

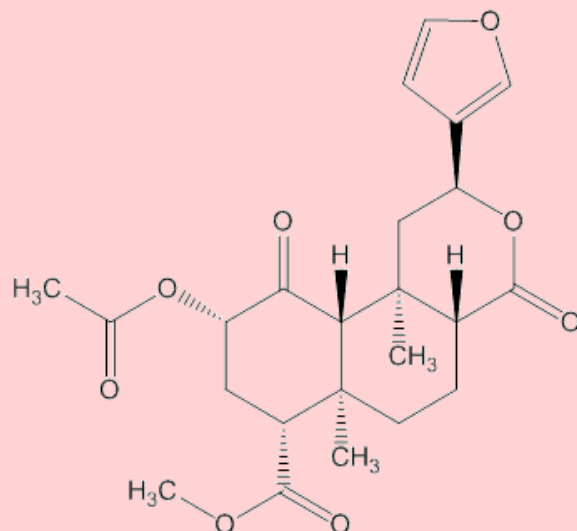
Salvinorin A

The key ingredient in Mexican Magic Mint.

Simon Cotton
University of Birmingham

Molecule of the Month July 2014

Also available: [JSMol](#) version.



Nice bit of alliteration, but what does that mean?

Mexican Magic Mint is a member of the mint family (and sage genus), *Salvia divinorum*, which is used by the Mazatec Indians of northeastern Oaxaca, a province in southern Mexico; it is either chewed or crushed with water and drunk, as a "herbal tea". Some, like the great ethnobotanist [Gordon Wasson](#), think that it was the narcotic *Pipiltzintzintli* used by the Aztecs, though this may actually have been cannabis. Unlike "magic mushrooms", whose active ingredient is psilocybin ([MOTM October 1999](#)), *Salvia divinorum* has only been described relatively recently.



Mexican Magic Mint - *Salvia divinorum*



Gordon Wasson

Why do they eat it?

Salvia divinorum is a member of the sage family, most familiarly illustrated by common or garden sage, *Salvia officinalis*, used in sage and onion stuffing, for example. But *Salvia divinorum* contains an entheogen, Salvinorin A, a psychoactive stimulant that brings on mystical experiences. Mazatec shamans used *Salvia divinorum* to induce visionary states for divinatory rituals; it is said to have a shorter duration than hallucinatory mushrooms. It also has some medicinal applications for the Mazatec (e.g. treating diarrhoea and rheumatism). It has been said that it is the most potent naturally occurring psychoactive drug known to humans.

How does it do that?

Salvinorin A is a kappa-opioid-receptor agonist.

Pardon?

Opioid receptors are the sites where the body's natural painkillers like endorphins bind, and where opiate drugs like morphine also have their effect. There are several types (delta, kappa and mu) of opioid receptors, each favoured by different opiates; heroin and morphine bind to the mu receptors, for example. The kappa receptors occur in areas like the brain and spinal cord. An agonist is a molecule that binds to a receptor and produces a response.

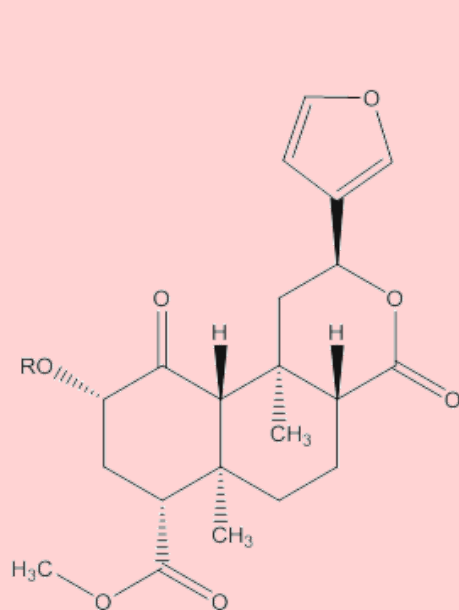


So if there are other kappa-opioid-receptor agonists around, what is special about Salvinorin A?

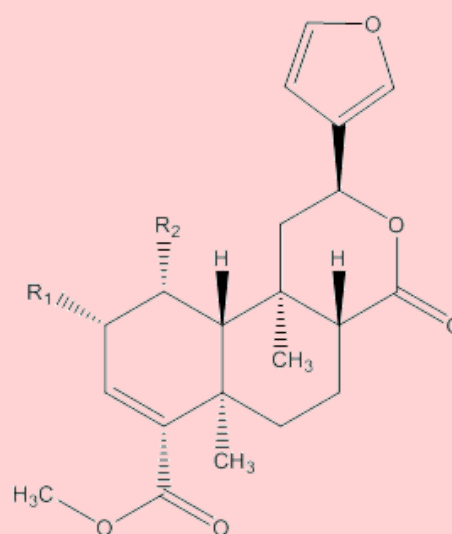
It is the first compound discovered to act upon this receptor that isn't an alkaloid. Hallucinogens like this usually act on a serotonin receptor. It is also reportedly about the most potent natural psychoactive drug known. It seems to have similar potency to LSD, but acts in a different way

If this is Salvinorin A, presumably there are other molecules like it?

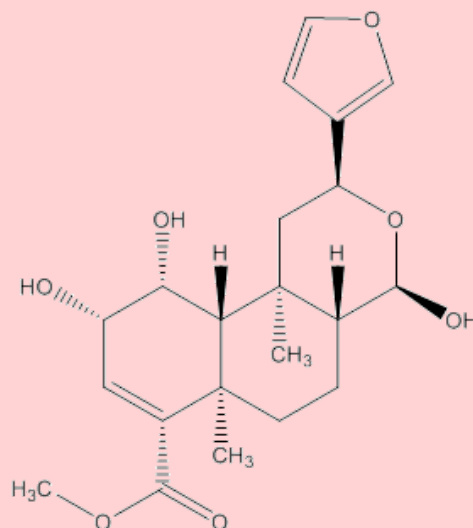
Yes and no. Chemists have isolated other molecules with the same core structure, but none have any psychoactive properties. It appears that the methyl-ester group and also the five-membered furan ring are essential to its activity. Salvinorin B is quite inactive.



Salvinorin A, R: CH₃CO
Salvinorin B, R: H



Salvinorin C: R₁: CH₃COO; R₂: CH₃COO
Salvinorin D: R₁: CH₃COO; R₂: OH
Salvinorin E: R₁: OH; R₂: CH₃COO
Salvinorin F: R₁: OH; R₂: H
Salvinorin G: R₁: =O; R₂: CH₃COO
Salvinorin H: R₁: OH; R₂: OH



Salvinorin I

So why has it been in the news?

It has gained a lot of publicity through exposure of its use on YouTube, and politicians have reacted to this. Long before she twerked, Miley Cyrus (photo, right) celebrated her 18th birthday at a party, after which a video of her using a bong (allegedly smoking salvia) was widely circulated.



Isn't that illegal?

It is illegal in over half the states of the U.S.A., but not in California. It has been banned in a number of countries, including Australia, Japan and several European countries, including Belgium, Denmark, Germany, Italy, Poland, Sweden and Switzerland. It is still legal in the UK, though.

What does it do?

Salvia has been described like this: - "It looks like a cross between sage and mint. It smells like herbal tea. It's also a more powerful hallucinogen than LSD". Its effects seem qualitatively different from other hallucinogens. People taking it sometimes report feelings of madness but some effects seem frequent, involving distortion of perception, such as moving in a particular direction like spinning or stretching; interacting with strange entities or beings; cartoon-like images and revisiting childhood memories. People taking it can lose control of their bodies, and are advised always to take it seated or lying down, and to have a companion who is not taking the drug. It is metabolised quickly and rapidly disappears from the system.

Is it really safe?

Tests show that at the doses used, there is no effect on blood pressure or heart rate. It has been linked with the suicide of one American teenage boy, whilst in testing in rats, salvinorin A has been shown to have bad effects on learning and memory. Part of the problem is that when it is still legal, people will argue that because it is a natural, "herbal" substance, it must be safe to take. Scientists want to be able to carry on testing it as it might be a lead molecule for making other pharmaceuticals.

And overall?


At present, there is no scientific evidence that it is toxic to humans, but not all people taking it have had good experiences. But it is worth remembering that the fact that a chemical is "natural" does not necessarily mean that it is a good thing.

Bibliography

- A. Ortega, J. F. Blount and P. D. Manchard, *J. Chem. Soc., Perkins Transactions I*: 1982, 2505–2508 (crystal structure of Salvinorin A)
- L. J. Valdes, J. L. Diaz and A. G. Paul, *J. Ethnopharmacol.*, 1983, **7**, 287–312 (review of its ethnopharmacology)
- B. L. Roth, K. Baner, R. Westkaemper, D. Siebert, K. C. Rice, S. Steinberg, P. Ernsberger and R. B. Rothman, *PNAS*, 2002, **99**, 11934–11939 (Salvinorin A binds to kappa-receptor)
- T. A. Munro and M. A. Rizzacasa, *J. Nat. Prod.* 2003, **66**, 703–705 (Salvinorins D-F)
- C. Chavkin, S. Sud, W. Jin, J. Stewart, J. K. Zjawiony, D. J. Siebert, B. A. Toth, S. J. Hufeisen *et al.*, *J. Pharm. Exp. Ther.*, 2004, **308**, 1197–203 (Salvinorin A as a κ -Opioid Receptor Agonist)
- T. E. Prisinzano, *Life Sciences*, 2005, **78**, 527–531 (review of psychopharmacology of *Salvia divinorum*).
- T. A. Vorthers and B. L. Roth, *Mol. Interv.*, 2006, **6**, 257–265
- W. W. Harding, M. Schmidt, K. Tidgewell, P. Kannan, K. G. Holden, C. M. Dersch, R. B. Rothman and T. E. Prisinzano, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3170–3174; W. W. Harding, M. Schmidt, K. Tidgewell, P. Kannan, K. G. Holden, B. Gilmour, H. Navarro, R. B. Rothman and T. E. Prisinzano, *J. Nat. Prod.*, 2006, **69**, 107–112 (syntheses and reactions)
- J. R. Scheerer, J. F. Lawrence, G. C. Wang and D. A. Evans, *J. Am. Chem. Soc.*, 2007, **129**, 8968–8969 (synthesis of Salvinorin A)
- Philip Sherwell, "[Salvia: more powerful than LSD, and legal](#)", Daily Telegraph (UK), 29 March 2009
- D. Braida, A. Donzelli, R. Martucci, V. Capurro and M. Sala, *Int. J. Toxicol.*, 2011, **30**, 650–661. (learning and memory impairment in rats)
- J. Listos, A. Merska and S. Fidecka, *Pharmacol. Rep.*, 2011, **63**, 1305–9 (pharmacological activity of salvinorin A)
- M. W. Johnson, K. A. MacLean, C. J. Reissig, T. E. Prisinzano and R.R. Griffiths, *Drug Alcohol Depend.*, 2011, **115**, 150–155; K. A. MacLean, M. W. Johnson, C. J. Reissig, T. E. Prisinzano and R. R. Griffiths, *Psychopharmacology*, 2013, **226**, 381–392 (dose-related effects of salvinorin A)
- H. Wu, D. Wacker, M. Mileni, V. Katritch, G. W. Han, E. Vardy, W. Liu, A. A. Thompson, X.-P. Huang, F. I. Carroll, S. W. Mascal, R. B. Westkaemper, P. D. Mosier, B. L. Roth, V. Cherezov and R. C. Stevens, *Nature*,

2012, **485**, 327-332. (Structure of the human κ -opioid receptor)

- J. L. Diaz, *Current Drug Abuse Reviews*, 2013, **6**, 43-53. (review of its ethnopharmacology)
- E. Vardy, P. D. Mosier, K. J. Frankowski, H. Wu, V. Katritch, R. B. Westkaemper, J. Aubé, R. C. Stevens and B. L. Roth, *J. Biol. Chem.*, 2013, **288**, 34470-34483. (structural features of κ -Opioid-Receptor Agonists)

 [Back to Molecule of the Month page.](#)

[DOI: [10.6084/m9.figshare.5259124](https://doi.org/10.6084/m9.figshare.5259124)]

 000012