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Dear Honorable Doctor Manuel Mondragón y Kalb:

This letter summarizes the important medicinal properties of the plant *Salvia divinorum* and its primary active constituent salvinorin A. It also puts forth several objections to the information published by the Comisión Nacional Contra las Adicciones, where the proposal is described (I am citing textually): "Proposal of Inclusion of Salvia Divinorum and Salvinorin A in the list of substances with psychotropic effects that are included in the article 245 of the General Law of Health (where mescaline is enlisted) in section I".

For the last seven years, I have been studying *Salvia divinorum* and salvinorin A in depth. I hold a graduate degree on Psychology, a postgraduate degree on Neuroscience, and I am a Pharmacology PhD candidate at the Autonomous University of Barcelona. Both my postgraduate degree final work and my doctoral thesis analyze the human pharmacology of *Salvia divinorum* and salvinorin A. I have been working in two research experiments where we have given increasing doses of salvinorin A to healthy volunteers, in the Human Neuropsychopharmacology Department at the Santa Creu y Sant Pau Hospital at Barcelona. In experiments I am in collaboration with other researchers like Jordi Riba PhD, the director of the department, and Peter H. Addy PhD of Yale University.

During the last four years, I have been doing fieldwork where *Salvia divinorum* is endemic, at the Sierra Madre Oriental in Oaxaca. In concrete at the area inhabited by the Mazatec people, who has been using this plant for centuries for its medicinal properties. During my ethnobotanical work with Mazatec, I have done interviews and gathered scientific data documenting the current uses of *Salvia Divinorum,* which Mazatec know in their language as "Xka Pastora" (xka means leaf or herb).

The use of *Salvia divinorum* or "Xka Pastora" by the Mazatec is fully alive nowadays. The Mazatec traditional doctors use the leaves of the plant as efficient treatments for diverse diseases, as well as for ceremonies where they modify their awareness, being able of diagnose illness, and to solve problems in their communities.

My ethnobotanical research has led me to create the NGO 'Xka Pastora. International Center for Research and Ethnobotanical Conservation of *Salvia divinorum'.* The objectives of the NGO are: 1) to promote scientific research of *Salvia divinorum* and to integrate its traditional therapeutics in western medicine 2) to realize and to promote ethnobotanical research that compiles and conserves the native knowledge 3) to divulge and educate with objective and accurate information on *Salvia divinorum* and salvinorin A 4) to guarantee the conservation of the botanical species *Salvia divinorum.*

By all the exposed, I consider myself qualified to present the following facts about *Salvia divinorum:*

Medicinal properties

There are approximately one thousand species of *Salvia* worldwide. The genus name *Salvia* is

derived from the Latin *salvare,* meaning “to heal” or “to save”. The words *salvation* and *savior* also come from this same root. *Salvia divinorum* is one of the many species of salvias that are recognized for their multiple medicinal properties.

Mexico has the fifth highest botanical richness in the world. It contains twenty per cent of the botanical species of the entire planet, and more than half are endemic to Mexico. Among them, *Salvia divinorum* is endemic to the Mazatec area, on the mountains of the Sierra Madre Oriental of Oaxaca. The Mazatec people use this plant for its psychoactive properties, and as an effective treatment for arthritis and inflammation, headaches, gastrointestinal problems, addictions, and eliminatory complaints. The validity of each of these different applications is well supported by recent pharmacological findings.

Salvinorin A is a terpene found in the leaves of the plant *Salvia divinorum*. It is a uniquely potent and highly selective kappa-opioid receptor agonist, and as such, it has tremendous potential for the development of a wide variety of valuable medications. Among them, the most promising of these include safe non-addictive analgesics, antidepressants, anti-inflammatories, neuroprotectors, short-acting anesthetics that do not depress respiration, medications for the treatment of addiction to stimulants and alcohol, drugs to treat disorders characterized by alterations in perception, including schizophrenia, Alzheimer’s disease, and bipolar disorder, and drugs to treat diverse types of tumors.

Kappa-opioid receptor agonists are of particular interest to pharmacology because they provide effective pain medications that are not habit forming and do not produce dependence. In fact, there is a growing body of evidence that indicates that kappa-opioid agonists are actually “aversive” (the opposite of addictive). This is an important advantage over most powerful analgesics currently prescribed. The effectiveness of salvinorin A as an analgesic has been repeatedly demonstrated in animal studies. Salvinorin A also has anti-inflammatory properties. The traditional Mazatec use of *Salvia divinorum* to treat headaches and arthritis also attests to its effectiveness as an analgesic and as an anti-inflammatory.

The ability of salvinorin A to block perception of pain also suggests that it may prove useful as a short-acting general anesthetic. The fact that it does not depress respiration is particularly interesting because it indicates that salvinorin A could be much safer than most general anesthetics currently in use.

Dr. Karl Hanes published a case report in the *Journal of Clinical Psychopharmacology* in which he described a patient that obtained relief from chronic depression by using *Salvia divinorum.* Subsequently he published another paper reporting that he obtained similarly positive results when he prescribed the herb to other patients who suffered from clinical depression. It is especially interesting that these people were able to obtain persistent relief from their depression after only a few treatments. *Salvia divinorum* often produces long-lasting clinical improvement, quite unlike conventional antidepressants such as Prozac, which in most cases only offer symptomatic relief from depression and require a continuous medication regimen.

Salvinorin A has been proven to protect the brain from injuries in hypoxia and ischemia, reducing neonatal deaths in animal research.

Salvinorin A inhibits intestinal motility and reduces abdominal pain in irritable bowel syndrome, which is in concordance with the traditional Mazatec uses.

Because salvinorin A alters various perceptual modalities by acting on kappa-opioid receptors, it is clear that these receptors play a prominent role in the modulation of human perception. This suggests the possibility that novel psychotherapeutic compounds derived from salvinorin A could be useful for treating diseases manifested by perceptual distortions (e.g., schizophrenia, dementia, and bipolar disorder). This is a promising area of research that is important to pursue further.

Terpenes found in *Salvia divinorum* and other Salvia species have anti-cancer properties for diverse types of tumors. When tumors are present in the brain, one difficulty of medications is to cross the

blood-brain barrier and to reach the tumor. The terpene salvinorin A is capable of crossing the blood-brain barrier in less than a minute and to reach tumors in the encephalon and in other structures of the Central Nervous System. Analogs of salvinorin A has shown anti-proliferative properties inhibiting the grown of 77-86% of tumoral cells in breast cancer.

Salvia divinorum has several properties that make it useful in psychotherapy: It produces a state of profound self-reflection, it improves one's ability to retrieve childhood memories, and it provides access to areas of the psyche that are ordinarily difficult to reach. This type of application is not new: the Mazatec have long used *Salvia divinorum* to treat psychological complaints, creating a dialog between healer and patient until the problem and the possible solution is found.

Salvinorin A is also an important neurochemical probe for studying the dynorphin/kappa-opioid-receptor system. As such, it is useful for research into the neurological mechanisms of perception and awareness. Salvinorin A is remarkable in that it belongs to an entirely different chemical class than any previously identified opioid receptor ligand. This fact is of great interest to pharmacologists because it opens up a vast new area for future drug development.

No potential for long-term abuse

There are many popular misconceptions about *Salvia divinorum*. Presumably, the CONADIC proposal is based on some of these, and on a lack of actual information. Many of these misconceptions have their origins in sensationalistic stories presented by misinformed journalists.

The fact is that the effects of *Salvia divinorum* are not appealing to recreational drug users. The DEA (Drug Enforcement Administration) concluded that the majority of people who try it find that they do not enjoy its effects and do not continue using it. Salvia's potential to induce anxiety is limited by its brief duration of effects, which can be interrupted or terminated by speaking to the affected person or introducing other noise stimuli.

It does produce an altered state of awareness, but does not produce euphoria or stimulation. The scientific research, conducted with volunteers with previous experience in the use of psychoactive substances who were given smoked *Salvia divinorum* or pure vaporized salvinorin A, shows that participants almost unanimously reported that the effects are different to any other psychoactive compound previously experienced.

Salvia divinorum produces a state of increased self-awareness. For this reason, some people use it as an aid to meditation, contemplation, and spiritual reflection. There are people who are intrigued by salvia's effects, but even these people use it infrequently. Because it increases self-awareness, it is useless as an escapist drug. When used in a careless manner, it tends to produce unpleasant experiences, and that of course discourages further use.

Salvia divinorum is not addictive or habit forming. This has been demonstrated in several animal studies, and it has been recently reconfirmed in a study published on January 2015 in the *Journal of Psychopharmacology*. In the study (Serra et al., 2015), researchers conclude that even if salvinorin A affects dopamine transmission on the nucleus accumbens, it is different to other compounds that act on the same brain area and that have abuse potential: Salvinorin A is unable to sustain or to maintain stable self-administration behavior in animals.

In fact, animal research shows that salvinorin A has anti-addictive properties. Current research for the development of drugs to treat addictions to stimulants like cocaine, and to alcohol addiction, shows that salvinorin A could be very promising for these diseases. Once again, this is not new: Mazatec use the leaves of *Salvia divinorum* to treat addiction to alcohol and to volatile solvents.

Safety

Salvia divinorum is non-toxic. Toxicological studies have been performed by Dr. Leander Valdés at the University of Michigan, Jeremy Stewart at the University of Mississippi, Dr. Frank Jaksch of Chromadex Inc., and Dr. Wayne Briner at the University of Nebraska.

Neither *Salvia divinorum* nor salvinorin A showed toxicity in any of these studies.

No toxic effects to any organs or organ systems have resulted from either acute or long-term administration of the substance to animals, even at doses much higher than any human would ever ingest.
No overdose or deaths have been reported because of *Salvia divinorum* consumption.
There is a vast body of empirical evidence that indicates *Salvia divinorum* is a remarkably safe herb. Indeed, the Mazatec, who have been using for centuries amounts of *Salvia divinorum* leaves that vary from a pair to hundreds of them, do not attribute any toxic properties to this plant.

Conclusions

Salvia divinorum has a wide variety of therapeutic potentials and holds an enormous medicinal value.

Salvia divinorum does not present a significant risk to public health or safety. It does not have potential for long-term abuse. It does not have toxicity.

Salvia divinorum does not meet the criteria exposed on the General Health Law of the United Mexican States, Chapter VI about psychotropic substances, article 245, section I: "The ones that have scarce or does not even have therapeutic value and, by their potential of misuse or abuse, are an especially serious problem for public health". *Salvia divinorum* neither meet the criteria to be included in any of the other cases contemplated on the next sections of article 245.

The inclusion of *Salvia divinorum* or salvinorin A on regulatory lists of substances is not scientifically justified.

The Global Inform about Drugs published on 2014 by the United Nations Office on Drugs and Crime does not allude or mention *Salvia divinorum* or salvinorin A.

Placing it in regulatory lists would seriously hamper promising medical research. Because of its complex stereochemistry, salvinorin A is virtually impossible to produce synthetically. It is important that its source plant, *Salvia divinorum,* remains available so that researchers can continue to study this important compound. Taking into account that *Salvia divinorum* is endemic to Mexico, the study of the genetic diversity in its habitat of origin could lead to new medical applications that would continue to alleviate human suffering.

It is of **utmost importance** to understand the fact that *Salvia divinorum* rarely produce seeds: it has a very low viability rate of reproduction in the wild. *Salvia divinorum* spreads by cuttings made by humans, so the plant depends on our interest to survive. As such, the prohibition of the use, cultivation, consumption, ownership or management of *Salvia divinorum* in the country where it is endemic, Mexico, could lead to its eventual extinction.

We owe to the Mazatec people that this plant has survived until now. By the cultivation of cuttings in their homes and lands during generations over the centuries, the Mazatec have made it possible for all humankind to know its medicinal properties.

I appreciate your taking the time to read this letter. Please feel free to contact me if I can provide you with any additional information.

Sincerely,

Ana Elda Maqueda Sánchez

In Barcelona, May 21, 2015

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