

Salvia divinorum: A Psychopharmacological Riddle and a Mind-Body Prospect

José-Luis Díaz*

Department of History and Philosophy of Medicine, Faculty of Medicine, National Autonomous University of Mexico (UNAM), México

Abstract: The multidisciplinary research on *Salvia divinorum* and its chemical principles is analyzed concerning whether the ethnobotany, phytochemistry, mental effects, and neuropharmacology of this sacred psychoactive plant and main principle clarify its experienced effects and divinatory uses. The scientific pursuit spans from the traditional practices, continues with the botanical identification, isolation of active molecules, characterization of mental and neural effects, possible therapeutic applications, and impinges upon the mind-body problem. The departure point 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 water potion of crushed leaves produced short-lasting light-headedness, dysphoria, tactile and proprioceptive sensations, a sense of depersonalization, amplified sound perception, and an increase visual and auditory imagery, but not actual hallucinations. Similar effects were described using questionnaires and are attributable to 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 allowing to explore the differential ethnic effects. As is the case for other consciousness-altering preparations, a careful and encompassing research on this plant and principle can be consequential to endeavors ranging from the mind-body problem, a better understanding of shamanic ecstasy, to the potential generation of analgesic, antidepressant, and drug-abuse attenuating products.

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

THE VOICE OF THE LEAF¹

"You have to chant the voice of the leaf," admonished the Mazatec shaman during a ritual ceremony in the village of St. Bartolomé Ayautla after she gave me to drink a bitter watery potion made out with ground leaves of *Ška Pastora*, a divinatory plant known to botanical science as *Salvia divinorum* Epling & Játiva-M. I had arrived in Ayautla in 1973 following the steps of the amazing independent scholar R. Gordon Wasson, who some 10 years earlier described the ritual use and psychotropic effect of this plant of the mint family precisely on this remote village attached to the bottom of the Santo Domingo Canyon in the Mazatec Sierra of northern Oaxaca, México. Wasson's rediscovery and study of the Mexican hallucinogenic mushrooms was, of course, a pioneer and classic model of the trans disciplinary scientific approach that was already known as "Ethnopharmacology".

I had just returned from Boston trained in psychobiology and psychopharmacology, and decided to undertake a research project on lesser known Mexican psychoactive plants in search not only of new tools for brain and psychiatric research but precisely of a trans-disciplinary

ethnopharmacology taking advantage of the millenary knowledge of the native cultures of my country.² One of the first plants to be studied was *Salvia divinorum* and in the initial quest I found myself walking for more than 6 hours and under recurrent drizzle in the trails of the Mazatec Sierra along the Santo Domingo river canyon (Fig. 1) to find the small and hidden village of Ayautla (Fig. 2).

I had little idea about the place and only in theory the difficult struggle that indigenous communities and cultures faced in order to survive, but was lucky enough to come in contact with a clever and honest Presidente Municipal (local Mayor) who lodged me, inquired about my intentions, and studied me for a few days before sending me to a local shaman, a middle aged and gentle lady named Julia Aurelia Palacios, always dressed in a gorgeous customary *huipil* (Figs. 3, 4). Doña Julia spoke only Mazatec, but her young nephew and apprentice Felipe was bilingual, so I was able to start a long-term relationship with this family that, aside from being a traditional clan of shamans, lived with great effort and difficulty from cultivating and harvesting the brand of coffee from Ayautla, like almost everybody else in the village.

*Address correspondence to this author at the Cerrada de Cruz Verde 29-B, Lomas Quebradas, México, D.F. 10000, México; Tel: 52-55-5683-2316; E-mail: jldiaz43@gmail.com

¹This initial section is a present recount of the ethnopharmacology of *Salvia divinorum* published in Spanish some 37 years ago (Díaz, 1975).

²The present article represents an attempt to employ a transdisciplinary approach to magic plants where ethnobotanical, phytochemical, psychopharmacological, and neurochemical data are not merely juxtaposed but interrelated and integrated to any possible extent.

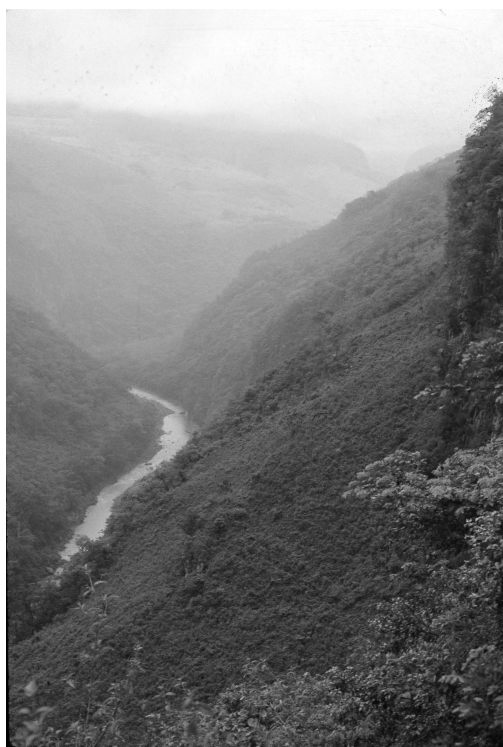


Fig. (1). The river and canyon of Santo Domingo in the Mazatec Sierra of northern Oaxaca State, México, photographed by the author in 1973



Fig. (2). View of the Southern slope of the Santo Domingo canyon photographed by the author in 1973 during the ascent to the sacred places where *Salvia divinorum* grows wild.



Fig. (3). The Mazatec shaman Doña Julia Aurelia Palacios posing in her hut of Ayautla in 1973, photographed by Jacobo Checinski.



Fig. (4). Doña Julia humming and singing a propitious chant in her hut of Ayautla in 1973 photographed by Jacobo Checinski.

Soon I learned that Doña Julia used four traditional psychotropic plants in her divinatory and healing practice: hallucinogenic mushrooms (*Psilocybe* spp), morning glory seeds (*Rivea corymbosa*), wild tobacco (*Nicotiana rustica*), and specially *Ška*³ *Pastora* (*Salvia divinorum*). When I declared to be interested in *Ška Pastora*, Doña Julia decided to show me about the collection and ceremony of the plant as an apprentice because I was not sick or had not an inquiry requiring divination on her part. I had to undergo a ritual preparation that involved a special fast, sexual abstinence, and ritual harvest of the plant before undertaking the first ceremony. The sunrise after the preparation period was accomplished, Felipe guided me up the steep mountain of the Santo Domingo Canyon for several trying hours until we reached the previously undisclosed and sacred place where *Ška Pastora* grew wild (Fig. 5). The gathering of the plant leafs was done with respect and care because it was a part or

³*Ška*⁴ is pronounced shka with the sound of the final a being the most deep in the 4-tone spectrum of the Mazatec vowel.

a manifestation of a revered mythical or saintly figure: the *Pastora*, the Shepherdess, a syncretic aspect of Virgin Mary. I was glad to photograph the isolated place and for the first time the white corolla and violet calix flower of this secret and sacred mint (Fig. 6).



Fig. (5). A humid and foggy place where *Salvia divinorum* grew wild in the highlands of the Santo Domingo Canyon of Sierra Mazateca as photographed by the author in 1973. The shape in the center of the image is Felipe, Doña Julia's nephew and apprentice.

Later that night, the ceremony took place in Doña Julia's poor and constantly busy earth-ground shack. After calculating the dose according to my body mass, she sat down, counted in pairs some 40 leaves and cautiously piled them in her hand upon a burning aromatic *Burseria* (Torchwood) exudate resin. At the same time she started to chant, with a coarse and monotonous voice, a long, entrancing, and auspicious song that I recorded and later translated into Spanish with the help of the bilingual daughter of the Presidente Municipal. In the song she called upon supernatural idols and forces of the Canyon, the Holy Trinity and catholic saints *Señor San Pedro* and *Señor San Pablo* and to the Sun as a supreme being to protect me and show me the way. For this occasion, I translate into English only a few of the poetic and deeply religious invocations:

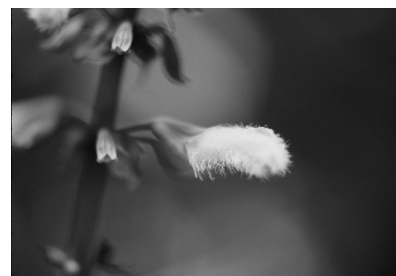


Fig. (6). The flower of *Salvia divinorum* photographed by the author in its natural environment located in the highlands of the Santo Domingo Canyon in 1973.

Wind of the Mazatec house!
Wind of the precipice!
Let them pass well in their path.
May the Sun rise well and protect you
while you travel in the ravines
in search of *la Pastora*.
God is creating us!

At the end of the song, Doña Julia vigorously crushed the leaves with her hands on a *jícara* (calabash bowl) containing water until all "the blood of the leaf" was extracted in a green and foamy potion. Then she handed me the *jícara* with the instruction to drink its content all at once. The liquid was very bitter and even revolting, but I managed to hold it in. I was then laid on a *petate* (grass mat) extended on the earth, and even though the candle lights were turned off and it was quite dark except for the wavering bonfire, I was instructed to close my eyes. Doña Julia remained silent but as I sensed, quite watchful. I did not know what to expect, but felt thrilled, privileged, and safe under the care and guidance of a knowledgeable traditional shaman.

Soon I experienced muscular sensations and chills not very unlike a period of fever, noticed that the multiple faint noises around seemed quite near and amplified, and also that inner visual images slowly acquired relevance in my attention undergoing a fascinating, automatic, colorful, and dynamic flow. They never became hallucinations in the sense of perceiving them "out there" in the visual field. I felt light headed, dizzy, somewhat elated or at times irritable and strange, as if I was not quite myself, but all of the effects, which did not last more than one hour, were mild and to a certain point disappointing. It took me several more visits to Doña Julia and her *Ška Pastora* bitter beverage to start grasping the meaning of the ceremony, of the psychotropic effects and what was expected of me when during the sessions I was urged by her through Felipe, as if it was quite peculiar that I had not done that by myself, that I had to chant the song of the leaf.

Now, when I described above the visual images that I experienced, I did not refer to their content or what they were about not only because I have mostly forgotten them, but also because it did not seem very important at that moment since my consciousness was, as it were, passively experiencing them. Moreover, as part of my culture and time, I was taking the psychoactive compound to undergo a personally meaningful experience and in the vein of the participatory observation proposed by a humanistic anthropology. With time I came to realize that for Mesoamerican shamans the mental contents

rising through a sacred plant consumption ceremony were what the whole ritual was about because in their worldview my spirit came in contact with the syncretic saint-like figure of the *Pastora* leaf through the communion of her very own plant. As an apprentice I was expected to be attentive to these images and sounds in my mind and to “chant” them, but I had not the clues about how to do that. During the next few ceremonies I started to be more attentive to the contents of the experience and at the end to verbally recount what I remembered of the images. Even though I never got to meet the demanding skill to chant the voice or the song of the plant my report was considered important and worthy of interpretation. In their remarkable world view, I was in contact with another realm, the very same where they obtained the answer to their pledge and thereby were able to divine the cause and cure of the ailment of patients and consultants, or the whereabouts of a person, an animal, or an important object.

In 1974 when I shared with Gordon Wasson these experiences in his Connecticut home, he was rounding up a sumptuous book with recordings on another Mazatec shaman, María Sabina. The careful translation into Spanish and English of her chants during a divinatory mushroom *velada* made in collaboration of the Cowan’s husband and wife team [1] made me realize more plainly what was expected of me, because María Sabina readily and powerfully delivered aloud the songs she was noticing while psilocybin was flowing upon her neurons. Of course, I should haste to say that there was much more than this neurochemical fact going on in María Sabina to account for her unusual state of mind having to do with the circumstances named by anthropologists “set and setting”⁴: a collection of culturally shared beliefs, practices, expectations, a vast personal practice with psychotropic plants, and the ritual divinatory situation of the *velada*. What Doña Julia was urging me to do, and what María Sabina was actually doing in her chant, was to recite “voices,” presumably ongoing auditory images of particular cultural contents, that are not as paramount as visual experiences in the recounts of westerners describing their psychedelic experiences. The chanting of voices evoked by psychoactive plants consumed in ritual ceremonies may be a crucial issue in the analysis and interpretation of the mental variations of the effects depending on diverse cultural set and setting conditions. Years later I experienced several forms of Mindfulness or Insight *Vipassana* meditation that required a similar sustained detection of ongoing mental processes [33]. The difference between the two techniques is that while Insight meditation instructs a detached detection of mental contents, the Mazatec shamanic training requires a chanting expression of auditory images. The requirement is so demanding on attention and communication skills, that it could perhaps be considered a form of Mesoamerican meditation.

Through my visits to the Mazatec Sierra in the next few years, I had a growing glimpse about the divinatory practice and the fact that becoming a shaman required a progressive refinement of insight and attention skills needed to monitor and express the contents of one’s mind in the ever more familiar circumstance of a divinatory psychotropic daze. But, alas, I realized that I would no longer follow that path, and remained an academic researcher interested in the mind-body

problem and in psychobiology, a persistent vocation that took me to undertake other scientific and theoretical enterprises and that now, many years later, gives me the opportunity to look upon *Salvia divinorum* again and from another standpoint.

In the rest of this paper, I would like to ponder the research on *S. divinorum* and its chemical principles from a transdisciplinary view covering several disciplines with a leading psychobiological question in mind. The hard question that concerns me most is whether the research on the ethnobotany, chemistry, pharmacology and brain effects of this magic plant and its main chemical principle clarify its psychological properties and divinatory cultural uses. Far from pretending that a full understanding of the uses and effects of the plant would come solely from a scientific analysis, the most useful approach is to penetrate as far as possible in the knowledge and information arising from the points of view of the traditional users as conveyed by a participative ethnology, of the mental effects of the plant as portrayed by artistic renditions, first-person expressions and other phenomenological accounts, and by the objective data provided by the different sciences involved in ethnopharmacology. Even though the proposed domain is vast and probably inexhaustible, it seems worthy and challenging to advance the inquiry with such an open and integrative attitude.

ETHNOBOTANY AND PHYTOCHEMISTRY

As far as we know, the first mention of the plant was made in 1939 by the ethnologist J. B. Johnson who describes that leaves of a “yerba María” are beaten and drank as a tea by Mazatec Indians for divinatory purposes [2]. A few years later, the pioneer ethnobotanist Blas Pablo Reko described a “magic plant whose leaves produce visions and that is called leaf of divination.” in page 17 of his *Mitobotánica zapoteca* [3]. Seven years later, Robert Weitlaner (1952) described a divination ceremony by a Mazatec healer using the leaves of an unknown herb [4], and in 1957 the Mexican botanist Arturo Gómez Pompa collected and classified the plant as belonging to the *Salvia* genus⁵, finally described in 1962 by Epling and Játiva as a new species with samples delivered by R. Gordon Wasson [5, 6].

Salvia divinorum Epling & Játiva-M is a sage belonging to the Labiatae or Mint family. It receives the Mazatec names of *Ška Pastora* and *Ška María Pastora*. *Ška* means leaf in Mazatec and consequently in Spanish it is called *Hoja de la Pastora*, and *Hoja de María Pastora*. The names *Pastora* (Shepherdess) and *María* are probably a reference to a syncretic representation of the Virgin Mary. R. Gordon Wasson proposed that it corresponds to the *Pipiltzintzintli* of the ancient Nahuatl, but information from the reliable Colonial friar and universal scholar Antonio Alzate in 1772 indicated that the name was given to hemp and marijuana imported to New Spain from Asia and already a subject of divination use [7].

⁴Even though Timothy Leary was the first to propose this concept, its application to traditional psychotropic plant use was initially done by anthropologist Marlene Dobkin de Ríos (1975).

⁵The Mexican National Herbarium sample collected by Gómez Pompa on 1957 did not have flowers so that it was not possible to identify the species. The sample label mentions hallucinogenic properties among its uses. See also Gómez-Pompa’s description in his site: <http://gomezpompa.blogspot.mx/2010/11/capitulo-4.html>

The plant is a rare perennial herb endemic to the Mazatec Sierra of the state of Oaxaca in Mexico where it grows wild on very humid ravines and other rather isolated highlands but it has been widely cultivated for recreational use in the USA and Europe. The name *divinorum* was given by botanists Epling and Játiva in reference to the divinatory use of the plant mentioned briefly by J. B. Johnson in 1939, R. Weitlaner in 1952, and B. P. Reko in 1954, but more extensively by R Gordon Wasson in the Mazatec village of Ayautla in 1962 [2-4, 6]. Wasson described the preparation of a watery potion of pairs of leaves by the use of a *metate* (grinding stone). Thorough ethnopharmacological studies of the plant ceremonial use in Ayautla were published by me [7] and summarized above, and later on by Leander Valdés [8] who in 1981 contacted me in order to access and document a shamanic divinatory practice with *Salvia divinorum* for his Pharmacy thesis in the University of Michigan. Trying to avoid the long march to Ayautla from Huautla, Leander, his mentor Ara G. Paul and I entered the lower Mazatec region by car from the west and rapidly located Don Alejandro Vicente, a shaman living in the village of Chichicazapa, near the border of the extensive Miguel Alemán dam (Fig. 7). After collecting the plant in the faraway highlands of Cerro Rabón having crossed the Miguel Alemán dam by boat and the customary preparations, we had the opportunity to partake in several divinatory rituals involving the plant that there was named Hoja de María, and additionally documented the use of an infusion of 4-5 pairs of leaves to treat diarrhea, headache and rheumatism. From then on, Leander Valdés made several important contributions to the chemistry and pharmacology of *Salvia divinorum*.

During the decade of the 1970's *Salvia divinorum* was drawn and described in the well-known textbooks of Richard Schultes and Albert Hofmann [9, 10] concerning sacred psychotropic plants, their history, distribution, native uses, and effects. The intimate link between these plants, their capacity to induce ecstatic and dream-like episodes, and shamanic beliefs and practices in México has been repeatedly documented by diverse ethnological [11] and historical sciences [12].

Kindled by the ethnopharmacological descriptions and personal conversations about the plant, in 1982 the group of the skilled phytochemist Alfredo Ortega, from the Institute of Chemistry of the National University of Mexico, gathered enough material from the Mazatec region and promptly isolated a novel neoclerodane diterpene than was named salvinorin A [13]. Independently from this work, Valdés isolated two compounds that were named divinorin A and divinorin B [14] but later confirmed they corresponded to the structure of salvinorin A and salvinorin B, and established their stereochemistry.

MENTAL EFFECTS OF *SALVIA DIVINORUM* AND SALVINORIN A

In his pioneer description, Wasson mentioned mild visual effects of the water infusion of *Salvia divinorum* prepared in divinatory rituals and compared the effect to an initial intoxication with *Psilocybe* mushrooms [6]. As summarized above I was able to partake in many divination ceremonies conducted by Mazatec shamans in Ayautla and Chichicazapa

and described beliefs, rituals, psychological effects, and behavioral models in a book in Spanish concerning psychotropic plants from Latin America [7]. In a chapter of this book on obscure or lesser-known Mexican psychotropic plants I described that the traditional *Ška Pastora* Mazatec ceremony required complete silence and darkness and noted that the water potion produced short-lasting light headedness, mood modifications, such as elation, dysphoria, irritability or malaise, tactile and proprioceptive feverish sensations, a sporadic mild sense of strangeness and depersonalization, an amplified sound perception, and an increase visual and auditory imagery, but not true hallucinations in the sense of perceptions without consensual external objects to be perceived. I did not report kaleidoscopic figures similar to those of "classic hallucinogens"; the sensorial effects were mainly a short-lived but intense heightening of visual imagery and fantasy, sometimes wrongly called "hallucinations". In this paper I also described that we used an animal model to test possible psychodysleptic effects of *Salvia divinorum* extracts but despite the fact that cats injected with extracts showed some "hallucinatory" behaviors, such as staring and threat motions directed at unoccupied space, the model was not specific or simple enough to guide in the isolation of the active principle that later on in 1982 was successfully accomplished in the organic chemistry laboratory of Alfredo Ortega [13]. Valdés [14] reported that salvinorin A and active extracts of *Salvia divinorum* showed non-specific sedative effects on mice and some behavioral effects similar to mescaline.



Fig. (7). The author photographed in 1981 by Ara G. Paul in the hut and company of Mazatec shaman Don Alejandro Vicente in Chichicazapa, Oaxaca, México.

The ritual use of *Salvia divinorum* in water extracts remained baffling since these diterpenes were not water soluble and there was a question concerning their possible psychoactivity. But this problem deserves a longer consideration, as we shall see now.

In two subsequent papers concerning psychotropic plants and drugs [15, 16], I proposed to classify psychodysleptic, psychedelic or consciousness-altering compounds according to their common mental and neural effects in 6 classes: (1) **hallucinogens** producing strong perceptual, cognitive and affective modifications in the frame of an amplified consciousness state and a sympathetic or ergotropic stimulation, comprising mescaline cacti such as Peyote

(*Lophophora williamsii*), psilocybin mushrooms (*Psilocybe* spp), Dymethyltryptamine (DMT) Amazon inhalants and species added to the Ayahuasca brewage, and the synthetic indol ergoline LSD, all of them agonists of the serotonin 2A brain receptors; (2) **trance-inducing** plants drugs producing stimulation of imagery in the context of parasymphathetic or trophotropic sedation, isolation and apathy, and comprising ergoline-containing morning glory seeds (*Rivea corymbosa*) and a Sinicuiche (*Heimia salicifolia*) fermented beverage; (3) **cognodysleptics** producing dream-like states of sensory enhancement with effects upon imagery and impaired recollection comprising marijuana (*Cannabis sativa*), *Salvia divinorum* and the oneirogenic *Calea zacatechichi* of the indigenous Chontal Indians of Southern Oaxaca, México; (4) **deliriant**s, producing hallucinations, delirium, disorientation, strong sensory distortions and cognitive impairment in a cloudy consciousness, and comprising scopolamine and other tropane-alkaloid containing solanaceous (nightshade family) plants of the Old World (*Mandragora* and *Hyoscyamus* spp) and New World (*Datura* and *Brugmansia* spp), antagonists of brain muscarinic receptors; (5) **narcotics** comprising opium preparations and morphine derivatives that produce euphoria, sensory delight, lethargy, mental clouding, as well as a potent pain and anxiety relief by acting as agonists of opioid receptors to endogenous endorphins and enkephalins, and (6) **dissociative** psychodysleptics such as ketamine or pentazocine that produce derealization, modified self-perception, and spatiotemporal dislocation leading in higher doses to catalepsy and dissociative anesthesia by acting as NMDA brain receptor antagonists.

In the case of cognodysleptics, where I tentatively placed *S. divinorum*, I later felt that their non-nitrogenous terpenes shown to be psychoactive strengthened the categorization since the rest of the psychoactive chemicals in this group were also non-alkaloidal terpenes. Nevertheless, the precise classification of the mental effects of *S. divinorum* required further evidence to be accomplished, and even today, as we shall soon see, the task is not easy.

Contrary to the mild effects achieved with traditional water extracts of the crushed leaves in ritual Mazatec ceremonies, further research using other routes of administration demonstrated that salvinorin A is a very powerful psychoactive substance. The definite proof that salvinorin A is a psychoactive molecule of *Salvia divinorum* came from Daniel Siebert [17] who demonstrated mental effects at less than the 0.5 mg level of a crude precipitate, making this compound the most active natural psychoactive product, almost in the same range as LSD. Visual images of kaleidoscopic nature, changes in depth perception, sensual and aesthetic appreciation, and creative dream-like experiences were also reported by Siebert to have a relatively short duration, lasting less than 2 hours and starting with a short latency of about 20 minutes. Doses above 1 mg produced disturbing effects since the subjects lose awareness and control over their body, move about aimlessly, report out of body experiences and later are unable to remember the event, a description that seems similar to those of synthetic dissociative psychodysleptics like ketamine and phencyclidine. Siebert concluded that salvinorin A induces in humans intense and short-lived mental effects that are distinct from those of "classical"

hallucinogens. Soon after this report, in a learned and detailed history of the plant, Jonathan Ott [18] described that the sublingual application of salvinorin A in acetone and DMSO was highly active, with a threshold for "psychoactivity" at 250-500 mcg and "visionary activity" above 1 mg.

The relatively mild effects reported after the ingestion of the water extract of the whole plant in the Mazatec Sierra and the strong psycho-dissociative effects of the principle are not contradictory since it is well known, for example, that the relatively innocuous alerting, energizing, and stimulating effects of chewing coca leaves (*Erythroxylon coca*) in the Andean high mountains are very different in grade and quality from the strong euphoric and "high" rush state attained immediately after the inhalation of pure cocaine powder [19]. The different route of administration and the material employed ("the green and the white" in Andrew Weil's recount) explain the strong dissimilarities in terms of the huge difference in blood cocaine concentrations and clearance attained, not to mention the more difficult to demonstrate modulation of the experience by culture, purpose, and circumstance. In the first Tucson "Towards a Science of Consciousness" conference where I also presented a stream model of phenomenological consciousness [20], Andrew Weil wrote a chapter called "Pharmacology of Consciousness: A Narrative of subjective experience" [19] where he analyzed the psychopharmacology of *Salvia divinorum* mentioning in detail the images that Leander Valdés and I shared when, during a ceremony with Don Alejandro Vicente, and upon his request, we decided to mention some of the contents of our visual images, showing the utility of "chanting the voice of the leaf," albeit tentatively. The first person report of Valdés [21] is worth quoting:

After about 15 minutes, we began to have visions. This time I spoke mine out, alternating between English and Spanish, which helped to fix them in my mind. Díaz spoke first and mentioned flowers. I then saw eidetic images that evolved to plants and flowers. These later became giant fruits and seeds. At the same time I felt that I was twisting inside my body as well as spinning around. I saw a burning cross with two horizontal rays. It stopped flaming and began to emit light. Suddenly I seemed to be very heavy, as though something were pushing me into the bed. My arms felt sore. Later I saw what looked like a darkened picture in black and white. Díaz apologized to Don Alejandro for our inability to see the religious figures the *curandero* had described. My vision then changed back to color, with praying figures resembling those seen in Mexican churches. They were faceless and their clothing was covered with gold. The image of a jewel-encrusted single-rayed cross appeared. It converted itself slowly back and forth to a sword. In the center of the image I could see animals, plants and people. If the vision started to change or disappear, I could concentrate and bring it back. The last image was that of a castle that was transformed into a Byzantine church. Hooded, faceless, moonlike figures marched around it.

After the ceremony was finished and we were turning back, Leander Valdés underwent an intense experience with

strong mystical images and feelings occurring in the car and in the hotel where we stayed. Here is his report:

In the motel room, the imagery came back stronger than ever. Even though I didn't speak out, I saw a pulsating purplish light that changed to an insect-like shape, perhaps a bee or a moth, and then into a pulsating sea anemone. It expanded into a desert full of prickly pear cacti, and remained so for several minutes. During the first session and throughout the night, my visions had all appeared to be something like a cross between a silent moving picture and a cartoon. I felt myself to be an observer of these mute visions, rather than being an actual part of them. Suddenly, however, I was in a broad meadow with brightly colored flowers. I had just crossed a stream by way of a small wooden bridge. Next to me was something that seemed to be the skeleton of a giant model airplane made of rainbow colored inner tubing. The sky was bright blue and I could see a wood in the distance. I found myself talking to a man in a shining white robe who was either shaking my hand, or else holding on to it. It was an amazing hallucination, as I truly believed I was in the meadow. It was not like a dream. After a few moments the desert landscape returned and I slowly went to sleep after an hour or so. I rose early the next morning, feeling no adverse effects.

In this expressive first person phenomenological text it is important to remark that the visual scenes described were experienced in prescribed darkness and with eyes closed and not referred to the external visual field. Technically they were not hallucinations but enhanced visual images commanding a full attention due to the set and setting circumstances. When Valdés says that he *truly believed he was in the meadow*, more than the insertion of an object in his visual field, he felt implanted into another realm. If he did not immediately say that it was not like a dream, his description indeed seems like a dream-like experience. In what way was this experience different from a dream? Obviously the expression and analysis of phenomenological texts under the effects of psychotropic plants and drugs require a profuse methodological refinement.

A study on the mental effects of *Salvia divinorum* was published in 2006 by a Spanish team of the Psychology Department of the Autonomous University of Madrid and the Pharmacology Department of the University of Barcelona [22]. They used a sample of 32 recreational users of several psychedelics including *Salvia divinorum* under a protocol approved by an ethics committee. There was no administration of the plant, and the subjective effects were retrospectively recalled by means of 4 self-report questionnaires such as the Spanish version of the Hallucinogen Rating Scale (71 items) or the Altered State of Consciousness Questionnaire (72 items). These descriptive effects were reported for categorical variables and in average they were considered to be intense and brief, lasting usually for less than 15 minutes. "Psychedelic-like" modifications in visual perception, mood and somatic sensations, and a modified perception of self and reality were the main recorded effects. An intense derealization was considered characteristic of *Salvia*, while other psychological effects were dimmed similar to the "classical psychedelics" with serotonin-2A receptor agonistic activity. Even though the

authors acknowledge the preliminary nature of their results due to the small sample, the lack of control on the ingestion of the extracts and the recollection acuity of the volunteers, this investigation points to the necessary path to follow in order to assess the phenomenological nature of the psychoactive effects not only of *Salvia divinorum*, but of any other psychoactive molecules, plants or preparations.

The mental effects of the plant and its main diterpene principle are a psychopharmacological novelty and a riddle because three distinct types of actions have been consistently reported:

1. Visual and auditory imagery enhancement, dream-like experiences, light headedness, and increase alertness which are somewhat similar to initial stages of an experience with the classic hallucinogens that show serotonin and dopamine receptor agonist activity. Probably the visual image contents differ from being more kaleidoscopic for hallucinogens and more fantasy like for *Salvia*, but this needs further clarification.
2. Strangeness, derealization, depersonalization, modified self-perception, spatiotemporal dislocation, and out of body experiences similar to the effects of dissociative psychodysleptics that show NMDA receptor activity.
3. Dysphoria, "somatic" sensations such as hypo or hyperalgesia and proprioceptive feverish sensations that suggest opiate receptor involvement.

The main psychopharmacological task would be to produce justified and testable hypothesis concerning the neural foundations of these diverse mental effects. The unexpected discovery that salvinorin A is a strong and specific kappa opioid receptor ligand [23] along with the intense pharmacological research that ensued provide with information to envisage feasible hypotheses concerning such foundations.

THE KAPPA-OPIOID RECEPTOR AGONIST PHARMACOLOGY OF SALVINORIN A

In his paper on the psychopharmacology of salvinorin A, Siebert [17] reported that there was no significant interaction of this compound with 42 known brain receptors that included monoamine, amino acid, and other neurotransmitter targets. Such lack of binding capacity to important CNS receptors was an obstacle to explain the psychological effects of an already proven psychoactive molecule. Nevertheless, a few years later Roth, *et al.*, [23] described the somewhat unexpected fact that salvinorin A is a highly selective and short-acting kappa opioid receptor agonist. Salvinorin A was a surprising class of kappa receptor ligand since it is a diterpene molecule lacking nitrogen that shows a very high selectivity for this receptor, and virtually no affinity for other psychoactive drug targets. Soon after this discovery, Chavkin *et al.*, [24] demonstrated that salvinorin A is a more efficient kappa agonist than traditional agonists of these receptors and also to be more efficacious than dynorphin 1–13 at activating kappa receptors under conditions of minimal reserve and indicating that salvinorin

A is the most highly efficacious, naturally-occurring non peptide kappa agonist known.

Kappa opioid receptors are one of the four known brain receptors that bind opium derivatives⁶, specifically the 32 amino-acid endogenous opioid peptides known as dynorphins [26]. Even though kappa opioid agonists have analgesic properties that were supposed to lack undesired morphine effects, Pfeiffer *et al.*, [27] reported that the benzomorphan kappa agonist MR2033 had dysphoric and “psychotomimetic” effects similar to phencyclidine. Dynorphins, which are abundant in the brain, particularly in the hypothalamus, modulate pain response in an intricate manner, sometimes showing analgesic and other times pain-stimulating properties. They also show some anti-cocaine effects attributed to their dopamine-release inhibitory capacity and are involved in stress-induced dysphoria, encourage appetite and alter thermoregulation. Since salvinorin A shares with dynorphins the affinity for kappa opioid receptors, it is not surprising that several of the effects reported for *Salvia divinorum* have also been demonstrated for these peptides, including possible antidepressant effects. Actually, the unusual agonistic binding of salvinorin A to kappa receptors raises the possibility that it could become a drug of interest in terms of several known functions or dysfunctions involving these receptors. In a zebra fish behavioral study [28] salvinorin A induced accelerated swimming behavior and a “trance-like” effect at doses as 5 and 10 µg/kg. Pretreatment with kappa or cannabinoid 1 antagonists blocked the effects. The compound also produced an increase in the time spent in the drug-associated compartment indicating that it exhibits rewarding effects mediated by the activation of kappa opioid and cannabinoid CB1 receptors.

In their review about the anti-nociceptive 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. Of particular potential therapeutic interest has been the fact that kappa opioid receptor agonists attenuate some of the neurochemical and behavioral effects of drugs of abuse. Kappa agonists decrease cocaine self-administration in non-human primates, and Potter *et al.*, [30] accordingly reported that the repeated administration of salvinorin A decreases the reward-potentiating effects of a cocaine challenge in an intracranial self-stimulation paradigm. These authors report that there is conflicting evidence concerning the effects of kappa agonists on the reward systems of the brain and proposed that it is possible that the interaction between kappa activation and drug reward involves a combination of opponent processes and negative reinforcement mechanisms.

The possible anti-nociceptive effects of salvinorin A have also been investigated. Even though McCurdy, *et al.*, [29] showed that this diterpene is a fast and short acting potent kappa opioid receptor analgesic when delivered by systemic administration, they caution that its clinical utility is limited due to the short range and the other psychoactive effects produced with similar doses. They propose that structurally related analogs may eventually show to have longer lasting

analgesic properties devoid of unwanted psychotropic activity.

THE POSSIBLE “MECHANISM OF ACTION,” A TOUGH MIND-BODY CHALLENGE

The concept of “mechanism of action” in pharmacology is intrinsically a reductionist proposal, to the extent that it hopes to explain the clinical effects of a drug in terms of its specific molecular effects upon “target” receptors and other biochemical functions located in tissues and organs relevant to such effects. In the case of psychoactive plants the concept is necessarily related to that of “active principle”, the molecule or molecules responsible for its mental effects in terms of its neural actions at the molecular level. For example, mescaline is taken to be the active principle of peyote (*Lophophora williamsii*) and its mechanism of action is attributed to the agonistic property of this alkaloid to brain serotonin 2A postsynaptic receptors that it shares with other hallucinogens like psilocybin, DMT, and LSD. This recount is scientifically accurate but it can hardly be considered a complete explanation. One of the missing links is a proper understanding of the *intermediate steps* between a symptom, for example a perceptual, cognitive or emotional modification, and a brain bio-molecular interaction. Indeed, the possible achievement of such a multi-level understanding would not only constitute a successful and scientific “mechanism of action” but, if complete and satisfactory, would appear to elucidate nothing less than the recalcitrant mind-body problem. Actually, the idea that hallucinogens would constitute an instrument to tackle the mind body problem was anticipated no so much by scientists or philosophers, but by the renowned poets and thinkers Aldous Huxley [31] and Octavio Paz [32].

But in the case of psychoactive drugs we come upon the baffling explanatory gap that philosophers of mind argue gorges between a neural correlate of consciousness and the subjective experience, two very different, perhaps unmatchable, pieces of third and first person information. The gap in the case of the “mechanism of action” of *Salvia divinorum* or any other psychoactive plant would prevent a convincing explanation of the mental effects, even if a complete description of the effects of its neuroactive principles at all levels of brain function had been achieved.

The advantage of consciousness-altering drugs is that a high-level mechanism of action can be eventually revealed by third-person brain imaging techniques coupled with first person phenomenological calibrated tools during the course of a carefully supervised psychotropic experience. A consistently-obtained correlation would empirically outline a neural correlate of the mental effect. In turn, this psychophysical correlation would allow the exploration of the high-level neural mechanism in reductive but non-eliminative terms using a top-down approach. A realistic next step toward this challenging goal at the present state of understanding would be to elucidate intermediate steps that stand between, in this case, the kappa opioid receptor agonist property of salvinorin A and the known mental effects of the plant. What would those intermediate steps consist on?

Brain structure and neuropsychological functions are hierarchically ordained in some 6 levels of operation:

⁶Interestingly enough, a sigma “opioid receptor” has affinity for DMT [25].

molecular, cellular, intercellular, modular, organic and organismic [33]. As it happens with many psychoactive compounds, there is limited information at the level of the organic and organismic level of the mental and behavioral effects of *Salvia divinorum*, but more detailed and secure data about the molecular, and cellular or neuronal interactions between salvinorin A and kappa receptor-containing neurons. Despite the gap, it is justified to infer or to propose a link bridging the intermediate levels of explanation, by saying for example that the dysphoric effects of both the plant and the principle may have to do with the proven selective kappa agonism since, among other reasons, the endogenous ligand of these opioid receptors, the dynorphin peptide, also produces such effects. Even in this case, a more complete explanation would require discerning which neuronal networks are responsible at the intermediate levels of the dysphoric effects. But, hard as it would be to fulfill, this would be only one aspect of the undertaking.

Another psychopharmacological riddle of the plant requiring intermediary explanations is that it shares with hallucinogens a remarkable sensory imagery enhancement and other consciousness-expanding effects that are not explained by the kappa receptor agonism alone. In this context it is important to consider other basic neuropharmacological facts, for example, that the Nucleus Raphe Dorsalis, one of the main serotonergic neuron sites in the brain, has also a high density of kappa receptors [34]. Such clinical and neurochemical junctures call for intercellular mechanism explanations since there are probably brain networks comprising at least dopamine, serotonin and opioid neurons and receptors that probably are more integrally and directly responsible for these so-called “psychedelic” effects at the intercellular level. At present, it is not known how these feasible circuits are wired, what are the roles of each neurotransmitter and receptor type in the network, where is the system located, how does it become active, and, even more puzzling, how is that it modulates or corresponds to the mental and behavioral process involved in the clinical effect. The bottom-up task of finding and matching the jigsaw molecular pieces of information using neuropharmacological tools is on its way and very much justified, but it is also conceptually difficult and challenging because there are no realistic and feasible neural network models to aid in the enterprise. In terms of gathering a more integral explanation of psychoactive action, it would be of novel interest to employ a top-down strategy of obtaining brain images during the effects of the plant and its principles to locate the modules involved by nuclear fNMR and some of the molecular topography by PET. A proper control for comparison could be the default network operating when the subject is at rest with no cognitive task to fulfill, while the mind wonders but without the influence of an exogenous psychoactive molecule.

The molecular and cellular approach and the bold leap from the molecular and cellular realm to the clinical symptom has been for a long time the main methodological tool in the design of useful psychiatric drugs, as it occurs in the strategy of considering potential antidepressants the substances that show brain monoamine reuptake blocking activity. The approach is far from infallible but, without a better alternative mechanism of action model, it is still used and practically justified. Within this framework, much work

is now being done with *Salvia divinorum*, its salvinorins, and eventually with their chemically-modified relatives with the feasible promise to generate anti-addiction, analgesic, or antidepressant agents.

Even if a wide inter-level approach can be scientifically justified and undertaken in the psychopharmacology of psychodysleptic or consciousness-altering drugs, there are other methodological challenges to tackle in terms of the psychophysical correlation between brain and conscious processes. The present balance between neural and psychological tools is clearly slanted in favor of the technically-sophisticated neurosciences and the relative scarcity of techniques and instruments to reliably ascertain the subjective mental effects of psychotropic substances. Phenomenological interview tools developed by classic European psychiatrists were used, among others, by my initial teacher and mentor, professor Dionisio Nieto, to carefully describe the mental effects of the mushroom *Stropharia cubensis* [35] and psilocybin [36]. But these resources have been marginalized by standardized questionnaires that are now difficult to apply due to the fact that many of the plants and drugs are controlled and many times wrongly categorized as addicting or potentially dangerous. The feasibility of well-calibrated first-person phenomenological tools has been reviewed and redefined in the neurophenomenological approach of Francisco Varela [37] and the narratological model [33,38].

The field of the clinical psychopharmacology of consciousness-altering drugs is problematic. There is still considerable confusion concerning the mental effect profiles of the different compounds, and the terms psychodysleptic, psychedelic, mind-expanding, psychotomimetic, consciousness-altering, hallucinogenic, entheogen, narcotic, stupeficient, and others are used without a clear agreed-upon consensus or even a distinctive denotation. With a proper operational definition many if not all of these terms would be useful to convey restricted, specific, and understandable meanings in the wide screen of the psychoactive spectrum. It is necessary to characterize with reliable phenomenological tools the mental effects and profiles of the different drugs in order to typify their psychological pattern and to correlate well-established mental effects with the known mechanisms of brain action particularly at the highest leaves of integration, where consciousness probably emerges along with a possible swarm-like trans-modular function [20, 33].

Even if these requisites are already difficult to fulfill, there is an even greater challenge to explain the diverse mental effects of the same plant or drug in persons and circumstances of different cultures [39]. An ethnographic neuroscience approach⁷ applied to study sacred plants actions comparatively among such subjects could shed some light about the role that belief systems, set and setting, and other cultural variables have in determining the contents of consciousness. Perhaps in this way it would be possible to approach and understand the existential interest and even fascination that the traditional and modern ingestion of these remarkable plants and compounds exert upon their users and that not only produced, refined and maintained for many

⁷The concept of ethnographic neuroscience was introduced by Roberto Mercadillo in 2011.

centuries shamanic practices in dozens traditional cultures in the Americas, but also played a kindling role in the western cultural revolution that developed in the 1960's and remains to be the source of genuine interest among diverse groups of developed present-day countries and societies. Such a heuristic avenue to tackle the mind-body problem concerning unusual but ascertainable consciousness states and their neural correlates could be tackled only if these legitimate research endeavors are appreciated and encouraged.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

During the 1973-1983 initial project on the ethnopharmacology of *Salvia divinorum* and other (at that time), obscure Mexican hallucinogens I had the great privilege of receiving the advice and obtaining the friendship of the late R. Gordon Wasson (1898-1986), and Richard Evans Schultes (1915-2001) from the Botanical Museum of Harvard University, of Efrén de Pozo (1907-1979) and Alfredo López Austin from the National University of Mexico and from Salomón Nahmad, the Director of the Instituto Nacional Indigenista. I thank professor Ara Paul for his reading and corrections of this manuscript. I also thank my former student Héctor Vargas-Pérez for his enduring friendship and at this point for his invitation to write this chapter and his aid in its preparation.

REFERENCES

- Wasson RG, Cowan G, Cowan F, Rhodes W. María sabina and her mazatec mushroom velada. Harcourt Brace Jovanovich; 1974.
- Johnson JB. The elements of mazatec witchcraft. Göteborg Etnografiska Museum Ethnologiska Studier ed. 1939.
- Reko BP. Mitobotánica zapoteca. General León 9; 1945.
- Weitlaner RJ. Curaciones mazatecas. Anales Del Museo Nacional De México 1952(4): 279-85.
- Epling C, Játiva-M CD. A new species of salvia from mexico. Botanical Museum Leaflets Harvard University 1962; 20(3): 75-6.
- Wasson RG. A new mexican psychotropic drug from the mint family. Botanical Museum Leaflets Harvard University 1962; 20(3): 77-84.
- Díaz JL. Etnofarmacología de plantas alucinógenas latinoamericanas. In: Díaz JL, editors. Etnofarmacología de plantas alucinógenas psicotrópicas latinoamericanas. Mexico: Cuadernos Científicos del Centro Mexicano de Estudios en Farmacodependencia; 1975. p. 135-201.
- Valdes LJ, Díaz JL, Paul AG. Studies of salvia divinorum (lamiaceae), an hallucinogenic mint from the sierra mazateca in oaxaca, central mexico. Economic Botany 1983; 41(2): 283-91.
- Schultes RE, Hofmann A. Plants of the gods: Origins of hallucinogenic use. New York: A. van der Marck Editions; 1987.
- Schultes RE, Hofmann A. The botany and chemistry of hallucinogens. Springfield, Ill.: Thomas; 1980.
- Fagetti A. Iniciaciones, trances, sueños--: Investigaciones sobre el chamanismo en México. Instituto de Ciencias Sociales y Humanidades "Alfonso Velez Pliego" Buap; 2010.
- De la Garza M. Sueño y alucinación en el mundo nahuatl y maya. illustrated ed. México, D.F.: UNAM; 1990.
- Ortega A, Blount JF, Manchand PS. Salvinorin, a new trans-neoclerodane diterpene from salvia divinorum (labiateae). J. Chem. Soc., Perkin Trans. 1 1982(0): 2505-8.
- Valdes LJ, Butler WM, Hatfield GM, Paul AG, Koreeda M. Divinorin A, a psychotropic terpenoid, and divinorin B from the hallucinogenic mexican mint, salvia divinorum. J. Org. Chem 1984; 49(24): 4716-20.
- Díaz JL. Ethnopharmacology of sacred psychoactive plants used by the indians of Mexico. Annu Rev Pharmacol Toxicol 1977; 17(1): 647-75.
- Díaz JL. Ethnopharmacology and taxonomy of mexican psychodysleptic plants. J Psychoactive Drugs 1979; 11(1-2): 71-101.
- Siebert DJ. Salvia divinorum and salvinorin A: New pharmacologic findings. J Ethnopharmacol 1994; 43(1): 53-6.
- Ott J. Ethnopharmacognosy and human pharmacology of salvia divinorum and salvinorin A. Curare 1995; 18(1): 103-29.
- Weil A. Pharmacology of consciousness: A narrative of subjective experience. In: Hammeroff SR, Kaszniak AW, Scott AC, editors. Toward a Science of Consciousness. Cambridge, Massachusetts: MIT Press; 1996. p. 677-89.
- Díaz JL. The stream revisited: A process model of phenomenological consciousness. In: Hammeroff SR, Kaszniak AW, Scott AC, editors. Toward a Scientific Basis of Consciousness. Cambridge, Massachusetts: MIT Press; 1996. p. 713-24.
- Valdés LJ. Salvia divinorum and the unique diterpene hallucinogen, salvinorin (divinorin) A. J Psychoactive Drugs 1994; 26(3): 277-83.
- González D, Riba J, Bouso JC, Gómez-Jarabo G, Barbanj MJ. Pattern of use and subjective effects of salvia divinorum among recreational users. Drug Alcohol Depend 2006; 85(2): 157-62.
- Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, et al. Salvinorin A: A potent naturally occurring nonnitrogenous kappa opioid selective agonist. Proc Natl Acad Sci U S A 2002; 99(18): 11934-9.
- Chavkin C, Sud S, Jin W, Stewart J, Zjawiony JK, Siebert DJ, et al. Salvinorin A, an active component of the hallucinogenic sage salvia divinorum is a highly efficacious kappa-opioid receptor agonist: Structural and functional considerations. J Pharmacol Exp Ther 2004; 308(3): 1197-203.
- Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science 2009; 323(5916): 934-7.
- Knoll AT, William AAC. Dynorphin, stress, and depression. Brain Res. 2010; 1314(0): 56 - 73.
- Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. Science 1986; 233(4765): 774-6.
- Braida D, Limonta V, Pegorini S, Zani A, Guerini-Rocco C, Gori E, Sala M. Hallucinatory and rewarding effect of salvinorin A in zebrafish: Kappa-opioid and cb1-cannabinoid receptor involvement. Psychopharmacology (Berl) 2007; 190(4): 441-8.
- McCurdy CR, Sufka KJ, Smith GH, Warnick JE, Nieto MJ. Antinociceptive profile of salvinorin A, a structurally unique kappa opioid receptor agonist. Pharmacol Biochem Behav 2006; 83(1): 109-13.
- Potter DN, Damez-Werno D, Carlezon WA, Cohen BM, Chartoff EH. Repeated exposure to the kappa-opioid receptor agonist salvinorin A modulates extracellular signal-regulated kinase and reward sensitivity. Biol Psychiatry 2011; 70(8): 744-53.
- Huxley A. The doors of perception: And heaven and hell. Vintage Digital; 2010.
- Paz O. Conocimiento, drogas, inspiración. In: Obras completas volumen 2: Excursiones/Incuriones: dominio extranjero. Mexico: Fondo de Cultura Económica. p. 238-72.
- Díaz JL. La conciencia viviente. Mexico: Fondo de Cultura Económica; 2007.
- DePaoli AM, Hurley KM, Yasada K, Reisine T, Bell G. Distribution of kappa opioid receptor mRNA in adult mouse brain: An in situ hybridization histochemistry study. Mol Cell Neurosci 1994; 5(4): 327-35.

- [35] Nieto D. Psicosis experimentales. Efectos psíquicos del hongo *stropharia cubensis* de Oaxaca. *Neurol. Neurocir. y Psiquiat* 1959; 1: 6-12.
- [36] Nieto D. Psicosis experimentales con psilocibina. *Neurol. Neurocir. y Psiquiat* 1962; 3: 140-6.
- [37] Varela FJ. Neurophenomenology: A methodological remedy for the hard problem. *J Conscious Stud* 1996; 3(4): 330-49.
- [38] Díaz JL, Paniagua R, Díez-Martínez E. El texto fenomenológico como objeto de análisis de procesos conscientes. *Salud Mental* 1998; 21(1): 14.
- [39] Dobkin de Rios M. Una teoría transcultural del uso de los alucinógenos de origen vegetal. *Am Indig* 1977; 37(2): 251-304.

Received: July 13, 2012

Revised: October 31, 2012

Accepted: November 28, 2012