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Review

Pharmacological activity of Salvinorin A, the major component of *Salvia divinorum*

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Abstract:
The hallucinogenic plant *Salvia divinorum* (i.e., "magic mint") is a member of the Sage family that has been historically used for divination and shamanism by the Mazatecs. Today, *S. divinorum* has become increasingly popular as a recreational drug for its hallucinogenic effects. The non-nitrogenous diterpene, salvinorin A, the major active component of *S. divinorum*, is responsible for the hallucinogenic effect of this plant. Here, we described the behavioral effects of salvinorin A in animals including the addictive, antinociception and antidepressant properties of the drug. The present paper also demonstrates the not well recognized (or unclear) mechanisms of action of salvinorin A. The last part of the paper presents information about the legal status of *S. divinorum* and its derivatives. Taking into account the increasing popularity and consumption of salvinorin A and *S. divinorum* today, it is important to collect all data on the pharmacological profile of this plant and its products.

Key words:
Salvia divinorum, Salvinorin A

Salvia divinorinum as a psychotropic plant

Salvia divinorum (Lamiaceae) is an herbal plant that is also described as "ska pastora," "diviner's sage," "an unregulated hallucinogen" or "illegal high". Most of the names, such as ska Maria Pastora (the herb of Mary, the Shepherdess) or hojas de Maria (leaves of Mary), illustrate the relationship between the plant and the Virgin Mary. In popular tradition, the plant is believed to be an incarnation of the Virgin Mary and is treated with great respect [19]. *S. divinorum* grows in shady and cloudy evergreen forests in Mexico. Originally, the plant was used by Mazatec Indians for medical purposes including headaches, rheumatism, abdominal swelling or diarrhea as well as non-medical practices. Today, *S. divinorum* has become increasingly popular as a recreational drug due to its hallucinogenic effects. Notably, it is sold on internet sites as dried leaves, an extract or other preparations that promise the sensation of traveling through time, an "answer and secret knowledge" and also a very vivid, intense but short-lived hit.

One of the first experiments related to the pharmacological activity of *S. divinorum* in humans was performed in 2006 [9]. The volunteers described both the best and worst aspects of taking salvia. In this study, all participants declared having experienced psychotropic effects described as "slight" for 6% of volunteers, "moderate" for 22 % of the sample, "intense" for 12%, "very intense" for 41% and "extremely intense" for 19%. Most volunteers described the feelings as an instantaneous and short-lived "trip", "enter-

ing another reality", happiness, well-being, separation from the body or visual effects. Some of the volunteers have described their feelings as unpleasant: tiredness, heaviness of head (similar to after smoking many marihuana joints), dizziness, physically exhausted, grogginess and mental slowness.

Generally, the hallucinogenic potency of *S. divinorum* is often comparable with other classical hallucinogens, such as lysergic acid diethylamide (LSD). As a matter of fact, both can be equally intense, but *S. divinorum* is able to produce short-lasting effects compared with the effects of LSD.

In recent years, the active ingredients of *S. divinorum* have been identified [18, 19]. The major component is a non-nitrogenous diterpene, salvinorin A, which is responsible for the hallucinogenic effect of *S. divinorum*. Moreover, there are other diterpene compounds such as salvinorin B, salvinorin C, salvinorin D and E, divinatorin A, divinatorin B and divinatorin C. However, the concentrations of these compounds are markedly lower than that of salvinorin A, and their pharmacological activity appears to be insignificant. At present, it is well known that the short-lasting psychotropic effects of *S. divinorum* are caused by rapid hydrolysis of salvinorin A to salvinorin B [16] (Fig. 1).

Pharmacological activity of Salvinorin A

As mentioned above, salvinorin A, referred in the next part of this article as "salvinorin", is the first known diterpene compound with psychotropic activity (most hallucinogens belong to alkaloids). Initially, it was thought that salvinorin was able to produce psychotropic effects only in relatively high doses. At present, however, it was repeatedly shown that salvinorin can induce short-lasting (up to 1 h), intense hallucinations by smoking 200 to 500 μg of salvinorin [18]; thus, it is the most potent naturally occurring hallucinogenic drug.

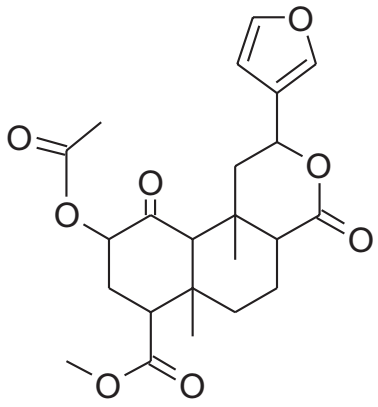

Fig. 1. Chemical structure of salvinorin A

One of the most important pharmacological effects of salvinorin is the addictive property of the drug. Although initial observations have not confirmed the addictive properties of salvinorin in humans, numerous behavioral studies have shown addictive effects in laboratory animals. The rewarding effect of salvinorin was demonstrated after administration of low doses (0.1, 10.0 and 40.0 μg/kg) of this drug in rats in place preference tests and in self-administration tests [3]. These changes were antagonized by nor-binaltorphimine, a selective κ opioid receptor antagonist, and rimonabant, a cannabinoid receptor antagonist. Conversely, the aversive effect of salvinorin was observed after injection of a high dose (160.0 μg/kg) of the drug in the same tests [3]. The rewarding effect of salvinorin was also demonstrated in discrimination tests in rats [1, 22], which was reversed by treatment with nor-binaltorphimine [22]. Moreover, the discriminative effect was produced in rhesus monkeys after administration of salvinorin [4].

The other important pharmacological effect of salvinorin is closely associated with a selective stimulation of κ opioid receptors by salvinorin, as demonstrated by the ability to induce the antinociception in mice in the tail-flick test [13]. However, this effect is a short-lived effect (up to 20 min).

For the first time, the antidepressant effect of salvinorin was demonstrated in a 26-year-old woman who chronically suffered from depression [11]. She took minimal oral doses of *S. divinorum* leaves three times per week. After therapy, the woman had complete remission of depressive symptoms as measured by the Hamilton Depression Scale. Currently, the antidepressant effect of salvinorin was also confirmed in behavioral experiments both in the forced swim test in rats and in the suspension test in mice [2]. In that study, salvinorin induced an antidepressant effect at doses of 0.001–1000 μg/kg, which was reversed by nor-binaltorphimine treatment [2]. On the other hand, in another study [6], a higher dose of salvinorin (2.0 mg/kg) produced depressive-like effects in rats. This effect was manifested as an attenuation of motivational behavior

and a decrease in locomotor activity of animals, which is associated with a decrease in dopamine levels in the nucleus accumbens.

Moreover, the involvement of salvinorin in anxiety and memory disturbances has also been indicated in rats. The anxiolytic effect of salvinorin (0.001–1000 μg/kg) was shown in the elevated plus-maze test, an effect that was antagonized by nor-binaltorphimine [2]. A high dose of salvinorin (2.0 mg/kg) produced a pattern of cognition impairment similar to that of ketamine [14].

In our laboratory, we have investigated the role of salvinorin in seizure activity in mice (data not yet published). However, we have not observed the involvement of salvinorin in pentetrazole-induced seizures even when high doses of the drug were administered.

In popular tradition, salvinorin has been known as a remedy for stomach trouble, including diarrhea. Currently, there are not enough scientific publications confirming its role in stomach disease, but the inhibitory effects on peristaltic movements and constipation after treatment with salvinorin have been described in a previous report [7].

In conclusion, salvinorin is able to produce a wide range of pharmacological effects in a dose-dependent manner. Interestingly, there are no cases of *S. divinorum* toxicity or deaths from overdose of salvinorin, which shows that *S. divinorum* is a relatively safe drug [10]. Thus, salvinorin may be a useful tool in the search for new strategies for treating diseases of central nervous system.

Mechanism of action of salvinorin A

In contrast to the classical psychodelics, such as LSD, salvinorin does not interact with serotonin 5-HT_{2A} receptors [5]. Instead, radioligand displacement and binding studies revealed salvinorin to be a full agonist of κ opioid receptors [15], but not μ or δ. The involvement of κ receptors has also been confirmed repeatedly in *in vitro* studies [2, 13, 21, 22]. Thus, salvinorin is the most highly efficacious, naturally occurring, nonpeptide agonist of κ opioid receptors. Whereas most κ opioid agonists are generally known to produce a conditioned place aversion and a decrease in locomotor activity in animals, low doses of salvinorin induce a place preference and enhance spontaneous locomotor activity suggesting that other mechanisms may be included in the pharmacological effects of this drug.

A growing body of evidence shows that salvinorin is able to modify dopaminergic pathways. It was experimentally confirmed [22] that salvinorin decreases dopamine levels in the caudate putamen. This dopamine-lowering effect of salvinorin (3.2 mg/kg, intraperitoneally – *ip*) is long-lasting (at least 20 h) and is predominantly due to activation of κ opioid receptors (up to approximately 50% of the baseline) because nor-binaltorphimine (κ opioid receptor antagonist) blocked the effect of salvinorin on mouse dopamine levels. In these mice, the aversive effects of salvinorin (3.2 mg/kg) were also observed in the conditioned place preference test. Additionally, changes in dopamine levels were not found after treatment with the same dose of salvinorin in the nucleus accumbens, the major brain structure involved in euphoria [23]. Another study [8] demonstrated that salvinorin (1.0 and 3.2 mg/kg) decreases the dopamine level in the dorsal striatum mainly by affecting dopamine release but not dopamine uptake. Moreover, the affinity of salvinorin for dopamine D2 receptors was demonstrated in a biochemical study [17]. Generally, the exact connections between salvinorin, κ opioid receptors and dopamine structures are not fully recognized. However, based on numerous experiments, it could be hypothesized that low doses of salvinorin are able to produce an increase in dopamine levels, manifested primarily as an increase in locomotor activity and feelings of pleasure. In contrast, high doses of salvinorin are able to produce the opposite effect, i.e., a decrease in dopamine levels, decrease in locomotor activity and an aversive reaction.

The ability of higher doses of salvinorin to decrease dopamine levels in the central nervous system may be an important use in therapy for states of dependence. Experimentally, salvinorin is able to inhibit the cocaine-induced seeking behavior in rats. Therefore, in some countries (e.g., Norway or Finland), salvinorin is prescribed by doctors as a remedy for cocaine and heroin addiction [12].

Some evidence suggests that the endocannabinoid system may also play a role in the pharmacological effects of salvinorin. First, the herb has been smoked as a marijuana substitute by young Mexicans [19]. Second, salvinorin is a trans-neoclerodane diterpenoid, a compound that resembles the structure and mechanism of action of typical hallucinogens. In addition, the aforementioned rewarding effects of a low dose of salvinorin can be reversed not only by nor-binaltorphimine, but also by rimonabant, the can-

nabinoid receptor antagonist, in both the place preference test and the self-administration test [3]. Further experiments, however, have shown that salvinorin has no affinity for cannabinoid CB_1 receptors *in vitro*, and the behavioral profile of salvinorin *in vivo* is different from that induced by cannabinoids. For example, tetrahydrocannabinol suppressed spontaneous activity in a dose-dependent manner, decreased body temperature and produced antinociception and catalepsion, whereas the efficacy of salvinorin for inducing hypothermia and catalepsy was significantly less [21]. Thus, it could be hypothesized that salvinorin does not act directly on cannabinoid receptors, but rather indirect pathways may be included in its activity.

Thus, the mechanism of action of salvinorin is not fully understood. It was first thought that salvinorin has affinity only to κ opioid receptors because the significance of serotonin receptors was ruled out quite early. At present, we know that dopaminergic pathways are involved in the effects of salvinorin. Moreover, another neurotransmitter system may be involved in salvinorin activity. Therefore, further investigations are needed to recognize the exact mechanism of action of salvinorin and find new uses of salvinorin in current therapies.

Legal status of *S. divinorum*

The opinions about legalization of *S. divinorum* remain divided. According to some scientists, the legalization of salvinorin or *S. divinorum* should be accepted because the toxicity of the drug is very low, and there is no convincing evidence that salvinorin and *S. divinorum* lead to addiction. Moreover, there are many over-the-counter drugs that cause similar hallucinogenic effects that have legal status. In opinion of these scientists, salvinorin and *S. divinorum* are completely unique, and there is a good reason for seeking derivatives as breakthrough medications for chronic pain, addiction, depression, stomach trouble or Alzheimer's disease and other forms of dementia. In contrast, there is no question that *S. divinorum* is frequently used for non-medical purposes, especially by young people, to induce extremely strong hallucinations. Therefore, despite the relatively low dependence and toxic activity, salvinorin and *S. divinorum* cannot be considered as safe drugs.

Australia (January 1, 2002) became the first country in the world to ban the possession and selling of *S. divinorum*. Then, other countries such as Belgium, Croatia, Denmark, Germany, Italy, Latvia, Lithuania, Romania, Sweden, Japan and South Korea also placed bans on *S. divinorum* and salvinorin trafficking. In Poland, the possession and selling of the plant and its derivatives (e.g., extract) have been banned since March 20, 2009. In Norway, Finland, Estonia and Iceland, *S. divinorum* is legal but only for medical purposes, i.e., it can only be prescribed by doctors as a therapy for cocaine and heroin dependence. In Russia and Spain, the regulation not only prohibits the possession of the plant but also the sale of *S. divinorum* (http://www.sagewisdom.prg/legalstatus.html).

In conclusion, *S. divinorum* is a valuable medicinal herb because it possesses a widespread pharmacological activity, particularly its primary active ingredient, salvinorin A. Salvinorin A is unique and shows great promise as a key compound in the development of useful medications. Moreover, as much evidence has confirmed, this herb is relatively safe and has a low potential for addiction. Undoubtedly, possessing and selling *S. divinorum* should be regulated, especially among the youth, but the plant should also be accessible for future scientific experiments and, in special cases, for use in psychotherapies.

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