kg Experiment 2 (ketamine) 0.25–3.0 mg/kg	i.p.	Rat	LSD, Ketamine	Salvinorin A in 75% DMSO	Salvinorin A did not substitute for either LSD or ketamine in rats trained to discriminate these substances. The psychoactive mechanism of salvinorin A is different from these	Killinger et al. (2010)
Effects of salvinorin A on dopamine	1.0–10 mg/kg	i.p.	Mouse	Vehicle	Salvinorin A in vehicle—saline, tween 80, L-ascorbic acid and ethanol	Compulsive chewing in mice may be mediated by dopaminergic mechanisms	Phipps and Butterweck (2010)
Anxiolytic and antidepressant effects of salvinorin A	0.000001–1.0 mg/kg	s.c.	Mouse	Vehicle	Salvinorin A in vehicle—ethanol, Tween 80 and saline (1:1:8)	Salvinorin A showed anxiolytic and antidepressant-like effects. Salvinorin A has a weak affinity for cannabinoid CB1 receptors	Braida et al. (2009)
Metabolism and pharmacokine-tics of salvinorin A	10.0 mg/kg	i.p.	Rat	No control reported	Salvinorin A in vehicle—Cremophor EL and ethanol (70:30)	Blood–brain barrier transport, metabolism and pharmacokinetics of salvinorin A contributes to rapid onset and short duration of action	Teksin et al. (2009)
Effect of salvinorin A, and other KOR agonists on KOR	Experiment 1: 0.125–1.0 mg/kg Experiment 2: 0.25–3.0 mg/kg Experiment 3: 0.25–2.0 mg/kg	i.p.	Rat	U69593, U50488.	Salvinorin A in 75% DMSO	Stimulus effects of salvinorin A is mediated by KOR	Baker et al. (2009)
Effects KOR agonist on drug seeking behaviour	0.3, 1.0 mg/kg	i.p.	Rat	Vehicle	Salvinorin A in 75% DMSO	Salvinorin A reduces cocaine-induced drug-seeking behaviour	Morani et al. (2009)
Effects of salvinorin A on dopamine uptake or release	1.0 or 3.2 mg/kg	i.p.	Rat	Vehicle	Salvinorin A in 75% DMSO	Salvinorin A decreases mesostriatal neuro-transmission by affecting dopamine release but not uptake	Gehrke et al. (2008)
Effects of salvinorin A and the interaction of the kappa opioid and endocannabinoid system	0.05–160 μg/kg (CPP) 0.01–1 μg/ infusion (ICV)	s.c.	Rat	Vehicle	Salvinorin A in vehicle—ethanol, tween 80 and saline (1:1:8)	Salvinorin A has rewarding effects for both the conditioned place preference (CPP) test and intracerebroventicular self administration test (ICV) via interaction between kappa-opioid and endocannabanoid system	Braida et al. (2008)
Effects of salvinorin A on intestinal inflammation	3 mg/kg	i.p.	Mouse	Vehicle	99% Salvinorin A	Salvinorin A affects on GI mobility show an interaction between CB1receptors and KORs in inflamed intestines but not in normal mice GI tracts.	Capasso et al. (2008a)
Effects of salvinorin A on quinpirole sensitization	0.04–2.0 mg/kg	Not reported	Rat	Vehicle	Salvinorin A in vehicle—DMSO and propylene glycol (1:1)	Co-administration of salvinorin A and U69593 can potentiate sensitization to quinirole. The co-administration of a low dose of salvinorin A has an attenuating effect on quinpirole sensitization	Beerepoot et al. (2008)
Effects of standardized *Salvia divinorum* extract and salvinorin A on GI mobility	Standardized extract (SDE) 1–100 mg/kg salvinorin A 0.01–10 mg/kg	i.p.	Mouse	U50488	Salvinorin A in DMSO	Inhibited GI mobility only in high doses, not through KOR mediated mechanisms	Capasso et al. (2008b)

Table 6 (*continued*)

Model	Dose range	Route	Animal	Control	Extract	Key outcomes	Reference
Effect of salvinorin A on the swimming behaviour of zebrafish	0.1–10 μg/kg (swimming activity) 0.2 and 1 μg/kg (CPP)	i.m.	Zebrafish	Cocaine and spiradoline dissolved in saline CPP—vehicle	Salvinorin A in vehicle—cremophor, ethanol and saline (1:1:8)	Low doses of salvinorin A induced accelerated swimming where as high doses induced "trance-like" state	Braida et al. (2007)
Measure salvinorin A discriminative stimulus effects	1–3 mg/kg	i.p.	Rat	U69593	Salvinorin A in vehicle—DMSO and saline	Discriminative stimulus cue is KOR mediated	Willmore-Fordham et al. (2007)
Antinociceptive and hypothermic effect of salvinorin A, salvinorinyl-2-propionate and salvinorin B	0.001–0.03 mg	i.c.v.	Mouse	50% DMSO	– Salvinorin A – salvinorinyl-2-propionate – Salvinorin B	Salvinorin A and salvinorinyl-2-propionate produced antinociception and reduced rectal body temperature	Ansonoff et al. (2006)
Depressive effects of salvinorin A administration	0.125–2.0 mg/kg	i.p.	Mouse	Vehicle	99% Salvinorin A in 75% DMSO	Dose dependent increase of immobility in the forced swimming test and increases intracranial self-stimulation thresholds	Carlezon et al. (2006)
Antinociceptive activity	11.6–23.1 nmol	i.t.	Mouse	Vehicle	Salvinorin A in DMSO	Salvinorin A increased tail-flick latency	John et al. (2006)
Antinociceptive activity of salvinorin A	0.5–4.0 mg/kg	i.p.	Mouse	Vehicle	Salvinorin A in vehicle—DMSO and propylene glycol (10:90)	Dose-dependent antinociception that peaked at 10 min post-injection	McCurdy et al. (2006)
Effects of salvinorin A on sedation and motor coordination	2.0 mg/kg	i.p.	Mouse	U69,593, remifentanil	Salvinorin in vehicle—ethanol, alkamuls and water (1:1:8)	No dose-dependent effects on sedation or motor coordination	Fantegrossi et al. (2005)
Effects of salvinorin A on basal dopamine levels and place aversion	1.0 and 3.2 mg/kg	i.p.	Rat/ mouse	Vehicle	Salvinorin A in vehicle—ethanol, Tween 80 and water (1:1:8)	Inhibitory effect of salvinorin A on striatial dopamine levels may contribute to its induction of conditioned place aversion and decreased locomotion in mice	Zhang et al. (2005)
Acute toxicity effects of salvinorin A in rats chronic effects in mice	0.4–6.4 mg/kg	i.p.	Rat/ mouse	Vehicle	Salvinorin A in DMSO	Administration of salvinorin A had little effect on the cardiovascular function of rats; long term administration in mice did not produce detectable histological change	Mowry et al. (2003)

Table 7
In vivo animal studies (non-human primate) with salvinorin A.

Model	Dose range	Route	Animal	Control	Duration of effect	Extract	Key outcomes	Reference
Effects of salvinorin A on modulation of *P*-glycoprotein transporter	0.0032–0.032 mg/kg	i.m.	Rhesus monkey	5 min loperam-ide pretreatment (0.32 mg/kg)	60 s	Salvinorin A in vehicle—ethanol, Tween 80 and saline (1:1:8)	Behavioural affects and CNS residence of salvinorin A are sensitive to the functional status of *P*-glycoprotein	Butelman et al. (2012)
Sedation and postural relaxation	0.01–0.1 mg/kg	s.c.	Rhesus monkey	U69593	15 min	Salvinorin A in vehicle—ethanol, Tween 80 and saline (1:1:8)	Salvinorin A caused sedative affects and was detected by LC/MS in CSF 1 min after injection with Cmax observed after 2 min	Butelman et al. (2009)
Kinetic behaviour of salvinorin A	1.18–4.01 mg/kg	i.v.	Baboon	No Control reported	60 min	Salvinorin A, 99% salvinorin B	Salvinorin A rapidly crosses blood–brain barrier ($\pm$40 s) and has a half-life of 8 min. High concentrations found in cerebellum and cortex. Less than 10 μg in the brain can account for its psychoactive properties	Hooker et al. (2008)
In vivo pharmacokinetics of salvinorin A	0.032 mg/kg	i.v.	Rhesus monkey	No control reported	60 min	Salvinorin A in vehicle—ethanol, Tween 80, water (1:1:8)	Elimination of salvinorin A was rapid. Differences in distribution, elimination and area under curve (AUC) were observed between sexes	Schmidt et al. (2005a)
Stimulus effects of salvinorin A compared with other KOR agonists	0.001–0.032 mg/kg	s.c.	Rhesus monkey	U69593	5–15 min	Salvinorin A in vehicle—ethanol, Tween 80, saline (1:1:8)	Salvinorin A produces stimulus effects similar to kappa-agonist U69,593	Butelman et al. (2004)

physiological effects of salvinorin A on cardiac conduction, temperature and galvanic skin response, as well, the major organs of the animals were dissected and analysed upon the conclusion of the study. This study reported a very low toxicity of salvinorin A (Mowry et al., 2003). Further research is needed to confirm the low toxicity of *Salvia divinorum* and its constituents.

8. Conclusion

Fifty years ago, *Salvia divinorum* was unknown outside Oaxaca, Mexico. While a single flowering specimen allowed for identification of the species in 1962, it was not until the early 1990s that the action of salvinorin A was elucidated. In the intervening years this

Table 8
Human studies of salvinorin A effects.

Summary	Dose range	Route	Min. active con'c	Control	Duration	Extract	Findings	Reference
Effects of inhaled salvinorin A in healthy, adults experienced with psychoactive substances	0.375–21 μg/kg	Inhaled	0.375 μg/kg	Double blind placebo controlled study ($n=8$)	Subjects monitored for 60 min	Salvinorin A	Dose-related effects peaked at 2 min and then rapidly dissipated	MacLean et al. (2013)
Psychophysiological effects of salvinorin A	0–12 mg salvinorin A	Inhaled	Not reported	Double-blind randomized crossover counter-balanced study ($n=10$)	Not reported	Salvinorin A	Elevated blood cortisol levels. Did not significantly change heart rate or blood pressure. Patterns suggest low addictive potential	Ranganathan et al. (2012)
Subjective experience of *Salvia divinorum*	1017 μg salvinorin A	Inhaled	N/A	Double—blind, placebo-controlled, randomized study ($n=30$)	70 min	*Salvia divinorum* leaf fortified with salvinorin A	Diastolic blood pressure and pulse rate declined during session. salvinorin A inhalation increased talking, laughing and movement while sitting. 87% of participants reported effects lasting less than 24 h, 13% reported effects lasting more than 24 h	Addy (2012)
Physiological behavioural and subjective effects of inhaled salvinorin A	0.375–21 μg/kg	inhaled	0.75 μg/kg	Double blind placebo controlled study ($n=4$)	20 min	Salvinorin A	Salvinorin A did not affect heart rate or blood pressure and determined to have a safe physiological profile at the studied doses	Johnson et al. (2011)
Physiological and subjective effects of sublingually administered salvinorin A	1000–4000 μg	subling-ual	N/A	Polyethylene glycol 400 and placebo ($n=8$)	Subjects monitored for 4 hours after admin	Salvinorin A in vehicle—DMSO and polyethylene glycol 400 (25:75)	Sublingual bio-availability of salvinorin A is poor. Sublingual doses up to 4.0 mg were not psychoactive	Mendelson et al. (2011)
Presence of salvinorin A in human biological matrices (urine, sweat and saliva)	Not reported	inhaled	N/A	Salvinorin A spiked *in vitro* samples of urine, sweat and saliva (n=2)	15–20 min	Dried leaves of *Salvia divinorum*	Salvinorin A was detected in saliva and urine after smoking *Salvia divinorum*	Pichini et al. (2005)
Role of the oral mucosa as absorption site of orally ingested *Salvia divinorum*	1. 30 g fresh leaves	Sublingual	200 μg	No control reported ($n=6$)	1. oral: 60 min	1. *Salvia divinorum* leaves	Salvinorin A can be absorbed through the oral mucosa or vaporized and inhaled to obtain psychoactive effects. salvinorin A is deactivated in the gastrointestinal system	Siebert (1994)
	2. 200–500 μg salvinorin A				2. Smoked: 10 min	2. 99% salvinorin A		

species has attained a global distribution, been readily adopted by an information-savvy global culture and captured the attention of a diverse set of scientific researchers.

Early ethnobotanical research documented the traditional Mazatec use of this species for both ritual and medical use. Although, as the use of this species has radiated globally, there remains a paucity of research documenting the modern use of this plant outside its endemic region.

The chemistry of the clerodane diterpene constituents of *Salvia divinorum* is well studied however, research on other chemical constituents including flavonoids, phenolics, tannins and other secondary plant metabolites is lacking. This begs the question, what other compounds are present in *Salvia divinorum* and do they have pharmacological potential?

While several genetic studies have included *Salvia divinorum* and its relationship to other *Salvia* species is understood, only one study has examined genetic variability within the species. *Salvia divinorum* readily propagates vegetatively and has been shown to have low sexual viability. Considering this, is it possible that all *Salvia divinorum* plants including recent cosmopolitan and endemic Mexican populations are clones derived from a single source plant? Further study of intraspecific genetic variability is needed to answer this question.

The pharmacology of this species warrants special consideration, particularly regarding the unique effect of salvinorin A has as a KOR antagonist. Several authors have hypothesized that *Salvia divinorum* and its major metabolites could have therapeutic applications, or at least be a foundation for the development of such developments (Roth et al., 2002; Sheffler and Roth, 2003; Vortherms and Roth, 2006; Appel and Kim-Appel, 2007; Prisinzano, 2013). What stands between current research and the development of a *Salvia divinorum* based pharmacotherapy? The current understanding of the pharmacology of salvinorin A relies heavily on non-human studies. While there is a growing body of human research, these studies are small and have been conducted with healthy adults who have experience with psychoactive substances. Published human studies have not reported any harmful effects when salvinorin A is administered within the dose range of 0.375–21 μg/kg (Siebert, 1994; Johnson et al., 2011; MacLean et al., 2013; Zawilska and Wojcieszak, 2013) but what are the implications when applied to a larger population? More data on the toxicology and safety of *Salvia divinorum* are needed before larger scale clinical trials of the potential therapeutic effects of *Salvia divinorum* and salvinorin A are undertaken.

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References

Addy, P.H., 2012. Acute and post-acute behavioural and psychological effects of salvinorin A in humans. Psychopharmacology 220, 195–204.
Adham, N., Tamm, J.A., Salon, J.A., Vaysse, P.J., Weinshank, R.L., Branchek, T.A., 1994. A single point mutation increases the affinity of serotonin 5-HT1D [alpha], 5-HT1D [beta], 5-HT1E and 5-HT1F receptors for [beta]-adrenergic antagonists. Neuropharmacology 33, 387–391.
Allen, J.W., 1994. Chasing the ghost of Maria Sabina, saint mother of the sacred mushroom. Psychedelic Illuminations 6.
Allen, J.W., 1997. Maria Sabina, Saint Mother of the Sacred Mushroom: Ethnomycological Journals Sacred Mushrooms Studies. Psilly Publications/Raver-Books.
Ansonoff, M.A., Zhang, J., Czyzyk, T., Rothman, R.B., Stewart, J., Xu, H., Zjwiony, J., Siebert, D.J., Yang, F., Roth, B.L., 2006. Antinociceptive and hypothermic effects of salvinorin A are abolished in a novel strain of kappa-opioid receptor-1 knockout mice. J. Pharmacol. Exp. Ther. 318, 641.
Appel, J., Kim-Appel, D., 2007. The rise of a new psychoactive agent: *Salvia divinorum*. Int. J. Ment. Health Addict. 5, 248–253.
Atanassova, M., Georgieva, S., Ivancheva, K., 2011. Total phenolic and total flavonoid contents, antioxidant capacity and biological contaminants in medicinal herbs. J. Univ. Chem. Technol. Metall. 46, 81–88.
Aviello, G., Borrelli, F., Guida, F., Romano, B., Lewellyn, K., De Chiaro, M., Luongo, L., Zjawiony, J.K., Maione, S., Izzo, A.A., Capasso, R., 2011. Ultrapotent effects of salvinorin A, a hallucinogenic compound from *Salvia divinorum*, on LPS-stimulated murine macrophages and its anti-inflammatory action in vivo. J. Mol. Med. 89, 891–902.
Baker, L.E., Panos, J.J., Killinger, B.A., Peet, M.M., Bell, L.M., Haliw, L.A., Walker, S.L., 2009. Comparison of the discriminative stimulus effects of salvinorin A and its derivatives to U69,593 and U50,488 in rats. Psychopharmacology 203, 203–211.
Bandara, B.M.R., Wimalasiri, W.R., Wickremasinghe, W.A., Bandara, K., 1990. Cyperenoic acid and (−)-hardwickiic acid from the chloroform extract of the roots of *Croton aromaticus*: isolation and insecticidal properties. J. Nat. Sci. Counc. Sri Lanka 18, 119–126.
Bandara, B.R., Wimalasiri, W.R., Bandara, K.P., 1987. Isolation and insecticidal activity of (−)-hardwickiic acid from *Croton aromaticus*. Planta Med. 53, 575.
Beerepoot, P., Lam, V., Luu, A., Tsoi, B., Siebert, D., Szechtman, H., 2008. Effects of salvinorin A on locomotor sensitization to D2/D3 dopamine agonist quinpirole. Neurosci. Lett. 446, 101–104.
Beifuss, W., 1997. Cultivating Diviner's Sage: A Step by Step Guide to Cultivation, Propagation, and Keeping your *Salvia* Plants Happy. The Resonance Project 1.
Bentham, G., 1876. Labiatae, in: Genera Plantarum. Reeve & Co., London.
Bertea, C.M., Luciano, P., Bossi, S., Leoni, F., Baiocchi, C., Medana, C., Azzolin, C.M., Temporale, G., Lombardozzi, M.A., Maffei, M.E., 2006. PCR and PCR-RFLP of the 5S-rRNA-NTS region and salvinorin A analyses for the rapid and unequivocal determination of *Salvia divinorum*. Phytochemistry 67, 371–378.
Bigham, A.K., Munro, T.A., Rizzacasa, M.A., Robins-Browne, R.M., 2003. Divinatorins A-C, new neoclerodane diterpenoids from the controlled sage *Salvia divinorum*. J. Nat. Prod. 66, 1242–1244.
Bonito, M.C., Cicala, C., Marcotullio, M.C., Maione, F., Mascolo, N., 2011. Biological activity of bicyclic and tricyclic diterpenoids from *Salvia* species of immediate pharmacological and pharmaceutical interest. Nat. Prod. Commun. 6, 1205–1215.
Braida, D., Capurro, V., Zani, A., Rubino, T., Viganò, D., Parolaro, D., Sala, M., 2009. Potential anxiolytic-and antidepressant-like effects of salvinorin A, the main active ingredient of *Salvia divinorum*, in rodents. Br. J. Pharmacol. 157, 844–853.
Braida, D., Donzelli, A., Martucci, R., Capurro, V., Sala, M., 2011. Learning and memory impairment induced by salvinorin A, the principal ingredient of *Salvia divinorum*, in wistar rats. Int. J. Toxicol. 30, 650–661.
Braida, D., Limonta, V., Capurro, V., Fadda, P., Rubino, T., Mascia, P., Zani, A., Gori, E., Fratta, W., Parolaro, D., Sala, M., 2008. Involvement of κ-opioid and endocannabinoid system on Salvinorin A-induced reward. Biol. Psychiatry 63, 286–292.
Braida, D., Limonta, V., Pegorini, S., Zani, A., Guerini-Rocco, C., Gori, E., Sala, M., 2007. Hallucinatory and rewarding effect of salvinorin A in zebrafish: κ-opioid and CB1-cannabinoid receptor involvement. Psychopharmacology 190, 441–448.
Butelman, E.R., Caspers, M., Lovell, K.M., Kreek, M.J., Prisinzano, T.E., 2012. Behavioural effects and central nervous system levels of the broadly available κ-agonist hallucinogen salvinorin A are affected by *P*-glycoprotein modulation in vivo. J. Pharmacol. Exp. Ther. 341, 802–808.
Butelman, E.R., Harris, T.J., Kreek, M.J., 2004. The plant-derived hallucinogen, salvinorin A, produces kappa-opioid agonist-like discriminative effects in rhesus monkeys. Psychopharmacology 172, 220–224.
Butelman, E.R., Mandau, M., Tidgewell, K., Prisinzano, T.E., Yuferov, V., Kreek, M.J., 2007. Effects of salvinorin A, a κ-opioid hallucinogen, on a neuroendocrine biomarker assay in nonhuman primates with high κ-receptor homology to humans. J. Pharmacol. Exp. Ther. 320, 300–306.
Butelman, E.R., Prisinzano, T.E., Deng, H., Rus, S., Kreek, M.J., 2009. Unconditioned behavioural effects of the powerful κ-opioid hallucinogen salvinorin A in nonhuman primates: fast onset and entry into cerebrospinal fluid. J. Pharmacol. Exp. Ther. 328, 588.
Campbell, R., 1997. The Resonance Project, 1. Sage Wisdom, pp. 27–31.
Capasso, R., Borrelli, F., Capasso, F., Siebert, D.J., Stewart, D.J., Zjawiony, J.K., Izzo, A.A., 2006. The hallucinogenic herb *Salvia divinorum* and its active ingredient salvinorin A inhibit enteric cholinergic transmission in the guinea-pig ileum. Neurogastroenterol. Motility 18, 69–75.
Capasso, R., Borrelli, F., Cascio, M.G., Aviello, G., Huben, K., Zjawiony, J.K., Marini, P., Romano, B., Di Marzo, V., Capasso, F., Izzo, A.A., 2008a. Inhibitory effect of salvinorin A, from *Salvia divinorum*, on ileitis-induced hypermotility: cross-talk between κ-opioid and cannabinoid CB1 receptors. Br. J. Pharmacol. 155, 681–689.
Capasso, R., Borrelli, F., Zjawiony, J., Kutrzeba, L., Aviello, G., Sarnelli, G., Capasso, F., Izzo, A.A., 2008b. The hallucinogenic herb *Salvia divinorum* and its active ingredient salvinorin A reduce inflammation-induced hypermotility in mice. Neurogastroenterol. Motility 20, 142–148.
Carlezon Jr, W.A., Béguin, C., DiNieri, J.A., Baumann, M.H., Richards, M.R., Todtenkopf, M.S., Rothman, R.B., Ma, Z., David, Y.W., Cohen, B.M., 2006. Depressive-like effects of the κ-opioid receptor agonist salvinorin A on behaviour and neurochemistry in rats. J. Pharmacol. Exp. Ther. 316, 440–447.
Casselman, I., Heinrich, M., 2011. Novel use patterns of *Salvia divinorum*: unobtrusive observation using YouTube. J. Ethnopharmacol. 138, 227–662.
Chaichantipyuth, C., Muangsin, N., Chaichit, N., Roengsumran, S., Petsom, A., Watanabe, T., Ishikawa, T., 2004. Crystal structure of (−)-hardwickiic acid, $C_{19}H_{27}OCOOH$. Z. Kristallogr.: New Cryst. Struct. 219, 111–113.

Chavkin, C., Sud, S., Jin, W., Stewart, J., Zjawiony, J.K., Siebert, D.J., Toth, B.A., Hufeisen, S.J., Roth, B.L., 2004. Salvinorin A, an active component of the hallucinogenic sage *Salvia divinorum* is a highly efficacious κ-opioid receptor agonist: structural and functional considerations. J. Pharmacol. Exp. Ther. 308, 1197–1203.

Comisión Nacional para el Desarrollo de los Pueblos Indígenas. México [WWW Document], 2013. URL ⟨http://www.cdi.gob.mx/index.php?id_seccion=660⟩ (accessed 9.2.13).

Diaz, J., 2013. *Salvia divinorum*: a psychopharmacological riddle and a mind–body prospect. Curr. Drug Abuse Rev. 6, 43–53.

Diaz, J.L., 1979. Ethnopharmacology and taxonomy of Mexican psychodysleptic plants. J. Psychedelic Drugs 11, 71–101.

Epling, C., Jativa, C.D., 1962. A New Species of *Salvia* from Mexico. Botanical Museum Leaflets, Harvard University 20, 297–299.

Estrada, A., 1977. La Vida de Maria Sabina: La Sabia de los Hongos. Ross-Erikson, Mexico.

Fantegrossi, W.E., Kugle, K.M., Valdés, L.J., Koreeda, M., Woods, J.H., 2005. Kappa-opioid receptor-mediated effects of the plant-derived hallucinogen, salvinorin A, on inverted screen performance in the mouse. Behav. Pharmacol. 16, 627.

Fichna, J., Dicay, M., Hirota, S.A., Traboulsi, D., Macdonald, J.A., Janecka, A., Beck, P.L., Zjawiony, J.K., Macnaughton, W.K., Storr, M.A., 2011. Differential effects of salvinorin A on endotoxin-induced hypermotility and neurogenic ion transport in mouse ileum. Neurogastroenterol. Motility 23, e212–e583.

Fichna, J., Schicho, R., Andrews, C.N., Bashashati, M., Klompus, M., McKay, D.M., Sharkey, K.A., Zjawiony, J.K., Janecka, A., Storr, M.A., 2009a. Salvinorin A inhibits colonic transit and neurogenic ion transport in mice by activating κ-opioid and cannabinoid receptors. Neurogastroenterol. Motility 21. (1326–1334+e127−e128).

Fichna, Jakub, Schicho, R., Janecka, A., Zjawiony, J.K., Storr, M., 2009b. Selective natural κ opioid and cannabinoid receptor agonists with a potential role in the treatment of gastrointestinal dysfunction-Analogues of salvinorin A, an active ingredient in *Salvia divinorum*, provide an attractive target as future therapeutics in human gastrointestinal dysfunctions. Drug News Perspect. 22, 383.

Fine, P.G., Portenoy, R.K., 2004. Chapter 2: The Endogenous Opioid System. A Clinical Guide to Opioid Analgesia. McGraw Hill.

Foster, S., 1984. Herbal Bounty! The Gentle Art of Herb Culture. Gibbs Smith.

Gehrke, B.J., Chefer, V.I., Shippenberg, T.S., 2008. Effects of acute and repeated administration of salvinorin A on dopamine function in the rat dorsal striatum. Psychopharmacology 197, 509–517.

Gibbons, S., 2012. "Legal Highs" novel and emerging psychoactive drugs: a chemical overview for the toxicologist. Clin. Toxicol. 50, 15–24.

Giovannini, P., Heinrich, M., 2009. Xki yoma' (our medicine) and xki tienda (patent medicine). interface between traditional and modern medicine among the Mazatecs of Oaxaca, Mexico. J. Ethnopharmacol. 121, 383–399.

Giroud, C., Felber, F., Augsburger, M., Horisberger, B., Rivier, L., Mangin, P., 2000. *Salvia divinorum*: an hallucinogenic mint which might become a new recreational drug in Switzerland. Forensic Sci. Int. 112, 143–150.

Grayer, R.J., Eckert, M.R., Veitch, N.C., Kite, G.C., Marin, P.D., Kokubun, T., Simmonds, M.S.., Paton, A.J., 2003. The chemotaxonomic significance of two bioactive caffeic acid esters, nepetoidins A and B, in the Lamiaceae. Phytochemistry 64, 519–528.

Grilli, M., Neri, E., Zappettini, S., Massa, F., Bisio, A., Romussi, G., Marchi, M., Pittaluga, A., 2009. Salvinorin A exerts opposite presynaptic controls on neurotransmitter exocytosis from mouse brain nerve terminals. Neuropharmacology 57, 523–530.

Grundmann, O., Phipps, S.M., Zadezensky, I., Butterweck, V., 2007. *Salvia divinorum* and salvinorin A: an update on pharmacology and analytical methodology. Planta Med. Nat. Prod. Med. Plant Res. 73, 1039–1046.

Guida, F., Luongo, L., Aviello, G., Palazzo, E., De Chiaro, M., Gatta, L., Boccella, S., Marabese, I., Zjawiony, J.K., Capasso, R., Izzo, A.A., de Novellis, V., Maione, S., 2012. Salvinorin A reduces mechanical allodynia and spinal neuronal hyperexcitability induced by peripheral formalin injection. Mol. Pain 8 (1), 60.

Hanson, J.R., 2010. Natural products from the hallucinogenic sage. Sci. Prog. 93, 171–180.

Harden, M.T., Smith, S.E., Niehoff, J.A., McCurdy, C.R., Taylor, G.T., 2012. Antidepressive effects of the κ-opioid receptor agonist salvinorin A in a rat model of anhedonia. Behav. Pharmacol. 23, 710–715.

Harding, W.W., Tidgewell, K., Schmidt, M., Shah, K., Dersch, C.M., Snyder, J., Parrish, D., Deschamps, J.R., Rothman, R.B., Prisinzano, T.E., 2005. Salvinicins A and B, new neoclerodane diterpenes from *Salvia divinorum*. Org. Lett. 7, 3017–3020.

Hine, C., 2008. Virtual ethnography: modes, varieties, affordances. In: Fielding, N., Lee, R.M., Blank, G. (Eds.), The SAGE Handbook of Online Research Methods, 0. Sage Publications Inc., Los Angeles, p. 257.

Hofmann, A., 1980. LSD: My Problem Child. McGraw-Hil p. 209.

Hofmann, A., 1990. Ride through the Sierra Mazateca in search of the magic plant "Ska Maria Pastora". In: Riedlinger, T.J. (Ed.), The Sacred Mushrooms Seeker: Essays for R. Gordon Wasson. Dioscorides Press/Timber Press, pp. 115–127.

Hooker, J.M., Xu, Y., Schiffer, W., Shea, C., Carter, P., Fowler, J.S., 2008. Pharmacokinetics of the potent hallucinogen, salvinorin A in primates parallels the rapid onset and short duration of effects in humans. Neuroimage 41, 1044–1050.

Hoover, V., Marlowe, D.B., Patapis, N.S., Festinger, D.S., Forman, R.F., 2008. Internet access to *Salvia divinorum*: implications for policy, prevention, and treatment. J. Subst. Abuse Treat. 35, 22–27.

James, I.F., Chavkin, C., Goldstein, A., 1982. Selectivity of dynorphin for [kappa] opioid receptors. Life Sci. 31, 1331–1334.

Jenks, A.A., Kim, S.-C., 2013. Medicinal plant complexes of Salvia subgenus *Calosphace*: an ethnobotanical study of new world sages. J. Ethnopharmacol. 146, 214–224.

Jenks, A.A., Walker, J.B., Kim, S.-C., 2010. Evolution and origins of the Mazatec hallucinogenic sage, *Salvia divinorum* (Lamiaceae): a molecular phylogenetic approach. J. Plant Res.

Jenks, A.A., Walker, J.B., Kim, S.-C., 2011. Evolution and origins of the Mazatec hallucinogenic sage, *Salvia divinorum* (Lamiaceae): a molecular phylogenetic approach. J. Plant Res. 124, 593–600.

John, T.F., French, L.G., Erlichman, J.S., 2006. The antinociceptive effect of salvinorin A in mice. Eur. J. Pharmacol. 545, 129–133.

Johnson, 1939. The Elements of Mazatec Witchcraft. Goteborgs Etnografiska Museum Etnologiska Studier 9 119–149.

Johnson, MacLean, Reissig, K.A., Prisinzano, C.J., Griffiths, R.R., T.E., 2011. Human psychopharmacology and dose-effects of salvinorin A, a kappa opioid agonist hallucinogen present in the plant *Salvia divinorum*. Drug Alcohol Depend. 115, 150–155.

Kelly, B.C., 2011. Legally tripping: a qualitative profile of *Salvia divinorum* use among young adults. J. Psychoact. Drugs 43, 46–54.

Killinger, B.A., Peet, M.M., Baker, L.E., 2010. Salvinorin A fails to substitute for the discriminative stimulus effects of LSD or ketamine in Sprague-Dawley rats. Pharmacol. Biochem. Behav. 96, 260–265.

Kowalczuk, A., Raman, V., Galal, A., Khan, I., Siebert, D., Zjawiony, J., 2013. Vegetative anatomy and micromorphology of *Salvia divinorum* (Lamiaceae) from Mexico, combined with chromatographic analysis of salvinorin A. J. Nat. Med., 1–11.

Kutrzeba, Dayan, F.E., Howell, J.L., Feng, J., Giner, J.L., Zjawiony, J.K., 2007. Biosynthesis of salvinorin A proceeds via the deoxyxylulose phosphate pathway. Phytochemistry 68, 1872–1881.

Kutrzeba, Ferreira, D., Zjawiony, J.K., 2009a. Salvinorins J from *Salvia divinorum*: mutarotation in the neoclerodane system. J. Nat. Prod. 72, 1361–1363.

Kutrzeba, Karamyan, V.T., Speth, R.C., Williamson, J.S., Zjawiony, J.K., 2009b. In vitro studies on metabolism of salvinorin A. Pharm. Biol. 47, 1078–1084.

Lee, D.Y.., Ma, Z., Liu-Chen, L.Y., Wang, Y., Chen, Y., Carlezon Jr, W.A., Cohen, B., 2005. New neoclerodane diterpenoids isolated from the leaves of *Salvia divinorum* and their binding affinities for human [kappa] opioid receptors. Bioorg. Med. Chem. 13, 5635–5639.

Lozama, A., Prisinzano, T.E., 2009. Chemical methods for the synthesis and modification of neoclerodane diterpenes. Bioorg. Med. Chem. Lett. 19, 5490–5495.

Mabberley, D.J., 2008. Mabberley's Plant-book: A Portable Dictionary of Plants, their Classification and Uses. Cambridge University Press.

MacLean, K., Johnson, M., Reissig, C., Prisinzano, T., Griffiths, R., 2013. Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. Psychopharmacology 226, 381–392.

McChesney, J.D., Clark, A.M., Silveira, E.R., 1991. Antimicrobial diterpenes of *Croton sonderianus*, 1. Hardwickic and 3,4-secotrachylobanoic acids. J. Nat. Prod. 54, 1625–1633.

McCurdy, C.R., Sufka, K.J., Smith, G.H., Warnick, J.E., Nieto, M.J., 2006. Antinociceptive profile of salvinorin A, a structurally unique kappa opioid receptor agonist. Pharmacol. Biochem. Behav. 83, 109–113.

Mendelson, J.E., Coyle, J.R., Lopez, J.C., Baggott, M.J., Flower, K., Everhart, E.T., Munro, T.A., Galloway, G.P., Cohen, B.M., 2011. Lack of effect of sublingual salvinorin A, a naturally occurring kappa opioid, in humans: a placebo-controlled trial. Psychopharmacology, 1–7.

Mexico Map [WWW Document], n.d. URL ⟨http://www.mapsopensource.com/mexico.html⟩ (accessed 9.24.13).

Misra, R., Pandey, R.C., Dev, S., 1968. The absolute stereochemistry of hardwickiic acid and its congeners. Tetrahedron Lett. 9, 2681–2684.

Mooney, J., 1911. Mixe Indians. Robert Appleton Company, New York.

Morani, A.S., Kivell, B., Prisinzano, T.E., Schenk, S., 2009. Effect of kappa-opioid receptor agonists U69593, U50488H, spiradoline and salvinorin A on cocaine-induced drug-seeking in rats. Pharmacol. Biochem. Behav. 94, 244–249.

Mowry, M., Mosher, M., Briner, W., 2003. Acute physiologic and chronic histologic changes in rats and mice exposed to the unique hallucinogen salvinorin A. J. Psychoact. Drugs 35, 379–382.

Munro, T.A., 2006. The Chemistry of *Salvia divinorum*.

Munro, T.A., Rizzacasa, M.A., 2003. Salvinorins DF, new neoclerodane diterpenoids from *Salvia divinorum*, and an improved method for the isolation of salvinorin A. J. Nat. Prod. 66, 703–705.

Murphy, T.M., Bola, G., 2013. DNA identification of *Salvia divinorum* samples. Forensic Sci. Int. Genet. 7, 189–193.

Ogata, J., Uchiyama, N., Kikura-Hanajiri, R., Goda, Y., 2012. DNA Sequence Analyses of Blended Herbal Products Including Synthetic Cannabinoids as Designer Drugs. Forensic Science International.

Okunade, A.L., Wiemer, D.F., 1985. (−)-Loliolide, an ant-repellent compound from Xanthoxyllum setulosum. J. Nat. Prod. 48, 472–473.

Olmstead, R.G., Bremer, B., Scott, K.M., Palmer, J.D., 1993. A parsimony analysis of the *Asteridae sensu* lato based on rbcL sequences. Ann. Missouri Bot. Garden, 700–722.

Ortega, A., Blount, J.F., Manchand, P.S., 1982. Salvinorin, a new trans-neoclerodane diterpene from *Salvia divinorum* (Labiatae). J. Chem. Soc. Perkins Trans. 1, 2505–2508.

Ott, J., 1993. Pharmacotheon: Entheogenic Drugs, Their Plant Sources and History. Natural Products Co.

Ott, J., 1995. Ethnopharmacognosy and human pharmacology of *Salvia divinorum* and salvinorin A. Curare 18, 103–129.

Ott, J., 1996. Psychoactive card IV. Eleusis 4, 31–39.

Paul, I.C., Sim, G.A., Hamor, T.A., Robertson, J.M., 1962. The structure of clerodin: X-ray analysis of clerodin bromo-lactone. J. Chem. Soc., 4133–4145.
Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br. J. Pharmacol. 153, 199–215.
Phipps, S.M., Butterweck, V., 2010. A new digitized method of the compulsive gnawing test revealed dopaminergic activity of salvinorin A—in vivo. Planta Med. 76, 1405–1410.
Pichini, S., Abanades, S., Farré, M., Pellegrini, M., Marchei, E., Pacifici, R., Torre, R., Zuccaro, P., 2005. Quantification of the plant-derived hallucinogen salvinorin A in conventional and non-conventional biological fluids by gas chromatography/mass spectrometry after *Salvia divinorum* smoking. Rapid Commun. Mass Spectrom. 19, 1649–1656.
Pompa, G., 1957. *Salvia divinorum* Herbarium Sheets: 87556 & 93216. Mexican National Herbarium (UNAM), Mexico City.
Prisinzano, T.E., 2005. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*. Life Sci. 78, 527–531.
Prisinzano, T.E., 2013. Neoclerodanes as atypical opioid receptor ligands. J. Med. Chem. 56, 3435–3443.
Prisinzano, T.E., Rothman, R.B., 2008. Salvinorin A analogs as probes in opioid pharmacology. Chem. Rev. 108, 1732–1743.
Rajab, M.S., Cantrell, C.L., Franzblau, S.G., Fischer, N.H., 1998a. Antimycobacterial activity of (E)-phytol and derivatives: a preliminary structure-activity study. Planta Med. Nat. Prod. Med. Plant Res. 64, 2–4.
Rajab, M.S., Cantrell, C.L., Franzblau, S.G., Fischer, N.H., 1998b. Antimycobacterial activity of (E)-phytol and derivatives: a preliminary structure–activity study. Planta Med. Nat. Prod. Med. Plant Res. 64, 2–4.
Ranganathan, M., Schnakenberg, A., Skosnik, P.D., Cohen, B.M., Pittman, B., Sewell, R.A., D'Souza, D.C., 2012. Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the κ opioid agonist salvinorin A in humans. Biol. Psychiatry.
Reddy, N.U., 2009. Molecular phylogeny of angiospermic plant families using RBCL gene sequences. Int. J. Bioinf. Res. 1, 27–36.
Reisfield, A.S., 1993. The botany of *Salvia divinorum* (Labiatae). SIDA 15, 349–366.
Roth, B.L., Baner, K., Westkaemper, R., Siebert, D., Rice, K.C., Steinberg, S.A., Ernsberger, P., Rothman, R.B., 2002. Salvinorin A: a potent naturally occurring nonnitrogenous κ opioid selective agonist. Proc. Nat. Acad. Sci. 99, 11934.
Schmidt, M.S., Prisinzano, T.E., Tidgewell, K., Harding, W., Butelman, E.R., Kreek, M. J., Murry, D.J., 2005a. Determination of Salvinorin A in body fluids by high performance liquid chromatography-atmospheric pressure chemical ionization. J. Chromatogr. B 818, 221–225.
Schmidt, Schmidt, M.S., Butelman, E.R., Harding, W.W., Tidgewell, K., Murry, D.J., Kreek, M.J., Prisinzano, T.E., 2005b. Pharmacokinetics of the plant-derived κ-opioid hallucinogen salvinorin A in nonhuman primates. Synapse 58, 208–210.
Schühly, W., Fabian, C., Jahangir, S., Fabian, W., 2007. Structure and Absolute Configuration of Loliolide Isomers Determined by Comparison of Calculated and Experimental CD Spectra. Presented at the International Electronic Conference on Synthetic Organic Chemistry.
Schultes, 1967. The place of ethnobotany in the ethnpharmacologic search for psychotomimetic drugs. In: , D.H.E. et al. (Eds.), Ethnpharmacologic Search for Psychotomimetic Drugs. US Government Printing Office, pp. 37–57.
Schultes, 1969. Hallucinogens of plant origin. Science 163, 245–254.
Schultes, 1970. The botanical and chemical distribution of hallucinogens. Annu. Rev. Plant Physiol. 21, 571–598.
Schultes, 1972. An overview of hallucinogens in the Western Hemisphere. In: Furst, P.T. (Ed.), Flesh of the Gods: The Ritual Use of Hallucinogens, pp. 3–54.
Schultes, 1976. Hallucinogenic Plants, A Golden Guide. Golden Press.
Schultes, Hofmann, A., Rätsch, C., 2001. Plants of the Gods—Their Sacred, Healing, and Hallucinogenic Powers. Healing Arts Press, Rochester.
Schwarzer, C., 2009. 30 Years of dynorphins—new insights on their functions in neuropsychiatric diseases. Pharmacol. Ther. 123, 353–370.
Sheffler, D.J., Roth, B.L., 2003. Salvinorin A: the "magic mint" hallucinogen finds a molecular target in the kappa opioid receptor. Trends Pharmacol. Sci. 24, 107–109.
Shirota, O., Nagamatsu, K., Sekita, S., 2006. Neo-clerodane diterpenes from the hallucinogenic sage *Salvia divinorum*. J. Nat. Prod. 69, 1782–1786.
Siebert, 1994. *Salvia divinorum* and salvinorin A: new pharmacologic findings. J. Ethnopharmacol. 43, 53–56.
Siebert, 2003. The History of the first *Salvia divinorum* plants cultivated outside of Mexico. Etheogen Rev. XII, 117–118.
Siebert, 2004. Localization of salvinorin A and related compounds in glandular trichomes of the psychoactive sage, *Salvia divinorum*. Ann. Botany 93, 763–771.
Sufka, Kenneth J., Loria, Melissa J., Lewellyn, Kevin, Zjawiony, Jordan K., Ali, Zulfiqar, Abe, Naohito, Khan, Ikhlas A., 2013. The effect of *Salvia divinorum* and *Mitragyna speciosa* extracts, fraction and major constituents on place aversion and place preference in rats. J. Ethnopharmacol.. (In Press) ⟨https://www.sciencedirect.com/science/article/pii/S0378874113007848⟩.
Teksin, Z.S., Lee, I.J., Nemieboka, N.N., Othman, A.A., Upreti, V.V., Hassan, H.E., Syed, S.S., Prisinzano, T.E., Eddington, N.D., 2009. Evaluation of the transport, in vitro metabolism and pharmacokinetics of salvinorin A, a potent hallucinogen. Eur. J. Pharm. Biopharm. 72, 471–477.
Tsujikawa, K., Kuwayama, K., Miyaguchi, H., Kanamori, T., Iwata, Y.T., Inoue, H., 2009. In vitro stability and metabolism of salvinorin A in rat plasma. Xenobiotica 39, 391–398.
Valdés, L.J., 1986. Loliolide from *Salvia divinorum*. J. Nat. Prod. 49, 171. (171).
Valdés, L.J., 1994. *Salvia divinorum* and the unique diterpene hallucinogen, salvinorin (divinorin) A. J. Psychoact. Drugs.
Valdés, L.J., 2001. The early history of *Salvia divinorum*. Entheogen Rev. 10, 73–75.
Valdés, L.J., Butler, W.M., Hatfield, G.M., Paul, A.G., Koreeda, M., 1984. Divinorin A, a psychotropic terpenoid, and divinorin B from the hallucinogenic Mexican mint, *Salvia divinorum*. J. Org. Chem. 49, 4716–4720.
Valdés, L.J., Chang, H.-M., Visger, D.C., Koreeda, M., 2001. Salvinorin C, a new neoclerodane diterpene from a bioactive fraction of the hallucinogenic Mexican mint *Salvia divinorum*. Org. Lett. 3, 3935–3937.
Valdés, L.J., Chang, H.M., Visger, D.C., Koreeda, M., 2002. ChemInform abstract: salvinorin C, a new neoclerodane diterpene from a bioactive fraction of the hallucinogenic Mexican mint *Salvia divinorum*. ChemInform 33. (no–no).
Valdés, L.J., Diaz, J.L., Paul, A.G., 1983. Ethnopharmacology of ska maria pastora (*Salvia divinorum*, Epling and Játiva-M.). J. Ethnopharmacol. 7, 287–312.
Valdés, L.J., Hatheld, G., Koreeda, M., Paul, A., 1987. Studies of *Salvia divinorum* (Lamiaceae), an hallucinogenic mint from the Sierra Mazateca in Oaxaca, Central Mexico. Econ. Bot. 41, 283–291.
Vohra, R., Seefeld, A., Cantrell, F.L., Clark, R.F., 2011. *Salvia divinorum*: exposures reported to a statewide poison control system over 10 years. J. Emerg. Med. 40, 643–650.
Vortherms, T.A., Roth, B.L., 2006. Salvinorin A: from natural product to human therapeutics. Mol. Interventions 6, 257.
Wagstaff, S.J., Hickerson, L., Spangler, R., Reeves, P., Olmstead, R., 1998. Phylogeny in Labiatae inferred from cpDNA sequences. Plant Syst. Evol. 209, 265–274.
Walker, Sytsma, Treutlein, K., Wink, M., J., 2004a. *Salvia* (Lamiaceae) is not monophyletic: implications for the systematics, radiation, and ecological specializations of *Salvia* and tribe Menthaea. Am. J. Bot. 91, 1115–1125.
Walker, Sytsma, K.J., 2007. Staminal evolution in the genus *Salvia* (Lamiaceae): molecular phylogenetic evidence for multiple origins of the staminal lever. Ann. Botany 100, 375.
Walker, Sytsma, Treutlein, K.J., Wink, M., J., 2004b. *Salvia* (Lamiaceae) is not monophyletic: implications for the systematics, radiation, and ecological specializations of *Salvia* and tribe Mentheae. Am. J. Bot. 91, 1115–1125.
Wasson, R.G., 1962. A New Psychotropic Drug from the Mint Family. Botanical Museum Leaflets, Harvard University 20.
Weitlander, R.J., 1952. Curaciones Mazatecas. Anales del Instituto Nacional de Antropologia e Historica 4, 279–285.
Willmore-Fordham, C.B., Krall, D.M., McCurdy, C.R., Kinder, D.H., 2007. The hallucinogen derived from *Salvia divinorum*, salvinorin A, has κ-opioid agonist discriminative stimulus effects in rats. Neuropharmacology 53, 481–486.
Wood, J.R.I., Harley, R.M., 1989. The genus *Salvia* (Labiatae) in Colombia. Kew Bull., 211–278.
www.salviasource.org, 2011. *Salvia divinorum* Seeds Have Set [WWW Document]. URL ⟨http://www.salviasource.org/forum/index.php?topic=876⟩ (accessed 1.16.12).
Yan, F., Mosier, P.D., Westkaemper, R.B., Stewart, J., Zjawiony, J.K., Vortherms, T.A., Sheffler, D.J., Roth, B.L., 2005. Identification of the molecular mechanisms by which the diterpenoid salvinorin A binds to κ-opioid receptors. Biochemistry 44, 8643–8651.
Zawilska, J.B., Wojcieszak, J., 2013. *Salvia divinorum*: from Mazatec medicinal and hallucinogenic plant to emerging recreational drug. Hum. Psychopharmacol.: Clin. Exp.
Zhang, Y., Butelman, E.R., Schlussman, S.D., Ho, A., Kreek, M.J., 2005. Effects of the plant-derived hallucinogen salvinorin A on basal dopamine levels in the caudate putamen and in a conditioned place aversion assay in mice: agonist actions at kappa opioid receptors. Psychopharmacology 179, 551–558.