

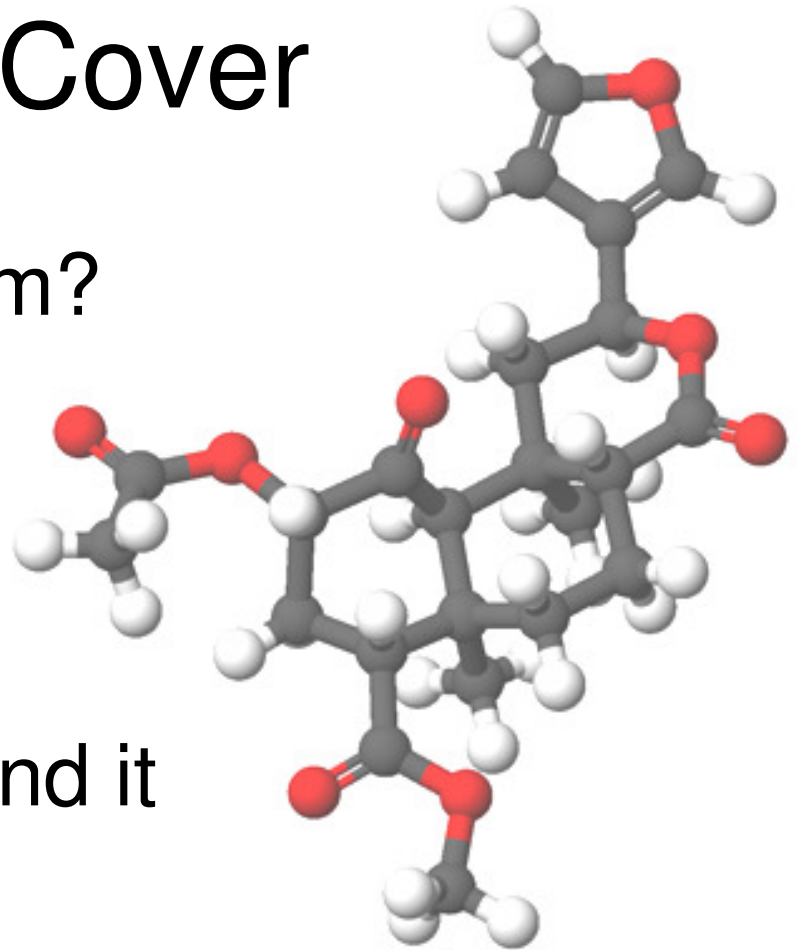
A photograph of several potted Salvia Divinorum plants. The plants are lush green with serrated leaves and are growing in terracotta pots. The background is a plain, light-colored wall.

# **Salvia Divinorum**

**John Clarke**

# Topics To Cover

- What is Salvia Divinorum?
- Brief history
- Traditional Use
- Effects
- The pharmacology behind it
- Clinical Significance



# What Is Salvia Divinorum?

- *A very potent hallucinogen!*
- Name → “Sage of the Seers”
- Member of the Mint family (Lamiaceae)
  - Along with a lot of common herbs such as basil, common mint, rosemary, common sage (**Salvia** genus), thyme, etc
- Native to Oaxaca region of Mexico



# Brief History

- Extensive use with the Mazatec people
- Traditions involve many other entheogenic plants and fungi
- Used to facilitate shamanic visions
  - Healing
  - Divination



*Maria Sabina*

# Brief History

- Also used remedially for a number of ailments
  - Diarrhoea
  - Headaches
  - Rheumatism

# Traditional Use

- Very ritualistic/ceremonial
  - Never taken recreationally
- How
  - Chewing fresh leaves
  - Drinking an extract prepared from crushed leaves
  - Little evidence for smoking
    - Active compound has high vaporisation temp
    - No butane lighters



# Effects

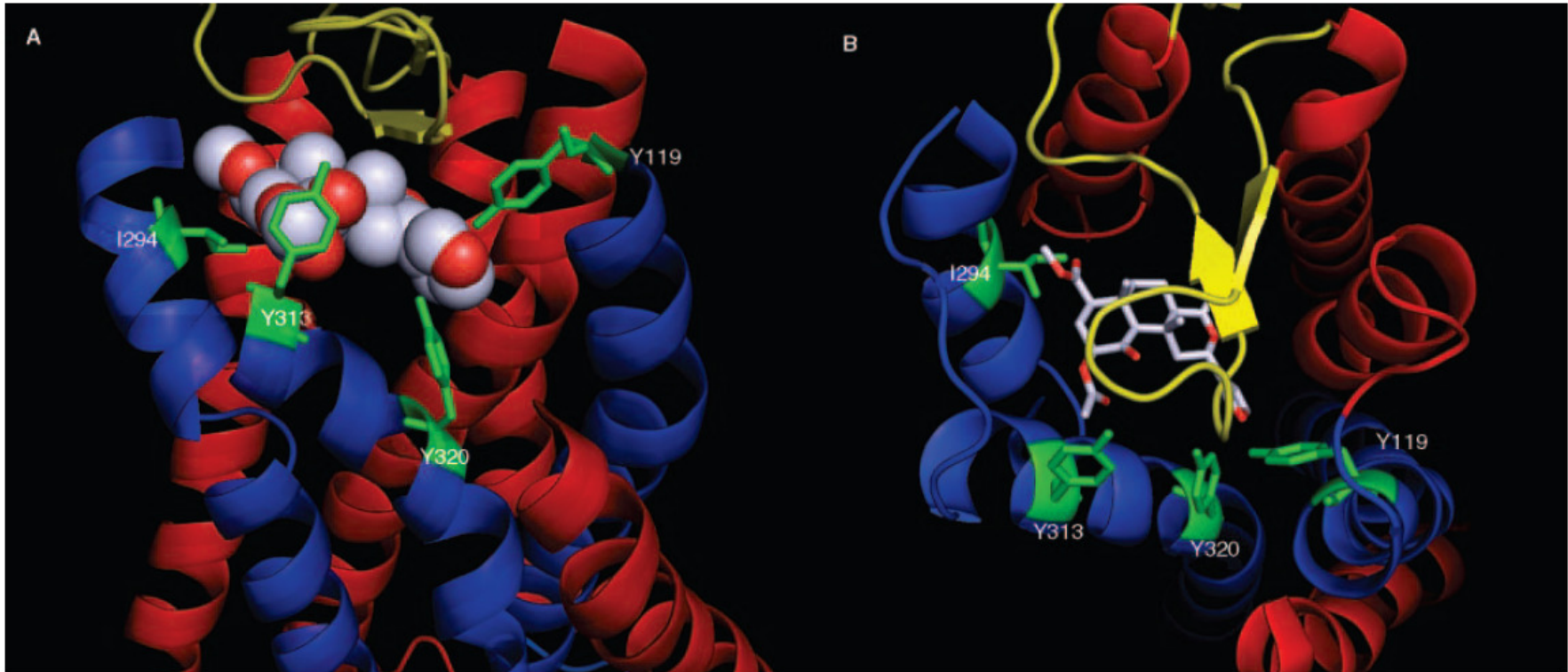
- Uncontrollable laughter
- Recollection of past memories
- Mind/body dissociation
- Sensations of motion/pressure
- Visions of membranes, films and various two-dimensional surfaces
- Merging with/becoming objects
- **Very unique – like no other hallucinogen**
- **Only lasts for 15 - 60mins!**

# Pharmacology

- Active compound: **Salvinorin-A**
- Chemical classification: **Diterpene**
  - Only known psychoactive diterpene
  - First non-nitrogenous hallucinogen to be identified
- Mechanism of action: **Agonist @ K – opioid receptors (KOR)**
  - Classical hallucinogens (eg LSD, Mescaline) act on 5-HT<sub>2A</sub> receptors
  - Other opioid receptor ligands tend to be alkaloids



# Receptor Binding



**Figure 4. Proposed KOR:salvinorin A binding complex.** Views are presented through the helical bundles (A) or from the extracellular side of KOR looking into the binding pocket of KOR (B). Salvinorin A is stabilized in the binding pocket through hydrogen bonding and hydrophobic interactions with Y119 (helix 2), Y313 and Y320 (helix 7), I294 (helix 6) (shown in green), and the second extracellular loop of KOR (shown in yellow). For clarity, some helical residues are not shown; figures were constructed using PyMOL.

(Vortherms & Roth, 2006)

# Pharmacology

- Very potent – active at doses as low as 200 micrograms
- Short duration – effects last for 15-60 mins
  - half life of Salvinorin-A in nonhuman primates is 56.6 ± 24.8 min

**A very unusual compound!**

# Clinical Significance

- Analgesia
  - Increased “tail flick” latencies in mice
  - Not seen with pre-treatment of KOR antagonist or with KOR knockout mice
    - (Proves KOR selectivity in vivo)
  - Other assays also show antinociceptive action of Salvinorin-A too
    - Hotplate assay
    - chemo-nociceptive acetic acid abdominal constriction assay

# Clinical Significance

- Diarrhoea
  - Originally used by Mazatec to stop diarrhoea
  - Recently shown to prevent myenteric cholinergic transmission in guinea pig ileum
  - Prevents contraction of smooth muscle

# Clinical Significance

- Depression
  - Selective KOR agonists show depressed behaviour in animals
  - Salvinorin-A shows similar results
    - Supports hypothesis that KOR signalling plays a role in depressive behaviours
  - **But**, there has been at least one report of using Salvia Divinorum to treat refractory depression!

**More work necessary!**

# Clinical Significance

- Drug Design
  - Salvinorin-A is a bit strange...
    - The first known non-nitrogenous KOR selective agonist
    - The first known non-alkaloidal hallucinogen
  - Chemical modification of Salvinorin-A has already lead to development of MOR selective agonists
    - May be modified further to produce other novel receptor-specific ligands

# Clinical Significance

- Hallucinatory Diseases (eg Alzheimer's and Schizophrenia)
  - Salvinorin-A (K agonist) → Hallucinations
    - (proof of KOR modulating our perception)
  - Could K antagonists be used clinically for diseases with prominent perceptual disturbances?

# References & Further Reading

- Papers

- Roth, B.L., Baner, K., Westkaemper, R., Siebert, D., Rice, K.C. Steinberg, S., Ernsberger, P. and Rothman, R.B. (2002) **Salvinorin A: A potent naturally occurring nonnitrogenous kappa opioid selective agonist.** *Proceedings of the National Academy of Sciences* 99, 11934–11939
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- Hanes, K.R. (2001) **Antidepressant Effects of the Herb Salvia Divinorum: A Case Report.** *Journal of Clinical Psychopharmacology* 21, 634-635
- Capasso, R., Borrelli, F., Capasso, F., Siebert, D.J., Stewart, D.J., Zjawiony, J.K., Izzo, A.A. (2006) **The hallucinogenic herb Salvia divinorum and its active ingredient salvinorin A inhibit enteric cholinergic transmission in the guinea-pig ileum.** *Neurogastroenterology & Motility* 18, 69–75

- Documentaries

- Sacred Weeds: Salvia Divinorum, 1998. Channel 4, 10th August 1998