

Salvia divinorum: a psychopharmacological enigma and the mind-body problem

José Luis Díaz¹

Original article

SUMMARY

In the present paper, the multidisciplinary research on *Salvia divinorum* and its chemical principles is analyzed regarding whether the ethnobotany, phytochemistry, psychopharmacology, and neuropharmacology of this sacred psychoactive plant and its primary chemical clarify its mental effects and divinatory uses. The scientific endeavor begins with the recorded traditional ceremonies and beliefs, continues with botanical identification, the isolation of active molecules, the characterization of mental and neural effects, possible therapeutic applications, and has begun to engage with the mind-body problem. The departure point of this research is ethnopharmacology, and therefore the traditional beliefs, ritual uses, and mental effects of this Mazatec sacred mint recorded during a 1973-1983 field research project are described. A watery potion of crushed leaves produced short-lasting light-headedness, dysphoria, tactile and proprioceptive sensations, a sense of depersonalization, amplified sound perception, and increased visual and auditory imagery, but no actual hallucinations. Similar effects were described using questionnaires and are attributable to the diterpene Salvinorin A, but cannot be explained solely by its specific and potent brain kappa opioid receptor agonist activity. Some requirements for a feasible classification and mechanism of action of consciousness-altering products are proposed and include the activation of neural networks comprising several neurochemical systems. Top-down analyses should be undertaken in order to characterize such neural networks and eventually allow an exploration of the differential ethnic effects. As is the case for other consciousness-altering preparations, careful and encompassing research on this plant and principle can be relevant to academic undertakings ranging from the mind-body problem and a better understanding of shamanic ecstasy, to the potential generation of analgesic, antidepressant, and drug-abuse attenuating products.

Key words: Consciousness-altering drugs, ethnopharmacology, kappa opioid receptor agonist, Mazatec shamanism, mechanism of action, mind-body problem, *Salvia divinorum*, Salvinorin.

RESUMEN

En el presente trabajo se considera la investigación multidisciplinaria sobre *Salvia divinorum* y sus principios químicos activos con el objeto de valorar si la etnobotánica, la fitoquímica, la psicofarmacología y la neurofarmacología de esta planta psicoactiva y su principal producto químico, la salvinorina A, clarifican sus efectos mentales y sus usos adivinatorios. Esta labor científica ha transcurrido desde el registro inicial de ceremonias y creencias, ha continuado con la identificación botánica, el aislamiento de los principios químicos, la caracterización de los efectos mentales y cerebrales, las posibles aplicaciones terapéuticas y ha llegado a incurrir en el problema mente-cuerpo. Dado que el punto de partida de esta investigación es la transdisciplina de la etnofarmacología, se retoman aquí las creencias tradicionales, los usos rituales y los efectos mentales de esta planta sagrada de los indios mazatecos tal y como fueron registrados durante un proyecto de campo y laboratorio llevado a cabo entre 1973 y 1983. Un brebaje acuoso de hojas maceradas produjo un breve periodo de ligereza cefálica, disforia, sensaciones táctiles y propioceptivas exacerbadas, un sentido de despersonalización, percepción amplificada de sonidos y un aumento de la imaginación visual y auditiva, pero no verdaderas alucinaciones. Posteriormente otros autores describieron efectos similares usando cuestionarios y eventualmente fueron imputados al diterpeno salvinorina-A, pero no es posible explicar los efectos mentales sólo por la potente actividad agonista del receptor kappa a los opioides encontrada para la salvinorina; de allí el enigma psicofarmacológico. Se proponen algunos requerimientos para una clasificación de drogas que alteran cualitativamente el estado de conciencia e incluyen la activación de redes neuronales que necesariamente comprenden diversos sistemas neuroquímicos y módulos nerviosos. Para caracterizar estas redes será necesario emprender un tipo de investigación *top-down*, es decir el análisis de imágenes cerebrales obtenidas durante la experiencia psicoactiva analizada mediante un método narrativo, lo cual eventualmente podría permitir la exploración de efectos étnicos diferenciales. Como sucede con otras preparaciones que alteran la conciencia, una investigación rigurosa de la psicofarmacología de esta planta y su principio psicoactivo será relevante a empresas académicas tan diversas como el problema mente-cuerpo, la mejor comprensión del éxtasis chamánico y la posible generación de fármacos analgésicos, antidepressivos y moderadores de la drogadicción.

Palabras clave: Drogas psicoactivas, etnofarmacología, agonista del receptor opioide kappa, chamanismo mazateco, mecanismo de acción, problema mente-cuerpo, *Salvia divinorum*, salvinorina.

¹ De la Academia Mexicana. Department of History and Philosophy of Medicine, Faculty of Medicine, UNAM. Member of the Editorial Committee of SALUD MENTAL.

Correspondence: Dr. José Luis Díaz. Cerrada de Cruz Verde 29-B. Colonia Lomas Quebradas. Magdalena Contreras. 10000 Mexico City. E-mail: |ldiaz43@gmail.com

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THE VOICE OF THE LEAF

"You have to sing with the voice of the leaf", the Mazatec shaman told me during a ritual in the town of San Bartolomé Ayautla. She had given me a bitter, watery infusion to drink, prepared with the ground leaves of the *Ŝka Pastora*, a plant known in botanical science as *Salvia divinorum* Epling & Játiva-M. I had arrived in Ayautla in 1973, following in the footsteps of the independent and erudite researcher R. Gordon Wasson who, some ten years previously, had described the ritual use and psychotropic effect of this plant in this exact remote town located behind the canyon of the Santo Domingo River in the Sierra Mazateca of northern Oaxaca, Mexico. At that time, the rediscovery of Mexican hallucinogenic mushrooms and their study by a plethora of European experts led by Wasson was a pattern of research pioneering the trans-disciplinary methodological focus which since that time has been known as *ethnopharmacology*.

I had returned to Mexico shortly before after having broadened my training in psychobiology and psychopharmacology in Boston, and I decided to undertake a research project into little-known Mexican psychoactive plants. The aim of the project was not only to find new tools for psychiatric and cerebral investigation, but also more specifically, to cultivate a new trans-disciplinary psychopharmacology that would take into account and apply the knowledge of thousands of years of the native cultures of my country. That project, and this work, represent an effort to approach the subject of psychoactive plants from a trans-disciplinary angle in which ethnobotanical, phytochemical, pharmacological, or neurochemical information is not simply juxtaposed, but is interrelated and integrated as far as possible. One of the first plants to study was the *Salvia divinorum*. In that first foray into the Sierra Mazateca, I had to walk ancient paths for more than six hours in constant drizzle through the Santo Domingo river canyon to finally find the small and hidden town of Ayautla.

I was lucky enough to meet an intelligent and honest Mazatec municipal president who put me up, inquiring about my proposal, and he kept me under friendly and understandable scrutiny for a few days before sending me to a local shaman, a friendly and serious older woman called Julia Aurelia Palacios, who always wore a beautiful traditional huipil. Doña Julia only spoke Mazatec, but her nephew and apprentice Felipe was bilingual, enabling me to foster a relationship with this family, who not only belonged to a traditional clan of shamans, but also made their livelihood, with much difficulty and effort, from the cultivation of Ayautla coffee, along with the majority of the inhabitants of this town, under an iniquitous chiefdom typical of indigent towns.

I soon learned that doña Julia used four traditional psychotropic plants in her healing and divinatory practices:

hallucinogenic mushrooms (*Psilocybe* spp), ololiuhqui seeds (*Rivea corymbosa*), wild tobacco or *piciete* (*Nicotiana rustica*), and in particular, *Ŝka* Pastora* (*Salvia divinorum*). When I expressed interest in *Ŝka Pastora*, doña Julia decided to teach me about gathering the plant and its ceremony as if I were an apprentice, as I was not ill and did not have any specific questions that merited divination. Before carrying out the first ceremony, I was to go through a ritual involving fasting, sexual abstinence, and gathering the leaves. In the morning on which my preparation was finished, Felipe guided me up the steep mountain of the Santo Domingo Canyon, and after a strenuous walk of several hours we arrived at the sacred place whose location had been kept a secret until now, and where the *Salvia divinorum* grew wild. The collection of the plant was done with care and respect, as it is considered a part or a manifestation of a mythical figure: la Pastora [the Shepherdess], an image syncretized with the Virgin Mary. It was in that remote place that I was lucky enough to photograph the white corolla and violet calyx of the ritual mint's flowers.

The ceremony took place that night in the constantly crowded dirt-floored cabin where doña Julia and her family lived. Doña Julia sat on a bench, chose and counted around forty pairs of leaves, and with her elbows supported on her knees, piled them in her hands and smoked them over copal (aromatic *Burseria* resin). At the same time, she sang a hypnotic and auspicious oration in a monotonous and hoarse voice, which I recorded and later translated into Spanish with the help of the bilingual daughter of the municipal president. This song was dedicated to idols and supernatural forces of the Canyon, to the Holy Trinity, to intercessors of the Catholic tradition such as *Señor San Pedro* or *Señor San Pablo*, and to the sun as the supreme being, in order to protect me and show me the way. What follows is the text translated to English of the recording I made on September 4th, 1974:**

«In the name of the *Father*, the *Son*, and the *Holy Spirit*, the *Holy Trinity*, Wind of the House of Mazatec, Wind of the Gully, Water of the River, may you go well on the journey. *Señor San Pedro*, *Señor San Pablo*, *José Luis*, may you go well on the journey. (...) May the Sun rise high and may you be watched over by the *Holy Trinity*, God the Father, the Mother of God. (...) May the Sun rise high and may it watch over you as you travel through the gully. May the Sun rise high and watch over you; nothing shall happen to anyone. (...) May the Sun rise high and watch over you. May you not break a leg when you start to walk, let there be no rheumatism, may God watch over you. Yes, they will walk along the Jalapa path, these poor things that will start to walk. God is

* *Ŝka* is pronounced "shka"; the sound of the "a" at the end is deeper, found in the fourth tone of the vocal spectrum of the Mazatec language..

** Díaz, 1976: 145-6. In italics the words pronounced in Spanish. The song has a respiratory rhythm: the shaman makes a deep inspiration and then sings until the end of the exhalation. The inspirations are marked (...) in the text.

creating us. (...) May the Sun rise high and watch over you. I speak in the name of the *Father*, the *Son*, and the *Holy Spirit*. If you bathe in the place of the Río Verde, in the place of the Río Frío, let them not harm you, let nothing happen, *Señor San Pedro*, *Señor San Pablo*. (...) May the Sun rise high and may the Saints watch over you. Let nothing happen to them throughout the journey, let them arrive safely. (...) They are seeking what the *piciete* gives to them, what the *Pastora* gives to them. May the *Holy Trinity* watch over them. May they go well throughout the town, by the houses they will pass. In the name of the *Father*, the *Son*, the *Holy Spirit*, and the *Holy Trinity*.»

When she had finished the invocation, doña Julia ground the plant vigorously with her hands in a gourd containing water, until the "blood of the plant" was all extracted into about 300 ml of green and foamy potion. She offered me the gourd and instructed me to drink the entire contents at once and lie down. The liquid was very bitter –even revolting– but I managed to drink it and keep it down. I was lying face up on a bedroll on the ground and, despite the candles being out and there being no other light apart from the frenetic bonfire, I was asked to close my eyes. Doña Julia remained quiet but attentive. I did not know what to expect but I was excited; I felt privileged and safe under the care and guidance of such an experienced shaman as doña Julia.

I soon began to have muscular sensations and shivers very similar to the kind which accompany a fever, and I noticed that the many sounds around me seemed closer and louder. I also noticed that internal visual images slowly became more relevant, while they moved in a fascinating, dynamic, and colorful automatic flow. They never became hallucinations in the sense of seeming to be "something beyond" as external visualizations. I felt dazed, dizzy, vaguely excited, though irritable at times; strange, as though I were not quite myself. All of the effects, which did not last more than an hour, were gentle, and to some extent disappointing in their subtlety and brevity. I had to make more visits to doña Julia and her bitter drink of *Ška Pastora* in order to start to learn the significance of the ceremony, the psychotropic effects, and what was expected of me when, during the sessions, she encouraged me, through Felipe, to "sing the song of the leaves", as though it was strange that I had not done so under my own initiative.

In the description I have just given of the images I experienced, I did not refer to their content –in other words, what they were about– not only because I have almost forgotten it, but also because at that time, it did not seem to be something transcendent, as my conscience was experiencing it in a passive manner, so to speak. Furthermore, consistent with my culture and context, I ingested this psychoactive preparation in order to have a personal experience and with the aim of making a participative observation, as proposed by the humanistic vision of anthropology with which I agree. Over time I realized that for Mesoamerican shamans,

the mental contents that come up through the ceremonial consumption of a sacred plant are the primary objective of the ritual because according to their beliefs, it is through the communion with this plant that the spirit of the consumer makes contact with the syncretic and holy figure of the *Pastora* represented by the leaves. As an apprentice, it was assumed that I would pay attention to the images and sounds that appeared in my mind and "sing them", but I had no idea how to do that. During the last ceremonies, I began to concentrate more on the content of the experience and at the end, I made a verbal retelling of what I remembered of the images. In spite of never acquiring the expertise necessary to sing the voice or the song of the plant, what I reported was considered relevant and worthy of interpretation by my friendly hosts.

When I shared these experiences with Gordon Wasson at his Connecticut home in 1974, he was concluding a magnificent book which included recordings of María Sabina, a Mazatec shaman from Huahutla de Jiménez, well known for her mediation. The careful translation of Mazatec to Spanish and English carried out by his partner Cowan¹ of María Sabina's songs during an evening of divination with hallucinogenic mushrooms gave me a clearer understanding of what was expected of me during the sessions, as through these songs, María Sabina articulated powerfully and immediately what was happening in her mind while the psilocybin circulated through her neurons. Of course, I should immediately say that María Sabina's singular mental state was not only the result of this crucial neurochemical event, but also of the circumstances that anthropologists call *set and setting*:* a number of beliefs, practices, and expectations shared by a culture, as well as vast personal practice with psychotropic plants, and the ritual and divinatory situation of the evening. What doña Julia had encouraged me to do, and what María Sabina did in her songs, was recite the "voices"; presumably auditory images that have a particular cultural content and which are not as representative in western accounts of psychedelic experiences as visual ones. Singing the voices evoked by the consumption of psychoactive plants during ritual ceremonies could be a crucial point in the analysis and interpretation of the mental variations of the effects according to various cultural conditions.*

Years later, I experienced forms of *Vispassana* meditation which require similar concentration in terms of detecting mental processes in the present. The difference between both techniques is that while introspective meditation or *Vispassana* seeks the conscious, objective, and detached detec-

* *Set and setting*: IWhat the subject (history, personality, attitude, etc) and the circumstances (time, place, company, etc) contribute to occurrence of a particular experience.. In spite of the fact that Timothy Leary was the first to propose this concept, its application to the traditional use of psychotropic plants was done initially by Marlene Dobkin de Rios (1975).

** What I mean by this is that records of verbal or sung expressions of the experience constitute "phenomenological texts" that allow for a narrative analysis of conscious processes (Díaz, Paniagua, Díez Martínez, 1998; Díaz, 2013).

tion of mental content, Mazatec shamanic practice requires the expression of poly-sensory mental images through song. This is a very demanding skill in terms of attention and the capacity to communicate the content could be considered a Mesoamerican form of meditation which requires subtle, firm, and extensive learning.

Over the course of my series of visits to the Sierra Mazateca during the following years, I managed to achieve a greater perspective on divinatory practice and realize that becoming a shaman would require a progressive refining of my capacities for attention and introspection that are necessary to record and express the mental content taking place in a divinatory psychotropic trance. I realized, however, that I would not follow this path, and I would remain an academic researcher interested in the mind-body problem and psychobiology; a vocation that has led me to other theoretical and empirical ventures and which now, many years later, has allowed me to consider *Salvia divinorum* once again, from a more current and careful perspective.

What follows is my discourse around research into *Salvia divinorum* and its primary chemicals from a point of view that leans towards a central psychobiological question: ascertaining whether ethnobotanical, chemical, pharmacological, and psychological research into this magical plant and its primary active on the brain explains its phenomenological properties and its divinatory cultural use. Now, far from pretending that a deep understanding of the uses and effects of this plant can solely be gleaned from scientific analysis, I consider that the most useful approximation is to understand the knowledge and information provided by its traditional consumers as far as possible; from a participative ethnology, from the representations of the mental effects of the plant, first-person and other testimonies, as well as from objective data from various sciences involved in ethnopharmacology. In spite of the proposed area of study being vast and seemingly endless, an open and integrated attitude will give stimulating and promising results for progress in this inquiry.

ETHNOBOTANY AND PHYTOCHEMISTRY

As far as we know, the first mention of this plant was made in 1939 by the ethnologist J. B. Johnson, who described some "yerba María" leaves that were macerated and drunk as a tea for divinatory purposes by Mazatec indigenous people.² Some years later, Blas Pablo Reko, pioneer of Mexican ethnobotany, described on page 17 of his *Mitobotánica zapoteca* a magical plant whose leaves produced visions and which was called "the divination leaf".³ Seven years later, Robert Weitlaner (1952) described a divinatory ceremony conducted by a Mazatec healer, which involved the use of an unknown plant,⁴ and in 1952, the recognized Mexican botanist Arturo Gómez Pompa gathered and classified the plant as

belonging to the *Salvia* genus,* finally described in 1962 by Epling and Játiva as a new species, with herbal samples provided by R. Gordon Wasson.^{5,6}

Salvia divinorum Epling & Játiva-M is a sage belonging to the mint or *Labiatae* family. In Mazatec it is given the names *Ŝka Pastora* and *Ŝka María Pastora*. *Ŝka* means *leaf* in Mazatec; for this reason it is called the Leaf of the Shepherdess and the Leaf of the Shepherdess Mary in Spanish. The names *Pastora* and *María* make reference to a syncretic representation of the Virgin Mary. R. Gordon Wasson proposed that it corresponded to the *Pipiltzintzintli* of the ancient Nahuas, but the information set out in 1772 by a thoroughly reliable source, the Presbyterian Antonio Alzate -that encyclopedic recorder of the colony- explicitly indicates that this name was given to the hemp of marijuana imported on Chinese ships from Asia for its fiber and which had been used for divinatory purposes ever since.⁷

It is an uncommon perennial herb endemic to the Sierra Mazateca of the State of Oaxaca in Mexico, where it grows in its natural state in humid gullies and other high and quite isolated areas. Nowadays, however, it is widely cultivated for recreational use in the United States and Europe. The name *divinorum* was given by the botanists Epling and Játiva, alluding to its divinatory use, mentioned by R. Gordon Wasson in 1962.^{2-4,6} Wasson described the preparation of a watery potion made with pairs of leaves and with the use of a metate [flat grinding stone] to grind them. In the 1970s⁷ I published extensive ethnopharmacological studies of the ceremonial use of the plant, which I have summarized above, and later, additional data was published by Leander Valdés,⁸ who contacted me in 1981 to conduct his Pharmacy thesis on *Salvia divinorum* at the University of Michigan. In order to avoid the long walk from Huautla to Ayautla, I drove Leander and his mentor, Ara G. Paul by car from the east, and asking locals, we found don Alejandro Vicente, a shaman who lived in the town of Chichicazapa, near to the extensive Miguel Alemán reservoir. After crossing the reservoir to gather the plant in the distant heights of Cerro Rabón and do the traditional preparations, we had the opportunity to participate in various divinatory rituals that involved the use of the plant, known there as *Hoja de María*. From that point, Leander Valdés made various important contributions to the knowledge of the chemistry and pharmacology of *Salvia divinorum*.

During the seventies, *Salvia divinorum* was depicted and described in the well-known works of Richard Schultes and Albert Hoffman^{9,10} on sacred and psychotropic plants. Later, the close link between these plants, their capacity to induce ecstatic and dreamlike episodes, and the shamanic

* The sample from the National Mexican Herbarium collected by Gómez Pompa in 1957 did not have flowers, such that it was impossible to identify the species. The tag for the sample mentions hallucinogenic properties among the uses for the plant. See also the description by Gómez Pompa on his website: <http://gomezpompa.blogspot.mx/2010/11/capitulo-4.html>

beliefs and practices in Mexico have been documented on several occasions by various ethnological¹¹ and historical¹² sciences.

Inspired by ethnopharmacological descriptions and personal conversations about the plant, in 1982, Alfredo Ortega's phytochemistry group at the Institute of Chemistry at UNAM gathered enough material coming from the Mazatec region and quickly isolated in the laboratory a new neo-clerodane diterpene which they called Salvinorin A.¹³ Independently, Valdés isolated two components that were called Divinorin A and Divinorin B,¹⁴ but he later confirmed that these corresponded to the structures of Ortega's Salvinorin A and Salvinorin B. The ritual use of *Salvia divinorum* extracted in water continues to perplex, given that these diterpenes were not hydro-soluble and there is still a line of inquiry with respect to its possible psychoactive properties. But this problem deserves greater consideration, as we shall see later.

MENTAL EFFECTS OF SALVIA DIVINORUM AND SALVINORIN A

In his pioneering description, Wasson mentions mild visual effects from the watery infusion of *Salvia divinorum* prepared in the divinatory rituals, and compares them with an initial intoxication with hallucinatory mushrooms from the *Psilocybe* genus.⁶ As mentioned previously, I was able to participate in divinatory ceremonies conducted by Mazatec shamans in Ayautla and Chichicazapa, and I described the beliefs, rituals, psychological effects, and animal behavior in a book on psychotropic plants of Latin America published in 1976.⁷ In a chapter on lesser-known Mexican psychotropic plants, I described that the traditional watery potion produced short-term light-headedness, fluctuation in mood (excitement, dysphoria, irritability, or general ill-at-ease), tactile and proprioceptive sensations similar to fever, light and sporadic sensations of strangeness and depersonalization, amplification of sound perception, and an increase in visual and auditory images, but no actual hallucinations. I did not report kaleidoscopic figures similar to those of "classic" hallucinations; the sensory effects were primarily an intense but short-lived sharpening of visual images and fantasy, an effect mistakenly called "hallucination". In this book I also described the animal model we used to prove the possible psychodysleptic effects of the extracts of *Salvia divinorum*, but despite the cats injected with said extracts showing certain "hallucinatory" behaviors such as staring or making threatening movements towards an empty space, the model was not simple or specific enough to serve as a guide in isolating the primary active, which was later successfully achieved in 1982 by the laboratory of Alfredo Ortega.¹³ Valdés reported that Salvinorin A and the active extracts of *Salvia divinorum* showed non-specific sedative ef-

fects in mice and some behavioral changes similar to those produced by mescaline.

In two subsequent works around psychotropic plants and drugs,^{15,16} I proposed the classification of psychodysleptic and psychedelic drugs, or those that qualitatively alter conscience in accordance with their mental and neurological effects into six classes as follows:

1. *Hallucinogens*. These produce strong cognitive, emotional, and perceptive modifications in the context of an amplified state of conscience and a sympathomimetic or ergotropic stimulation. This category includes cacti that produce mescaline such as the peyote (*Lophophora williamsii*); mushrooms that contain psilocybin (*Psilocybe* spp); Amazonian inhalants (yopo and virola), and other species added to the Ayahuasca potion (chacruna: *Psychotria viridis*) which contain dimethyltryptamine (DMT); and the synthetic ergoline known as LSD, all of which are serotonin 2A receptor agonists in the brain.
2. *Trance-inducing drugs*. These stimulate the production of images in the context of a parasympathetic or trophotropic sedation, isolation, and apathy. This category includes ololiuhqui seeds (*Rivea corymbosa*) which contain ergolines, and the fermented Sinicuiche drinks (*Heimia salicifolia*) whose active principle is unknown.
3. *Cognodysleptics*. These produce dreamlike states, an increase in sensory perception that has an effect on imagery, and cognitive difficulties in memory and systematic thought. It includes marijuana (*Cannabis sativa*) and *Calea zacatechichi*, an oneirogenic plant utilized by Chontal indigenous people in the south of Oaxaca, Mexico. I tentatively placed *Salvia divinorum* in this category.
4. *Deliriant*s. These produce hallucinations, delirium, disorientation, strong sensory distortions, and cognitive impediment in the context of an obscured conscience. It includes scopolamine and other tropanic alkaloids found in various plants of the solanaceae family in both the Old World (*mandragora* and *Hyosciamus* spp) and the New World (*Datura* and *Brugmansia* spp), muscarinic receptor antagonists in the brain.
5. *Narcotics*. These include opium preparations, the latex of various papaveraceae, especially the adormidera [opium poppy] (*Papaver somniferum*) and derivatives of morphine, its principle psychoactive principle; in particular, heroin. These drugs produce intense sensations of wellbeing, euphoria, and pleasure within a framework of sedation, lethargy, sleepiness, mental cloudiness, and apathy, as well as powerful relief of pain, stress, and anxiety, as they act as powerful endorphin receptor agonists and endogenous enkephalins which makes them highly addictive.
6. *Dissociative psychodysleptics* such as ketamine, pentazocine, and nitrous oxide (N₂O or laughing gas). These produce derealization (the feeling of losing reality), modification of self-perception, and dislocation of

space-time notions; in high doses, they lead to catalepsy and dissociative anesthesia in acting like NMDA receptor agonists in the brain (N Methylaspartate or glutamate; an excitatory neurotransmitter in the brain).

In these works, I made other considerations around the category of cognodysleptics, where I had tentatively placed *Salvia divinorum*. It seemed to me that the fact that this plant's non-nitrogenous terpenes happened to be psychoactive would strengthen this categorization, given that the rest of the psychoactive molecules of this group such as the tetrahydrocannabinol (THC) in marijuana, were also terpenes, not alkaloids. However, the precise classification of the mental effects of *Salvia divinorum* requires further testing in order to be definitive, and even nowadays this is a difficult task, as we shall shortly see.

In contrast with the moderate effects of extracts prepared in traditional ways, later investigations carried out with other means of application demonstrated that Salvinorin A is a very powerful psychoactive substance. Salvinorin A was definitively proven as the principle psychoactive molecule of *Salvia divinorum* by Daniel Siebert,¹⁷ who demonstrated the existence of mental effects with a dose lower than 0.5 mg of the raw precipitate, which means that this compound is the most active natural psychoactive that is known, with almost the same level of potency as LSD. Siebert reported kaleidoscopic visual images, changes in depth perception, sensory or aesthetic appreciations, and experiencing creative dream states. All of these effects lasted a relatively short time –less than two hours– and with a short initial latency period of around 20 minutes. Doses over 1 mg produced disconcerting effects: a loss of control over mind and body caused experimental subjects to move aimlessly; they reported out-of-body experiences and were later incapable of remembering the episode; a psychopharmacological constellation similar to that of synthetic dissociative psychodysleptics such as ketamine and phencyclidine. Siebert arrived at the conclusion that Salvinorin A in humans caused intense and short-lived effects different from those of “classic” hallucinogens. After this report, the independent researcher Jonathan Ott described in quite a detailed history and critique of this plant,¹⁸ that the sublingual administration of Salvinorin A in acetone and DMSO was highly psychoactive, with a “psychoactivity” threshold between 250 and 500 mcg and “visionary activity” over 1 mg.

The relatively moderate effects that were reported through ingesting the plant extract in water in the Sierra Mazateca, and the strong psychodynamic effects of the primary active are not contradictory. The relatively innocuous effects of the coca leaf (*Erythroxylon coca*) when chewed, as is customary in the Andes and which act as energizers and stimulants, are very distinct in grade and quality from the intense exaltation and euphoria produced immediately after inhaling pure cocaine powder.¹⁹ The different forms of administration and the materials used explain this gap in

terms of the enormous difference in concentration in cocaine in the blood and its filtration in the body, by not mentioning a more difficult factor to demonstrate: the modulation of the experience according to culture, purpose of consumption, and circumstance.

In the first conference called “Towards a Science of Consciousness” held in Tucson, where I presented a flowchart of phenomenological conscience,²⁰ Andrew Weil wrote an interesting chapter entitled “Pharmacology of Consciousness: A narrative of subjective experience”¹⁹ in which he analyzed the psychopharmacology of *Salvia divinorum* and mentioned in detail the images that Leander Valdés and I shared during a ceremony with don Alejandro Vicente when we decided to mention some of the contents of the visual images to show, albeit tentatively, the usefulness of “singing the voice of the leaves”. It is worth quoting Valdés’ first-person account:²¹

After about 15 minutes we started to have visions. This time I narrated mine out loud, alternating speaking in both English and Spanish, which helped me to fix it in my mind. Díaz spoke first and mentioned something about flowers. Then I saw eidetic images that developed into forms of plants and flowers, and which then changed into giant fruits and seeds. I felt that I was twisting around within my own body and that I was spinning at the same time. I saw a flaming cross with two horizontal lines, which stopped burning and started to emit light. Then I felt very heavy, as though someone was pushing me onto the bottom of the bed. My arms hurt. Then I saw something that looked like a very dark photograph in black and white. Díaz apologized to don Alejandro for our inability to see the religious figures that the healer had described to us. My vision changed into color again and I saw figures praying, similar to those that can be seen in Mexican churches. They did not have a face and their clothing was covered in gold. The image of a jewel-encrusted cross appeared. It slowly and alternatively became a sword. At the center of the image I could see animals, plants, and people. If the image started to change or disappear, I could concentrate to make it come back. The last image was of a castle that turned into a Byzantine church. Some hooded figures like monks without faces were marching around it.

When the ceremony had finished and we were on our way back, Leander Valdés had an intense experience with markedly mystical feelings and images, which happened in the car and continued in the hotel we were staying in. Here is his account:

In the motel room, the images came back stronger than ever. Even though I did not describe them out loud, I saw a purple light that pulsed and changed into the form of an insect, maybe a bee or moth, and then transformed into a sea anemone that pulsed as well. It expanded to change into a desert full of nopales and stayed that way for several minutes. During the first session and throughout the night, all of my visions seemed to be a mix of a silent film and a caricature. I felt that I was an observer of these silent visions, rather than a part of them. However, I soon found myself in a large meadow with brightly colored flowers. I had just used a little wooden bridge to cross over a stream. Next to me was something that seemed to be a gigantic skeleton model of an airplane made with pipes that were all the colors of the rainbow. The sky was a brilliant blue and I could see a forest in the distance. I found myself speaking to a man who carried a bright white coat and he was holding or gripping my hand. It was an impressive hallucination because I really believed I was in the meadow. It was not like a dream. After a while I went back to the

desert landscape and slowly went to sleep after an hour, more or less. The following morning I woke up early without feeling any adverse effects.

It is important to highlight that the visual scenes described in this expressive first-person phenomenological text were experienced in darkness and with eyes closed, in accordance with what is prescribed for the ceremony. This means that the scenes do not refer to the external field of vision. Technically, these were not hallucinations, but intensified visual images that compelled complete attention due to the circumstances. When Valdés says "I really believed I was in the meadow", he is referring to feeling himself to be in another plane or dimension, rather than the insertion of objects into his field of vision. If he had not said that this was not like a dream, his description would appear to be an oneiric or dreamlike experience. Evidently, the expression and analysis of phenomenological testimonies produced under the influence of psychotropic plants and drugs requires profuse methodological refinement.

In 2006, a study was published on the mental effects of *Salvia divinorum* carried out by a Spanish research team from the Psychology Department of the Universidad Autónoma de Madrid and the Pharmacology Department of the Universidad de Barcelona.²² They used a sample of 32 consumers of different psychedelic substances for recreational purposes, under a protocol approved by an ethics committee. The plant was administered and the subjective effects were established by a retrospective testimony by means of four questionnaires, such as the Spanish version of the 71-question HRS or *Hallucinogen Rating Scale*, and the 72-question *Altered State of Consciousness Questionnaire*. The description of these effects was reported according to a series of categorical variables. On average, the effects were considered as brief and intense, with a duration of less than 15 minutes. The primary effects reported were "psychedelic type" modifications on visual perception, as well as psychic and somatic sensations, and modifications to the perception of oneself and reality. Intense *derealization* was considered a characteristic of *Salvia*, while other psychological effects were considered similar to "classic psychedelics". Although the authors recognize the preliminary nature of their results, this research points towards the need to assess the phenomenological nature of psychoactive effects, not only of *Salvia divinorum*, but also of other psychoactive molecules, plants, or preparations.

The mental effects of the plants and its primary active are a new psychopharmacology and also an enigma, due to the three types of responses that have been consistently reported:

1. Intensification of visual and auditory imagery, *oneiric* experiences similar to dreams, and a state of alertness somewhat similar to the initial phases of an experience with "classic hallucinogens" that show activity like serotonin and dopamine receptor agonists. The contents

of these visual images probably differ in that hallucinogens are more kaleidoscopic but with *Salvia* they are more fantasy-like and oneiric, but this would need greater specification.

2. Strangeness, *derealization*, depersonalization, modification of self-perception, space-time dislocation, and out-of-body experiences, similar to the effects of dissociative psychodysleptics that show activity on the NMDA receptor.
3. Dysphoria, "somatic" sensations such as hypo- or hyperalgesia and febrile-type proprioceptive sensations that suggest the participation of opioid receptors.

The primary task of psychopharmacology would be to produce justified and comparable hypotheses around the neurological bases of these mental effects. The unexpected discovery that Salvinorin A is a strong and specific ligand of the kappa opioid receptor,²³ and the intense activity in the field of pharmacological research that took place after this discovery provided valuable information to conceive feasible hypotheses around these bases.

PHARMACOLOGY OF SALVINORIN A, KAPPA OPIOID RECEPTOR AGONIST

In his investigation into the pharmacology of Salvinorin A, Siebert¹⁷ reported that there was not a significant interaction of this component with 42 cerebral receptors including receptors of monoamine, amino acid, and other neurotransmitters. This inability to join itself with other receptors of the Central Nervous System was an obstacle to explaining the psychological effects of a molecule whose psychoactive effects had already been proven. However, a few years later, Roth et al.²³ discovered the unexpected fact that Salvinorin A is a highly selective and fast-acting kappa opioid agonist. Salvinorin A turned out to be a surprising kappa ligand, given that it is a diterpene molecule, lacking in nitrogen, which shows a high selectivity for this receptor and virtually no affinity with other receptors of psychoactive drugs. Very soon after this discovery, Chavkin et al.²⁴ demonstrated that Salvinorin A is a more effective kappa agonist than traditional agonists of these receptors and also more effective than dynorphin 1-13 in activating kappa receptors, which indicated that Salvinorin A is the most effective known non-peptide kappa agonist of natural origin.

Kappa opioid receptors are one of four groups of cerebral receptors that bind to opium derivatives,* in this case, especially the endogenous opioid peptides of 32 amino acids known as dynorphins.²⁶ Despite the kappa opioid agonists having analgesic properties that supposedly lack the undesirable effects of morphine, Pfeiffer et al.²⁷ reported that the kappa agonist benzomorphan MR2033 had dysphoric and "psychotomimetic" effects similar to those of phencyclidine. Dynorphins, which are abundant in the brain and particu-

larly in the hypothalamus, modulate the response to pain in an intricate manner, given that it sometimes shows analgesic properties, and other times stimulates pain. They also show effects which counteract those of cocaine, which is attributed to its ability to inhibit the release of dopamine; they are linked to stress-induced dysphoria, increase the appetite and alter thermoregulation. Given that Salvinorin A shares the affinity of kappa opioid receptors with dynorphins, it is not surprising that many of the reported effects of *Salvia divinorum* have also been found in these peptides, including its possible anti-depressive effect. In fact, the unusual union of Salvinorin A with kappa receptors as an agonist opens the possibility that this could become a substance of interest in terms of the functions and disorders that involve the activity of these receptors. In one study on the behavior of zebra fish,²⁸ Salvinorin A induced accelerated swimming and an effect similar to a "trance" with a dose of 5 and 10 µg/kg. Prior treatment with kappa agonists or type 1 cannabinoid antagonists blocked the effects. A compound also increased the time spent in behavior associated to the drug, which indicates that this had pleasurable or rewarding effects that involved the activation of the kappa opioid receptors and CB1 cannabinoid receptors.

In their revision of the antinociceptive properties of Salvinorin A, McCurdy et al.²⁹ mention that kappa opioid agonists have been used in the treatment of pain, drug addiction, eating disorders, and depression. The fact that the kappa opioid receptor agonists weaken some of the neurochemical and behavioral alterations provoked by drug abuse is particularly interesting for its therapeutic potential. Kappa agonists reduce the consumption of self-administered cocaine in non-human primates and Potter et al.³⁰ reported that the repeated administration of Salvinorin A diminishes the enhanced reward effects in a test with cocaine (*cocaine challenge*) and in a paradigm of intra-cranial self-stimulation. The authors reported that some evidence in terms of the effects of kappa agonists in brain reward systems is contradictory, and they proposed that the interaction between the activation of kappa receptors and the reward response provoked by the drug possibly involves a combination of opposing processes and negative reinforcement mechanisms.

The possible antinociceptive effects of Salvinorin A have also been researched. Despite McCurdy et al.²⁹ demonstrating that this diterpene is a potent ligand of the kappa opioid receptor that can be a fast-acting analgesic in systemic administration, they also advise that its clinical use is limited by its short duration and by the psychoactive effects that are produced with similar doses. Their proposal is that structurally related analogues could have a longer lasting analgesic effect without this undesirable psychoactive activity.

* It is interesting to note the affinity of sigma opioid receptors with dimethyltryptamine (DMT).²⁵

THE POSSIBLE "MECHANISM OF ACTION", A RELEVANT CHALLENGE FOR THE MIND-BODY PROBLEM.

The concept of the "mechanism of action" in pharmacology is an intrinsically reductionist proposal as it seeks to explain the clinical effects of a drug in terms of its molecular effects on specific receptors and other biochemical functions located in relevant tissues and organisms for these effects. In the case of psychoactive plants, the concept is necessarily related to that of the "active principle" – the molecule or molecules responsible for the mental effects in terms of its neuropharmacological activity at a molecular level. For example, mescaline is recognized as the primary active of peyote (*Lophophora williamsii*) and its mechanism of action is attributed to the activity of this alkaloid as an agonist of post-synaptic serotonin 2A receptors in the brain; a property it shares with other hallucinogens such as psilocybin, DMT, and LSD. This description is quite precise, but difficult to consider complete. One of the lacking pieces of information is a correct understanding of the *intermediate steps* between a symptom such as a perceptive, cognitive, or emotional modification, and a biomolecular interaction. The understanding of these phenomena at their different levels would not only constitute a scientifically successful "mechanism of action" but would also elucidate nothing less than the stubborn mind-body problem. In reality, the idea that hallucinogens could be an instrument to approach and perhaps resolve the mind-body problem was not only anticipated by scientists or philosophers, but also by the renowned poets and thinkers Aldous Huxley³¹ and Octavio Paz.³²

However, in the case of psychoactive drugs, we find ourselves with the disconcerting gap that opens up between a neurological correlate of the conscience and subjective experience; two different pieces of information that are encountered and described in the first- and third person respectively. The gap in the case of the "mechanism of action" of *Salvia divinorum* or of other psychoactive plants could be an obstacle to a convincing explanation of its mental effects, even if a complete description of the effects of its neuroactive principles at all levels of cerebral functioning were to be achieved.

The advantage of conscience-altering drugs is that a description can be obtained of their mechanisms of action at a high level of functional integration through a combination of cerebral imaging techniques (third person) and the use of calibrated phenomenological tools during a carefully supervised psychotropic experience (first person). A consistently obtained correlation would empirically mark a correspondence between the neurological information and the mental effect. This psychophysical correlation would allow the exploration of high-level neurological mechanisms in reductive but not eliminatory terms. The next step towards this difficult challenge would be to set out the steps between

the property of Salvinorin A as a kappa opioid agonist and the known mental effects of the plant: What would the intermediate steps be?

The structural and neuropsychological functions of the brain are hierarchically ordered into six levels of action, roughly as follows: molecular, cellular, intercellular, modular, organic, and organismic.³³ As happens with many psychoactive compounds, information on the mental and behavioral effects of *Salvia divinorum* at the organic and organismic levels is limited, whereas information is more detailed and reliable in terms of the molecular and cellular interaction of Salvinorin A and the neurons that have kappa receptors. In spite of the gap, a link between the intermediate levels of explanation could be justifiably inferred or proposed saying, for example, that the dysphoric effects of both the plant and the active principle could be related with the selective agonism of the kappa receptor, as dynorfin, the endogenous ligand of these opioid receptors, also produces these effects. Even in this case, a more complete explanation would require discerning that the neuronal networks are responsible for the dysphoric effects at the intermediate levels.

Another pharmacological enigma that requires the explanation of intermediate steps is that along with hallucinogens, the plant shares a notable intensification of sensory imagery and other effects of broadening the conscience that are not exclusively explained by the agonism of the kappa receptor. In this context, it is important to consider other important neuropharmacological facts, for example, that the dorsal raphe nucleus, one of the primary serotonergic sites in the brain, also has a high density of kappa receptors.³⁴ This type of clinical and neurochemical juncture requires an explanation from the intercellular mechanism, as there are probably cerebral networks that join the neurons and receptors of at least dopamine, serotonin, and opioids, which could be directly and integrally responsible for the so-called "psychedelic" effects at an intercellular level. It is not currently known what these circuits would be, how they are connected, what is the role of each neurotransmitter and type of receptor within the network, where the system is located, how it is activated, and more difficult still, how it engenders or corresponds with the mental and behavioral process involved in the clinical effect. The work of finding and joining the molecular puzzle pieces together is a process that moves from the particular to the general.

The procedure of inference by means of neuropharmacological tools is justified and has advanced, but it is also very difficult, given that there are no models of neural networks that are realistic and viable to support this work. In order to consolidate a more integral explanation of the psychoactive effects, it would be interesting to employ a strategy of general to particular based on obtaining images of the brain under the effects of the plant and its primary actives

in order to localize the modules involved, by means of functional magnetic resonance imaging or positron emission tomography.

The molecular and cellular focus has for a long time been the primary tool for designing effective psychiatric drugs, such as in the case of substances considered antidepressive, because they show the capacity for blocking the reuptake of cerebral monoamines that exert neurotransmitters. This approach is far from being infallible, but with the lack of an alternative model of mechanism of action, it is still being used and is justified in pragmatic terms. Work has been done within this framework on *Salvia divinorum* and its salvinorins, and eventually with chemically-modified components to create analgesics, antidepressants, or agents which counteract the effects of addiction.

There are other methodological challenges to overcome in terms of the psychophysical relationship between cerebral and conscious processes. The present balance between neurological and psychological tools is clearly inclined in favor of neurosciences which are so technologically refined, and of the relatively scarce techniques and instruments that can reliably discern the mental effects of psychotropic substances. The clinical tools to carry out phenomenological interviews developed by classic European psychiatrists were used, among others, by Professor Don Dionisio Nieto, my initial teacher and mentor from the 1960s, in order to carefully describe the mental effects of the *Stropharia cubensis* mushroom³⁵ and psilocybin.³⁶ However, these procedures have been marginalized by standardized questionnaires that are now difficult to apply, because many of the plants and drugs are controlled and categorized, very often erroneously, as addictive or potentially dangerous substances. The viability of well-calibrated phenomenological tools that provide a first person perspective have been revised and redefined by the neurophenomenology of Francisco Varela³⁷ and by the narrative method that we have repeatedly proposed.^{33,38}

The field of clinical psychopharmacology of conscience-altering drugs is problematic. There is still considerable confusion with regard to the profiles of the mental effect of different compounds, such that terms or expressions like psychodysleptic, psychedelic, visionary, psychotomimetic, conscience-altering, hallucinogenic, entheogenic, narcotic, and intoxicating, among others, are used without really establishing a consensus; even indiscriminately. With careful and justified definition, many of these terms would be useful to refer to restricted, specific, and understandable meanings within the wider spectrum of psychoactive effects. Reliable phenomenological tools are necessary in order to characterize the mental effects and profiles of different drugs and so typify their psychological profile and correlate well-established mental effects with mechanisms of cerebral activity, specifically at the highest levels of integration, where conscience probably emerges together with a

possible transmodular function, similar to a swarm or flurry of neural activity.^{20,33}

If these requirements are in themselves difficult to meet, it is even more complicated to explain the diverse mental effects that the same plant or drug has in people and circumstances of different cultures.³⁹ An ethnographic-neuroscientific focus applied to the comparative study of the effects of sacred plants on different subjects could throw some light on the role played by belief systems, *set and setting*, and other cultural variables in determining the contents of the conscience. Perhaps in this way, it would be possible to approach and understand the existential interest and even fascination that traditional and modern ingestion of these remarkable plants and their compounds has held for their human users for millennia. This interest has not only produced, refined, and conserved shamanic practices in dozens of traditional cultures in the Americas; it has also played an important role in the renovation of ideas and attitudes provoked by the revolution of western culture during the 1960s and continues to have a genuine interest among various groups nowadays in developed countries and societies. This path to confronting the mind-body problem in relation to unusual but graspable states of conscience and their neurological correlates can only be effective if responsible and meticulous investigation is appreciated and supported.

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