Epilepsy Res. 2013 May;104(3):195-202. doi: 10.1016/j.eplepsyres.2012.11.006. Epub 2013 Jan 23.

Effects of cannabinoids and endocannabinoid hydrolysis inhibition on pentylenetetrazole-induced seizure and electroencephalographic activity in rats.

Vilela LR[1], Medeiros DC, Rezende GH, de Oliveira AC, Moraes MF, Moreira FA.

Author information

Abstract

Cannabinoids and drugs that increase endocannabinoid levels inhibit neuronal excitability and restrain epileptic seizures through CB1 receptor activation. Nevertheless, the results have not been entirely consistent, since pro-convulsant effects have also been reported. The present study aimed to further investigate the effects of cannabinoid-related compounds on seizures induced by pentylenetetrazole (PTZ) in rats. Video-EEG recordings were used to determine both electrographic and behavioral thresholds to ictal activity. The animals received injections of WIN-55,212-2 (0.3-3 mg/kg, non-selective) or ACEA (1-4 mg/kg, CB1-selective), two synthetic cannabinoids, or URB-597 (0.3-3 mg/kg), an anandamide-hydrolysis inhibitor (FAAH enzyme inhibitor), followed by PTZ. Both WIN-55,212-2 (1 mg/kg) and ACEA (1-4 mg/kg) reduced the threshold for myoclonic seizures and enhanced epileptiform EEG activity, typical pro-convulsive effects. On the contrary, URB-597 (1 mg/kg) had an anti-convulsive effect, as it increased the threshold for the occurrence of minimal seizures and reduced EEG epileptiform activity. None of the drugs tested altered the tonic-clonic maximal seizure threshold. These data suggest that the effects of CB1 signaling upon seizure activity may depend on how this receptor is activated. Contrary to direct agonists, drugs that increase anandamide levels seem to promote an optimal tonus and represent a promising strategy for treating myoclonic seizures.

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The Endogenous Cannabinoid System Regulates Seizure Frequency and Duration in a Model of Temporal Lobe Epilepsy

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Departments of Neurology (R.E.B., R.J.D.), Pharmacology and Toxicology (M.J.W., K.W.F., B.R.M., R.J.D.), and Molecular Biophysics and Biochemistry (R.J.D.), Virginia Commonwealth University, Richmond, Virginia

Received March 26, 2003; accepted June 16, 2003

ABSTRACT

Several lines of evidence suggest that cannabinoid compounds are anticonvulsant. However, the anticonvulsant potential of cannabinoids and, moreover, the role of the endogenous cannabinoid system in regulating seizure activity has not been tested in an in vivo model of epilepsy that is characterized by spontaneous, recurrent seizures. Here, using the rat pilocarpine model of epilepsy, we show that the marijuana extract Δ^9- tetrahydrocannabinol (10 mg/kg) as well as the cannabimimetic, 4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6*H*-pyrrolo[3,2,1-*i,j*]quinolin-6-one [*R*(+)WIN55,212 (5 mg/kg)], completely abolished spontaneous epileptic seizures. Conversely, application of the cannabinoid CB_1 receptor (CB_1) antagonist, *N*-(piperidin-1-yl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamidehydrochloride (SR141716A), significantly increased both seizure duration and frequency. In some animals, CB_1 receptor antagonism resulted in seizure durations that were protracted to a level consistent with the clinical condition status epilepticus. Furthermore, we determined that during an short-term pilocarpine-induced seizure, levels of the endogenous CB_1 ligand 2-arachidonylglycerol increased significantly within the hippocampal brain region. These data indicate not only anticonvulsant activity of exogenously applied cannabinoids but also suggest that endogenous cannabinoid tone modulates seizure termination and duration through activation of the CB_1 receptor. Furthermore, Western blot and immunohistochemical analyses revealed that CB_1 receptor protein expression was significantly increased throughout the CA regions of epileptic hippocampi. By demonstrating a role for the endogenous cannabinoid system in regulating seizure activity, these studies define a role for the endogenous cannabinoid system in modulating neuroexcitation and suggest that plasticity of the CB_1 receptor occurs with epilepsy.

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures

Nicholas A. Jones [a,b,*], Sarah E. Glyn [a,b], Satoshi Akiyama [b,c], Thomas D.M. Hill [a], Andrew J. Hill [a,b], Samantha E. Weston [a], Matthew D.A. Burnett [a], Yuki Yamasaki [b,c], Gary J. Stephens [a], Benjamin J. Whalley [a], Claire M. Williams [b]

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Motor function

ABSTRACT

Cannabis sativa has been associated with contradictory effects upon seizure states despite its medicinal use by numerous people with epilepsy. We have recently shown that the phytocannabinoid cannabidiol (CBD) reduces seizure severity and lethality in the well-established *in vivo* model of pentylenetetrazole-induced generalised seizures, suggesting that earlier, small-scale clinical trials examining CBD effects in people with epilepsy warrant renewed attention. Here, we report the effects of pure CBD (1, 10 and 100 mg/kg) in two other established rodent seizure models, the acute pilocarpine model of temporal lobe seizure and the penicillin model of partial seizure. Seizure activity was video recorded and scored offline using model-specific seizure severity scales. In the pilocarpine model CBD (all doses) significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD (≥10 mg/kg) significantly decreased the percentage mortality as a result of seizures; CBD (all doses) also decreased the percentage of animals experiencing the most severe tonic–clonic seizures. These results extend the anti-convulsant profile of CBD; when combined with a reported absence of psychoactive effects, this evidence strongly supports CBD as a therapeutic candidate for a diverse range of human epilepsies.

PeerJ. 2013 Nov 21;1:e214. doi: 10.7717/peerj.214. eCollection 2013.

Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression.

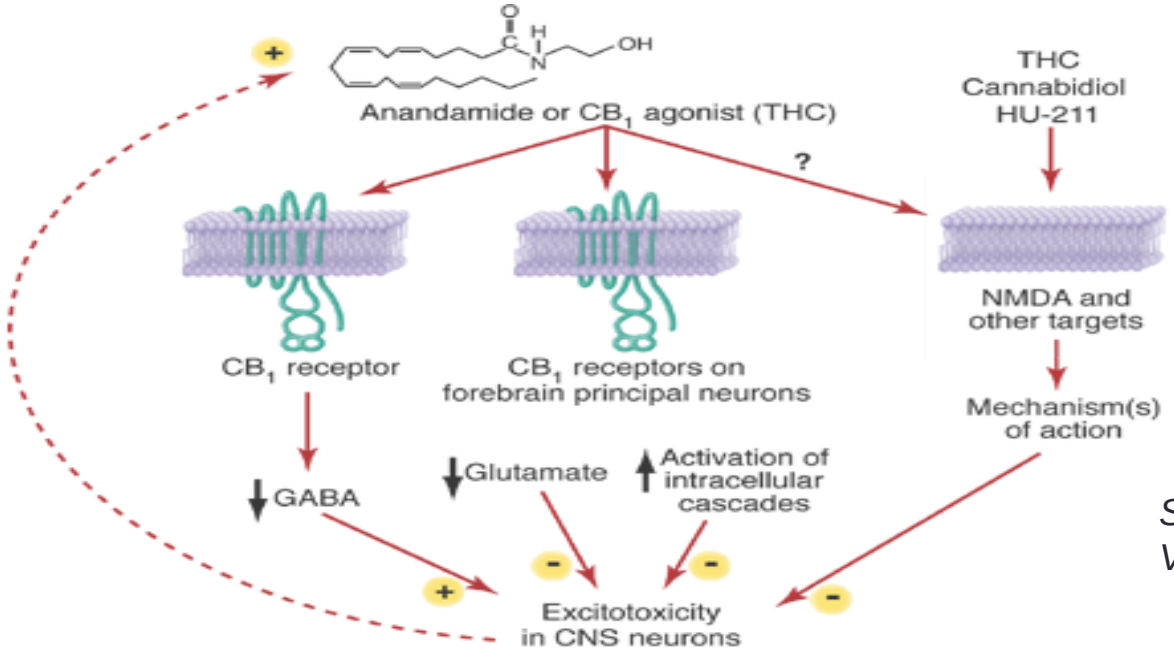
Amada N[1], Yamasaki Y, Williams CM, Whalley BJ.

Author information

Abstract

To date, anticonvulsant effects of the plant cannabinoid, cannabidivarin (CBDV), have been reported in several animal models of seizure. However, these behaviourally observed anticonvulsant effects have not been confirmed at the molecular level. To examine changes to epilepsy-related gene expression following chemical convulsant treatment and their subsequent control by phytocannabinoid administration, we behaviourally evaluated effects of CBDV (400 mg/kg, p.o.) on acute, pentylenetetrazole (PTZ: 95 mg/kg, i.p.)-induced seizures, quantified expression levels of several epilepsy-related genes (Fos, Casp 3, Ccl3, Ccl4, Npy, Arc, Penk, Camk2a, Bdnf and Egr1) by qPCR using hippocampal, neocortical and prefrontal cortical tissue samples before examining correlations between expression changes and seizure severity. PTZ treatment alone produced generalised seizures (median: 5.00) and significantly increased expression of Fos, Egr1, Arc, Ccl4 and Bdnf. Consistent with previous findings, CBDV significantly decreased PTZ-induced seizure severity (median: 3.25) and increased latency to the first sign of seizure. Furthermore, there were correlations between reductions of seizure severity and mRNA expression of Fos, Egr1, Arc, Ccl4 and Bdnf in the majority of brain regions in the CBDV+PTZ treated group. When CBDV treated animals were grouped into CBDV responders (criterion: seizure severity ≤3.25) and non-responders (criterion: seizure severity >3.25), PTZ-induced increases of Fos, Egr1, Arc, Ccl4 and Bdnf expression were suppressed in CBDV responders. These results provide the first molecular confirmation of behaviourally observed effects of the non-psychoactive, anticonvulsant cannabinoid, CBDV, upon chemically-induced seizures and serve to underscore its suitability for clinical development.

The CB receptor paradox



Science 3 October 2003:
Vol. 302 no. 5642 pp. 65-67

Stimulation of CB_1 receptors located on principal forebrain neurons provides protection against excitotoxicity by both dampening neuronal activity through blocking presynaptic release of glutamate and activating intracellular signaling cascades that might contribute to long-term adaptive cellular changes. The endocannabinoid anandamide is produced in the hippocampus in response to excessive neuronal excitability. Anandamide stimulates CB_1 receptors on principal neurons of the forebrain that protect against excitotoxic damage. Conversely, stimulation of CB_1 receptors on GABAergic interneurons of the cortex further augments excitotoxicity. Finally, THC, the psychoactive constituent of cannabis, as well as the nonpsychoactive compounds cannabidiol (natural) and HU-211 (**Dexanabinol**) exert their neuroprotective effects in part through a mechanism that does not involve CB_1 receptors.

British Journal of Cancer www.nature.com/bjc

REVIEW ARTICLE OPEN

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Cellular and Molecular Biology

Cannabinoids as anticancer drugs: current status of preclinical research

Burkhard Hinz[1]✉ and Robert Ramer[1]

Drugs that target the endocannabinoid system are of interest as pharmacological options to combat cancer and to improve the life quality of cancer patients. From this perspective, cannabinoid compounds have been successfully tested as a systemic therapeutic option in a number of preclinical models over the past decades. As a result of these efforts, a large body of data suggests that the anticancer effects of cannabinoids are exerted at multiple levels of tumour progression via different signal transduction mechanisms. Accordingly, there is considerable evidence for cannabinoid-mediated inhibition of tumour cell proliferation, tumour invasion and metastasis, angiogenesis and chemoresistance, as well as induction of apoptosis and autophagy. Further studies showed that cannabinoids could be potential combination partners for established chemotherapeutic agents or other therapeutic interventions in cancer treatment. Research in recent years has yielded several compounds that exert promising effects on tumour cells and tissues in addition to the psychoactive Δ^9-tetrahydrocannabinol, such as the non-psychoactive phytocannabinoid cannabidiol and inhibitors of endocannabinoid degradation. This review provides an up-to-date overview of the potential of cannabinoids as inhibitors of tumour growth and spread as demonstrated in preclinical studies.

British Journal of Cancer (2022) 127:1–13; https://doi.org/10.1038/s41416-022-01727-4

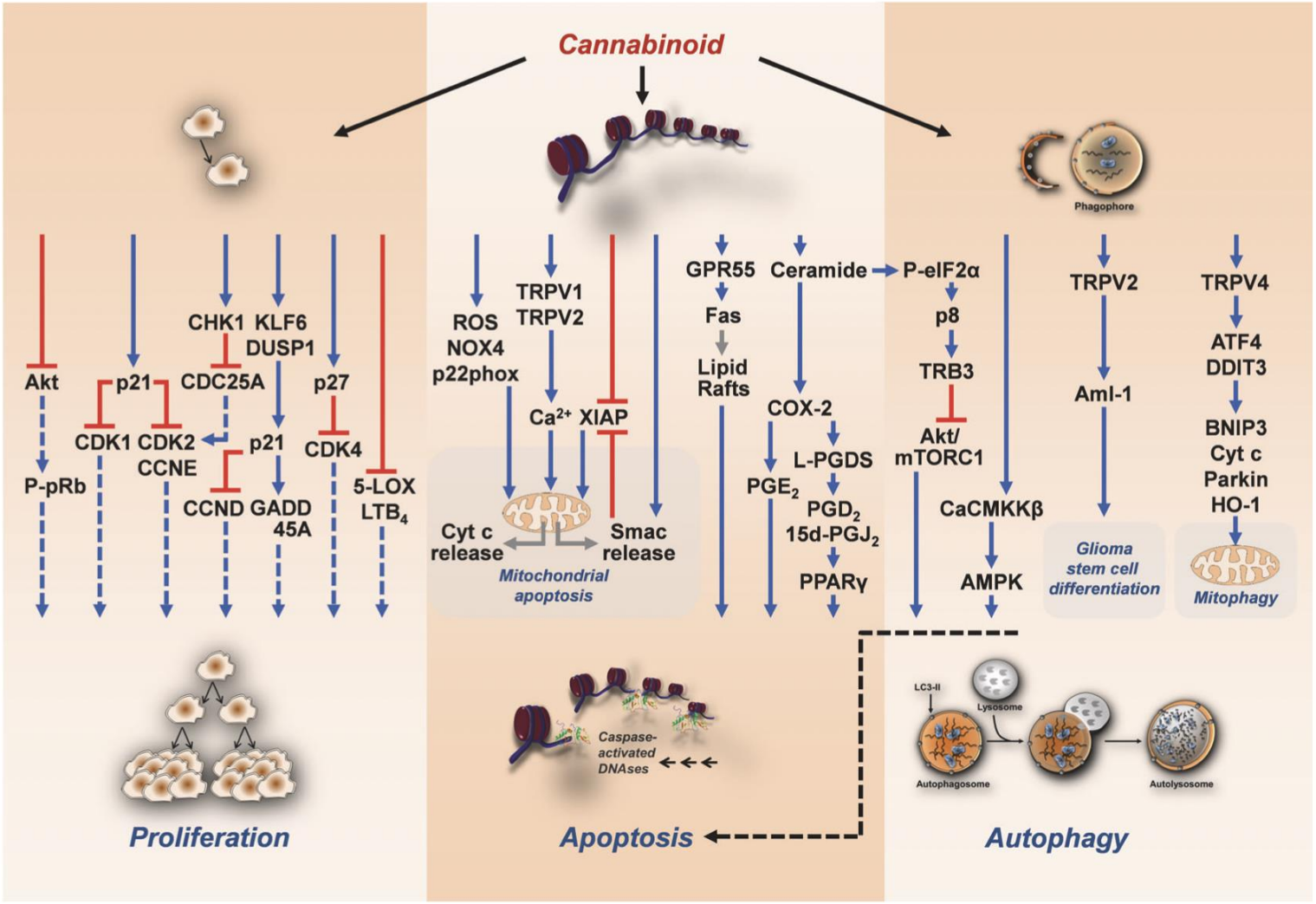


Fig. 1 Mechanisms of antiproliferative, proapoptotic and proautophagic effects of cannabinoids on cancer cells. The black arrows emanating from the cannabinoid show the respective modulated structures or levels. Coloured arrows indicate inhibitory (red) and stimulatory (blue) effects of cannabinoids on the indicated targets. Blue dashed arrows indicate reduced stimulation of the respective effect by cannabinoid treatment. The grey arrows indicate a shift in a parameter. The black dashed arrow indicates a functional relationship between autophagy and apoptosis. All abbreviations are explained in the text.

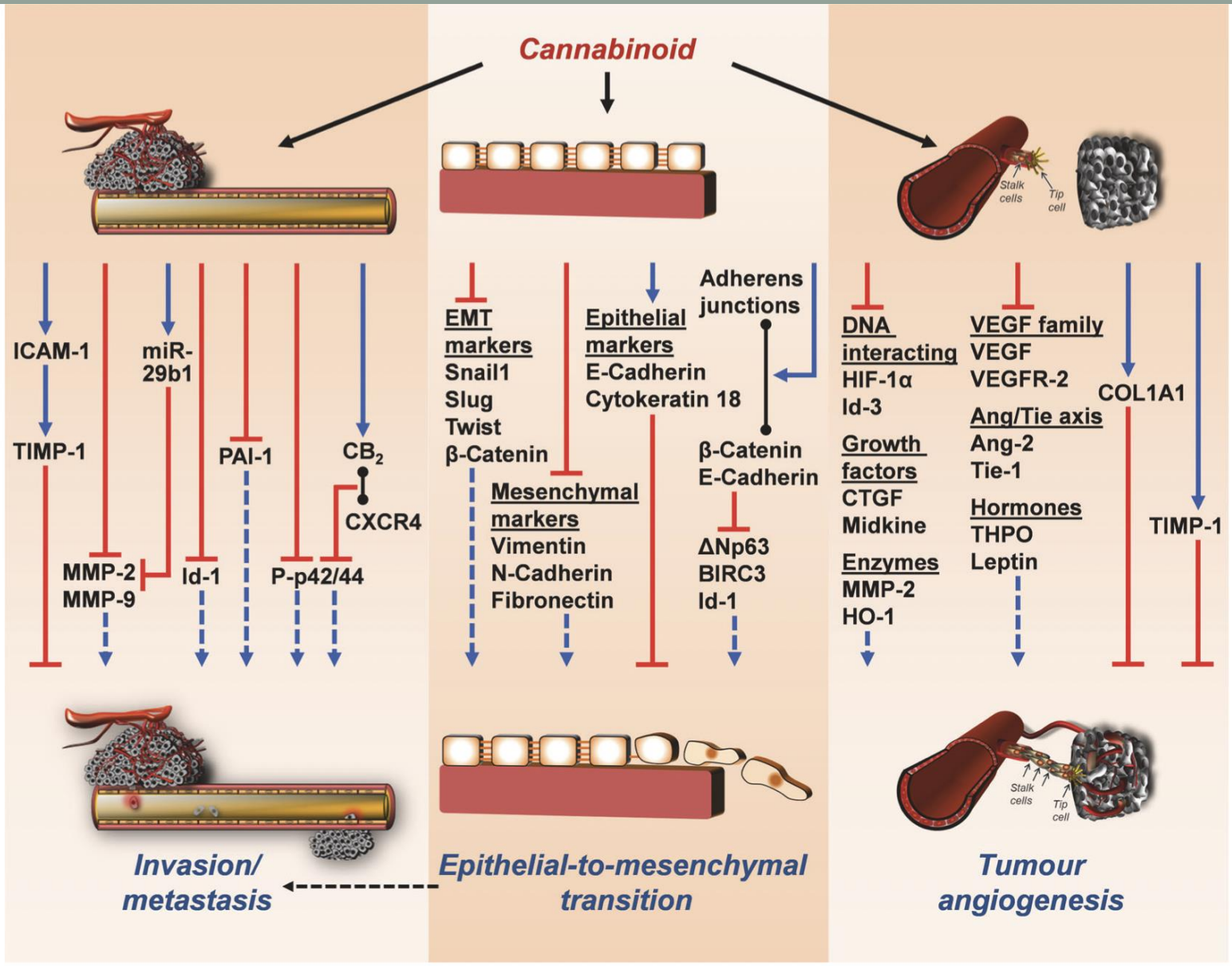


Fig. 2 Mechanisms of anti-invasive, antimetastatic, anti-epithelial-to-mesenchymal-transition and anti-angiogenic effects of cannabinoids on cancer cells. The black arrows emanating from the cannabinoid show the respective modulated structures or levels. Coloured arrows indicate the inhibitory (red) and stimulatory (blue) effects of cannabinoids on targets involved in cancer cell invasion/metastasis, angiogenesis and epithelial-to-mesenchymal transition. Blue dashed arrows indicate reduced stimulation of each effect by cannabinoid treatment. Black lines with circles at both ends indicate binding and dimer formation between the respective parameters. Black dashed arrow indicates functional

Effects of cannabinoid compounds on tumour-immune interaction

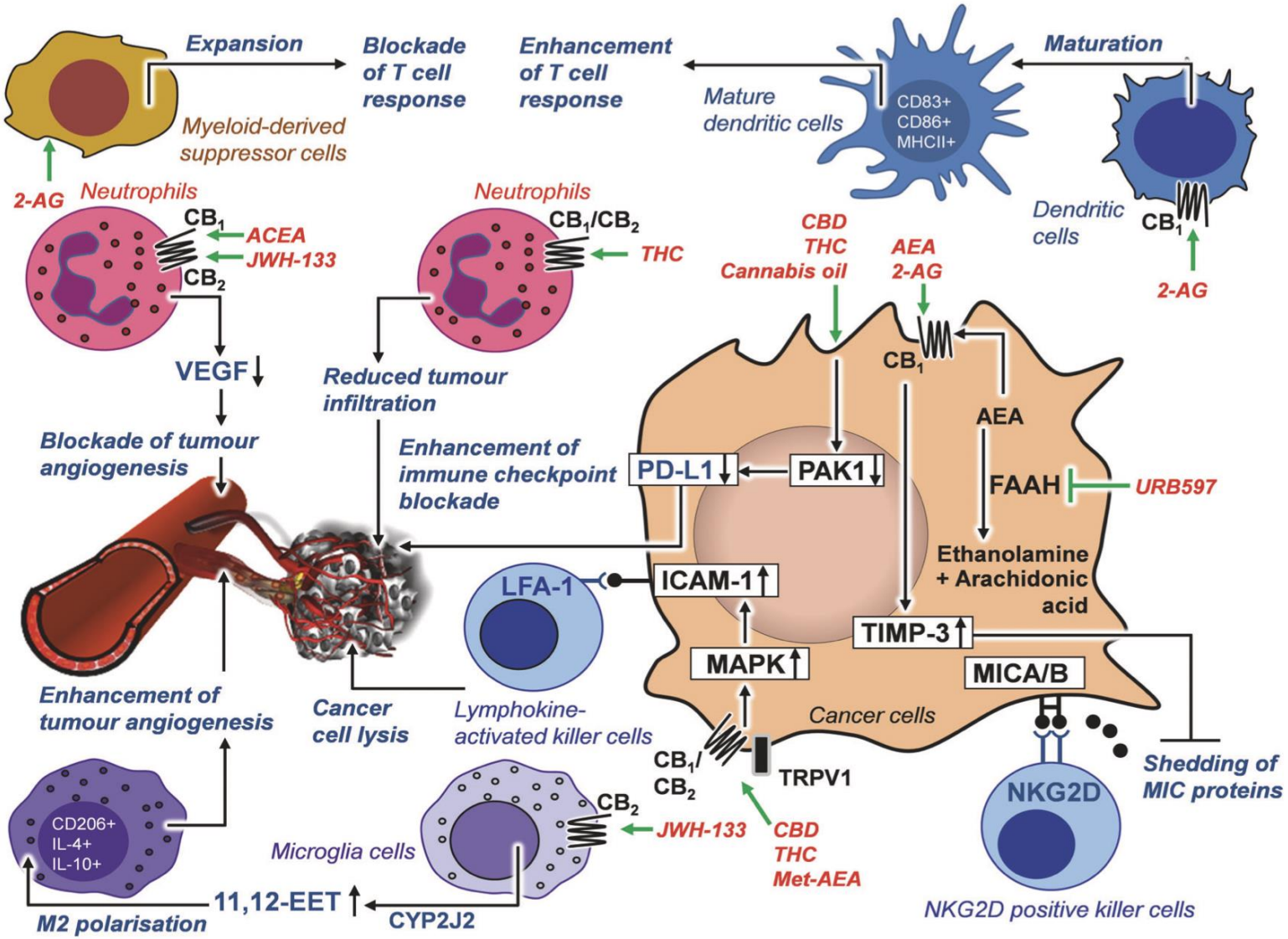


Fig. 3 Effects of cannabinoid compounds on tumour-immune interaction. Green arrows indicate the specific site of action of the indicated cannabinoids. Black lines with circles at the end indicate receptor interactions. Black arrows indicate a functional or regulatory consequence of cannabinoid treatment. The indication "CB_1/CB_2" means that the substances listed here act via both cannabinoid receptors. All abbreviations are explained in the text.

Cannabis: Acute intoxication

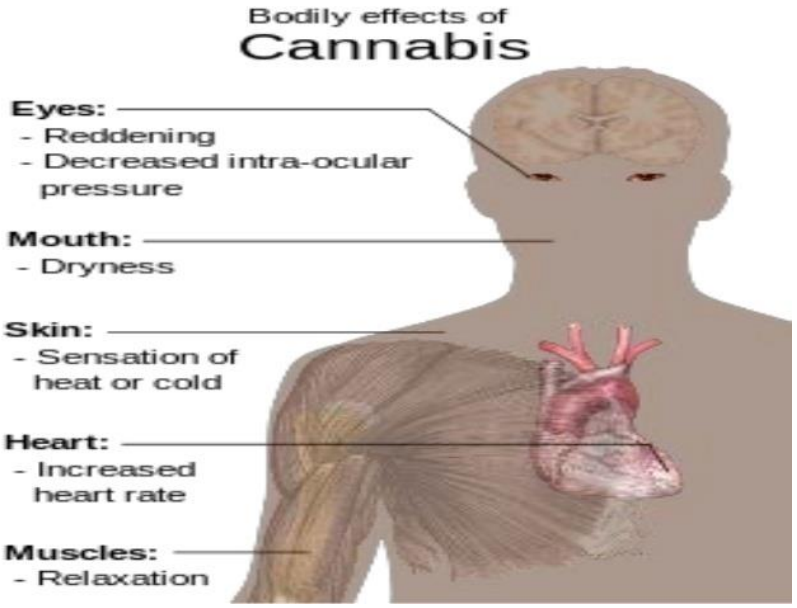
- Clinical manifestations - vary according to age.

Children

- sleepiness, euphoria, irritability, and other changes in behavior
- Vital signs may show sympathomimetic effects (eg, tachycardia and hypertension) or, in patients with depressed mental status, bradycardia.
- Nausea, vomiting, conjunctival injection, nystagmus, ataxia, and, in verbal children, slurred speech may also be present.
- Dilated pupils have frequently been reported, although miosis has also been described

Cannabis: Acute intoxication - Adolescents and adults

- Tachycardia
- Increased blood pressure or, especially in the elderly, orthostatic hypotension
- Increased respiratory rate
- Conjunctival injection (red eye)
- Dry mouth
- Increased appetite
- Nystagmus
- Ataxia
- Slurred speech



Medical Cannabis

Name of drug	Ingredients/ delivery	Where approved	Uses	Drawbacks
Marinol (dronabinol)	THC / Capsule	U.S.A. Canada	Nausea Weight loss Appetite stimulant	Need to be swallowed, Slow to act, Psychoactive effects
Cesamet	THC / Capsule	U.S.A. Canada U. K.	Nausea Weight loss Appetite stimulant	Need to be swallowed, Slow to act, Psychoactive effects
Sativex	THC, CBD and other cannabi-noids/spray	Canada	Cancer pain Multiple sclerosis	Contains alcohol
Epidiolex	CBD	U.S.A. Canada U.K.	Epilepsy - Dravet syndrome - Lennox-Gastaut	Diarrhea (fat malabsorption)

Long-term safety and efficacy of highly purified cannabidiol for treatment refractory epilepsy

Tyler E. Gaston [a, b], Steve B. Ampah [c], E. Martina Bebin [a], Leslie P. Grayson [a, b], Gary R. Cutter [c], Kathleen Hernando [a], Jerzy P. Szaflarski [a], for the UAB CBD Program

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https://doi.org/10.1016/j.yebeh.2021.107862

Highlights

- Investigated 2 year efficacy and safety of CBD for epilepsy in open label study.
- Seizure frequency and severity decreased from baseline and sustained for 2 years.
- One time point noted lower seizure severity in adults compared to children.
- Adverse Events Profile decreased from baseline and reductions stable for 2 years.
- CBD appears to have durable efficacy and tolerance in treatment resistant epilepsy.

> Epilepsy Behav. 2021 Sep;122:108190. doi: 10.1016/j.yebeh.2021.108190. Epub 2021 Jul 14.

Longitudinal impact of cannabidiol on EEG measures in subjects with treatment-resistant epilepsy

Leslie Grayson [1], Steve Ampah [2], Kathleen Hernando [3], Pongkiat Kankirawatana [4], Tyler Gaston [3], Gary Cutter [2], Jerzy P Szaflarski [5], Elizabeth Martina Bebin [3], UAB CBD Program

Affiliations + expand

PMID: 34273739 DOI: 10.1016/j.yebeh.2021.108190

Abstract

Objective: To assess the longitudinal impact of highly purified cannabidiol (CBD) on the electroencephalogram (EEG) of children and adults.

Methods: Participants received an EEG prior to starting CBD, after approximately 12 weeks of CBD (FU1) and after approximately one year of CBD therapy (FU2). Longitudinal changes in five EEG measures (background frequency, focal slowing, reactivity, frequency of interictal, and ictal discharges) were examined following CBD exposure. Data were compared between pediatric and adult groups at two follow-up time points and within groups over time. Population-averaged models with generalized estimation equations or linear mixed effects models were used to analyze data where appropriate. Correlation analysis was used to assess any association between changes in seizure frequency and changes in EEG interictal discharge (IED) frequency. An alpha level of 5% was used to assess statistical significance.

Results: At FU1, the adult group showed significant decrease in IED/minute (IDR 0.07, 95% CI [0.04, 0.14], $P < 0.001$); a nonsignificant decrease was observed among children (IDR 0.87, 95% CI [0.47, 0.64], $P = 0.67$). The difference in changes over time between participant groups was significant after adjusting for last CBD dose (IDR 11.8, 95% CI [4.86, 28.65], $P < 0.0001$). At FU2 both groups showed significant reduction from baseline after controlling for last CBD dose. This decrease was more pronounced in children (IDR 15.38, 95% CI [4.93, 47.99], $P < 0.001$). There was no significant correlation between changes in seizure frequency and EEG IED frequency at each timepoint ($P = 0.542$, 0.917 and 0.989 from baseline to FU1, FU1 to FU2 and baseline to FU2, respectively).

PROVINCIAL MEDICAL JOURNAL

And Retrospect of the Medical Sciences.

No. 123.] LONDON, SATURDAY, FEBRUARY 4, 1843. [PRICE SIXPENCE. Stamped Edition Sevenpence.

ON THE PREPARATIONS OF THE INDIAN HEMP, OR GUNJAH,*

(*Cannabis Indica*)

Their Effects on the Animal System in Health, and their Utility in the Treatment of Tetanus and other Convulsive Diseases.

By W. B. O'Shaughnessy, M.D., Bengal Army,
Late Professor of Chemistry and Materia Medica in the Medical College of Calcutta.

[Concluded from p. 347.]

Experiments by the Author—Inferences as to the Action of the Drug on Animals and Man.

Such was the amount of preliminary information before me, by which I was guided in my subsequent attempts to gain more accurate knowledge of the action, powers, and possible medicinal applications of this extraordinary agent.

There was sufficient to show that hemp possesses, in small doses, an extraordinary power of stimulating the digestive organs, exciting the cerebral system, of acting also on the generative apparatus. Larger doses, again, were shown by the historical statements to induce insensibility or to act as a powerful sedative. The influence of the drug in allaying pain was equally manifest in all the memoirs referred to. As to the evil sequelæ so unanimously dwelt writers, these did not appear to me so numerc mediate, or so formidable, as many whicl clearly traced to over-indulgence in other stimulants or narcotics—viz, alcohol, tobacco.

The dose in which the hemp preparation administered, constituted, of course, one o objects of inquiry. Ibn Beitar had mention or forty-eight grains of *churrus*; but this dose me so enormous, that I deemed it expedient with much smaller quantities. How fort this caution, the sequel will sufficiently den

An extensive series of experiments on an in the first place undertaken, among whic lowing may be cited:—

Expt. 1.—Ten grains of Nipalese *churrus* in spirit were given to a middling sized dog an hour he became stupid and sleepy, dozin vals, starting up, wagging his tail as if extre tented, he ate some food greedily, on being he staggered to and fro, and his face assun of utter and helpless drunkenness. These lasted about two hours, and then gradual away; in six hours he was perfectly well a

Expt. 2.—One drachm of *majoon* was small sized dog; he ate it with great delig

* Published in the Transactions of the Medica Calcutta for 1839, and now revised by the Aut Provincial Medical Journal.

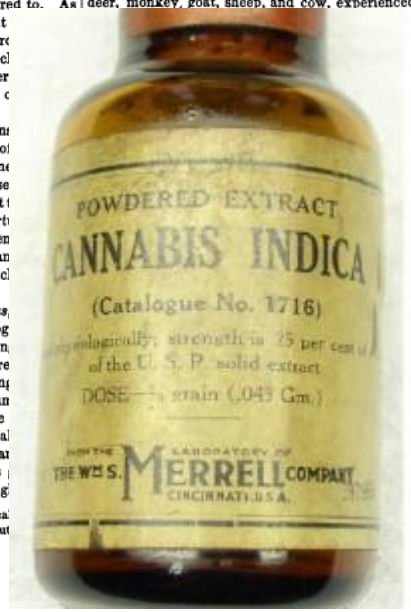
twenty minutes was ridiculously drunk; in four hours his symptoms passed away, also without harm.

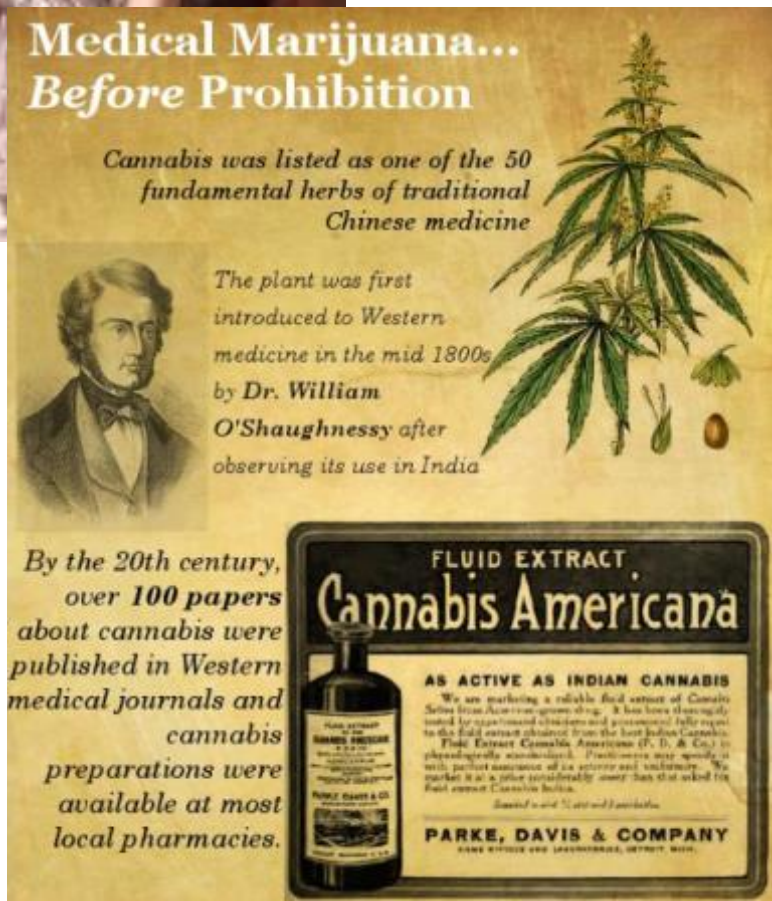
Expts. 3, 4, and 5.—Three kids had ten grains each of the alcoholic extract of *gunjah*. In one no effect was produced; in the second there was much heaviness, and some inability to move; in the third a marked alteration of countenance was conspicuous, but no further effect.

Expt. 6.—Twenty grains were given, dissolved in a little spirit, to a dog of very small size. In a quarter of an hour he was intoxicated; in half an hour he had great difficulty of movement; in an hour he had lost all power over the hinder extremities, which were rather stiff but flexible; sensibility did not seem to be impaired, and the circulation was natural. He readily acknowledged calls by an attempt to rise up. In four hours he was quite well.

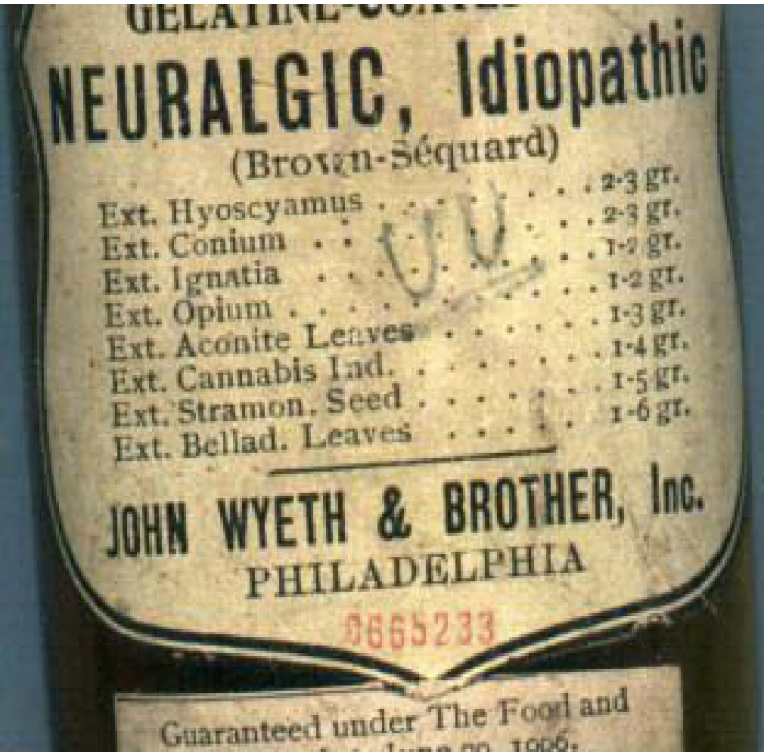
In none of these or several other experiments was there the least indication of pain, or any degree of convulsive movement observed.

It seems needless to dwell on the details of each experiment; suffice it to say that they led to one remarkable result—that while carnivorous animals and fish, dogs, cats, swine, vultures, crows, and adjutants, invariably exhibited the intoxicating influence of the drug, the graminivorous, such as the horse, deer, monkey, goat, sheep, and cow, experienced but





1850 - Marijuana Added to US Pharmacopeia



Cannabis for neuropathic pain in 1906

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA.

BY AUTHORITY OF THE

NATIONAL MEDICAL CONVENTION,

HELD AT

WASHINGTON,

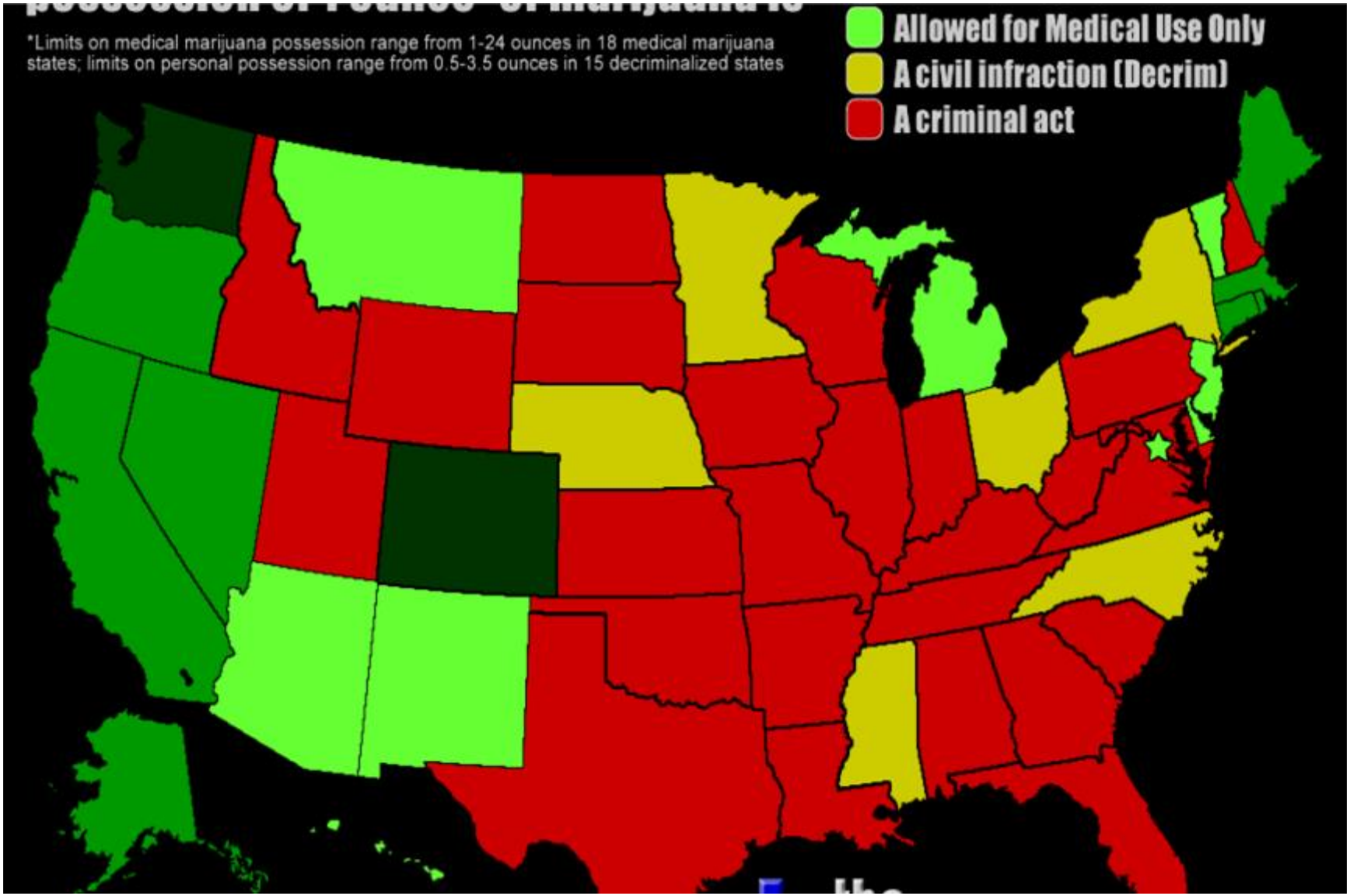
A. D. 1850.

EXTRACTUM CANNABIS. *Extract of Hemp.*

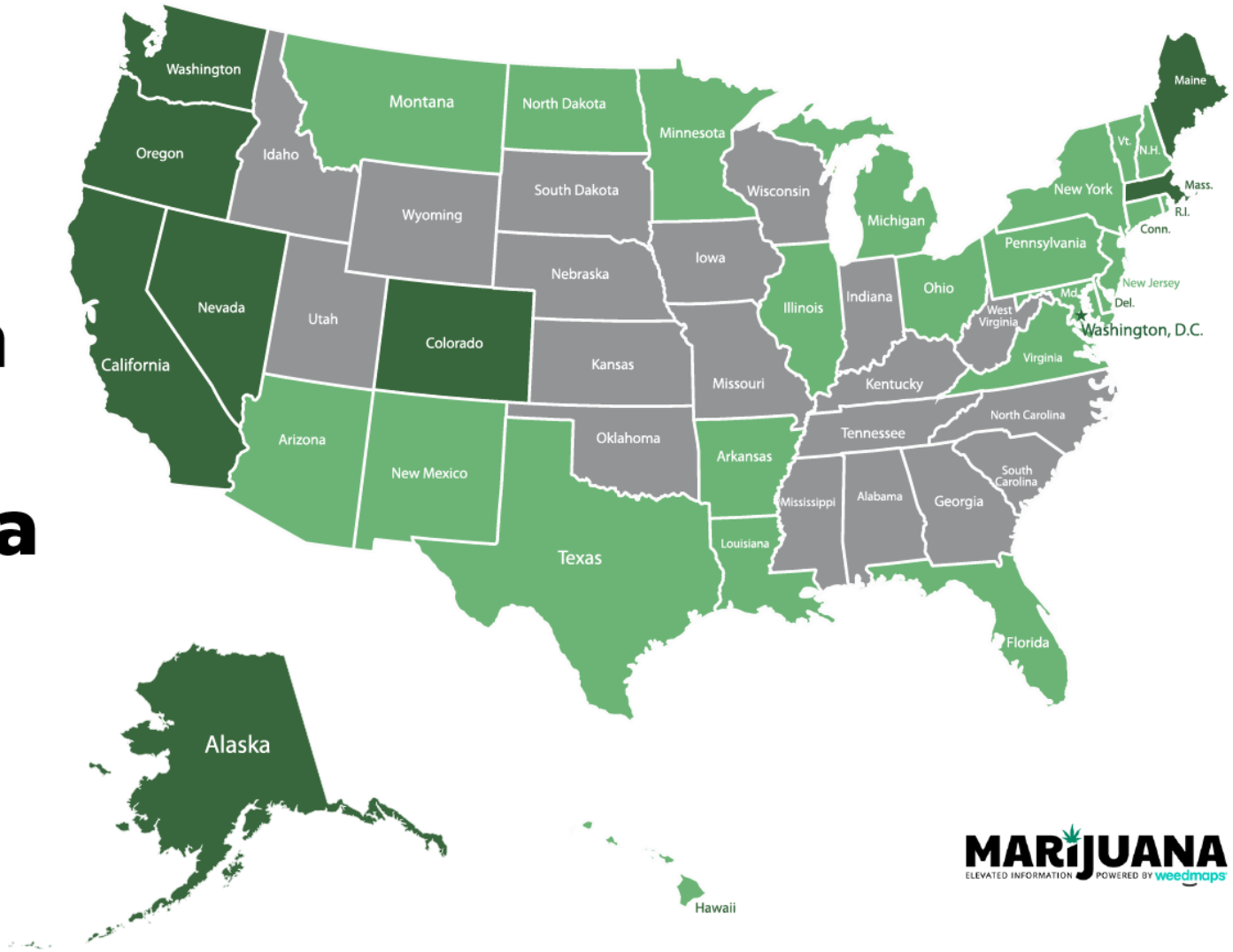
An alcoholic extract of the dried tops of Cannabis sativa—variety *Indica.*

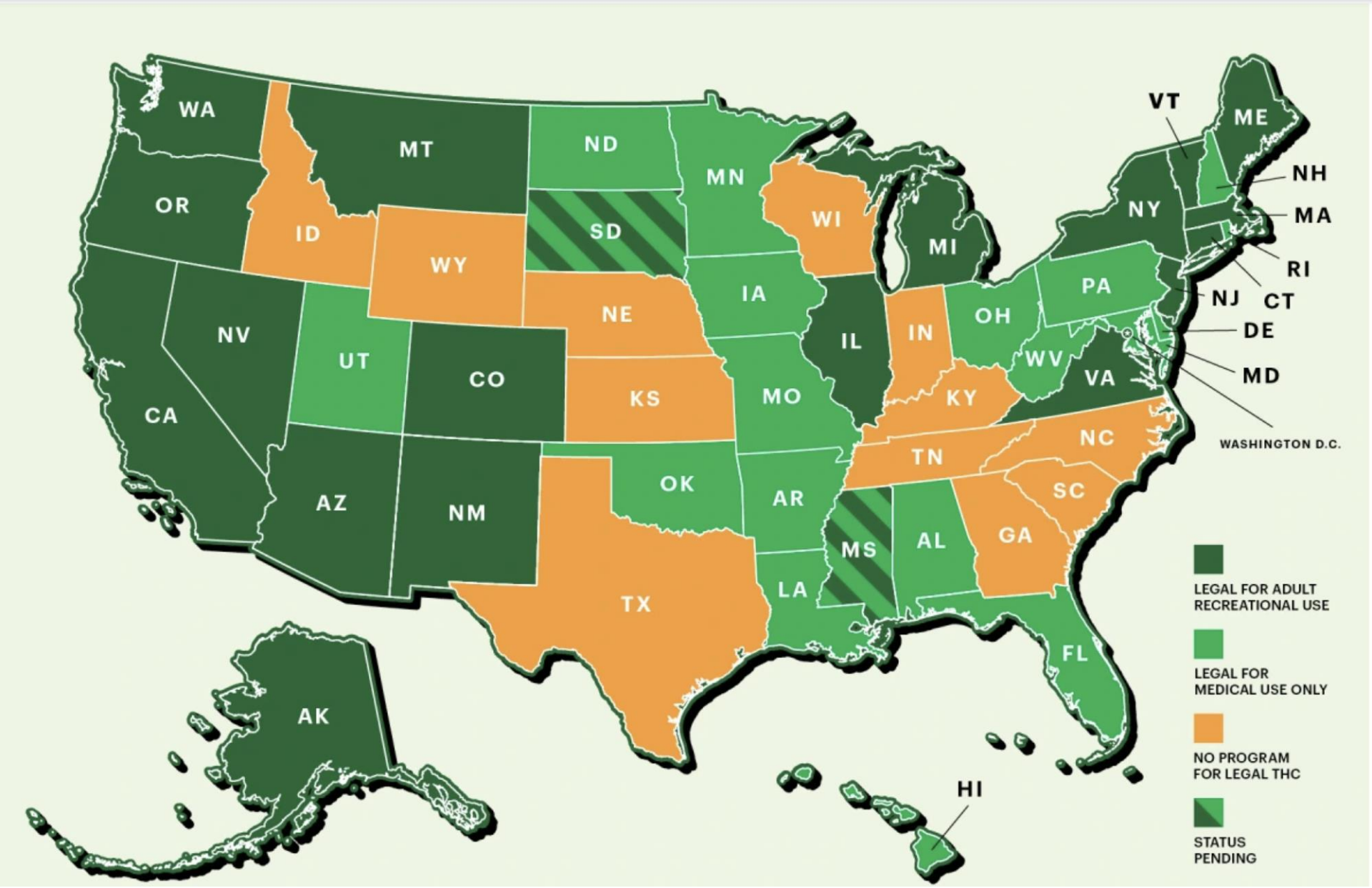
Page 50 of the 1851 United States Pharmacopeia

2013 Possession 1 oz is legal or not legal?



Where in the US is Marijuana Legal?

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MD
WASHINGTON D.C.
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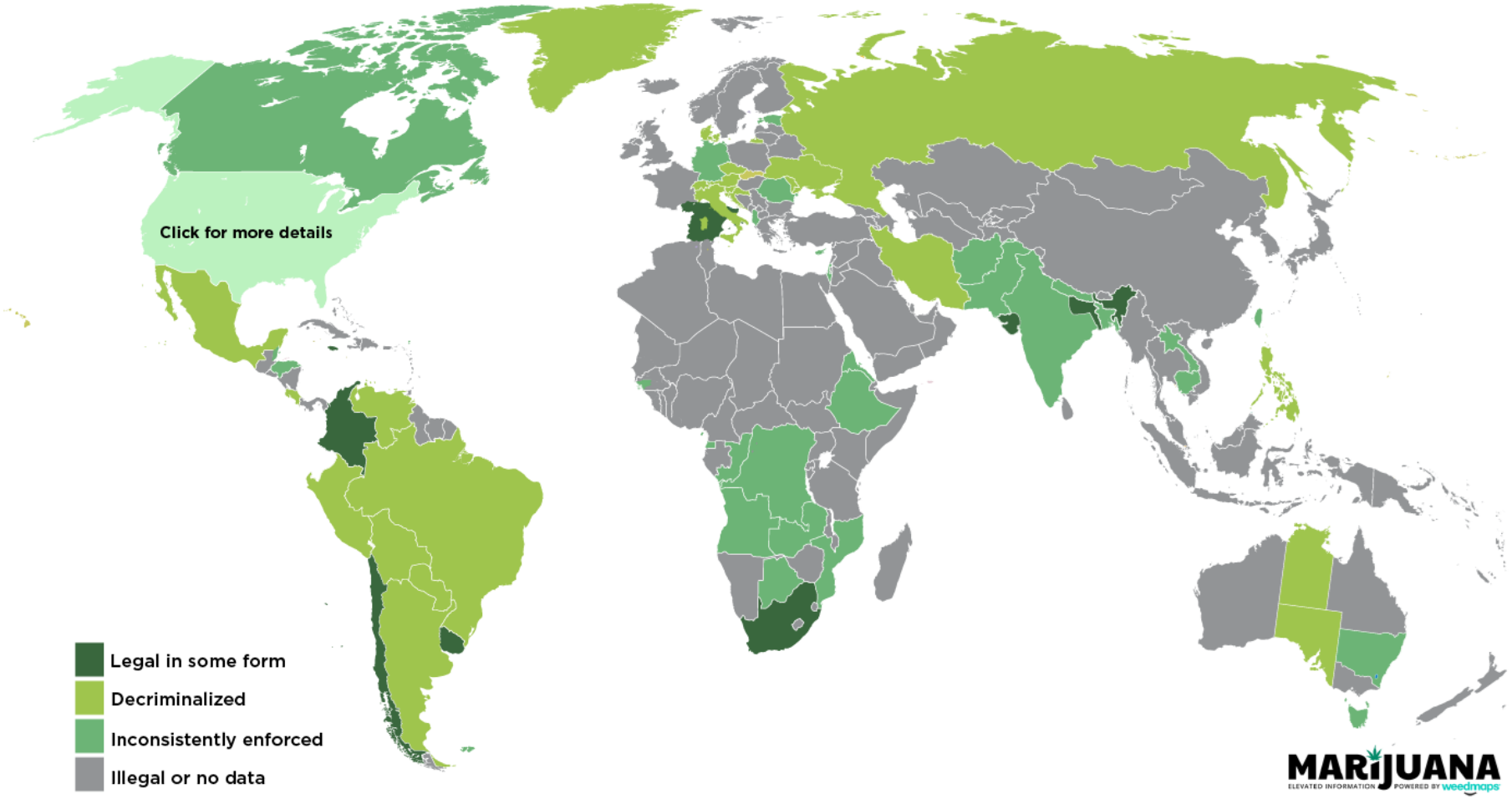
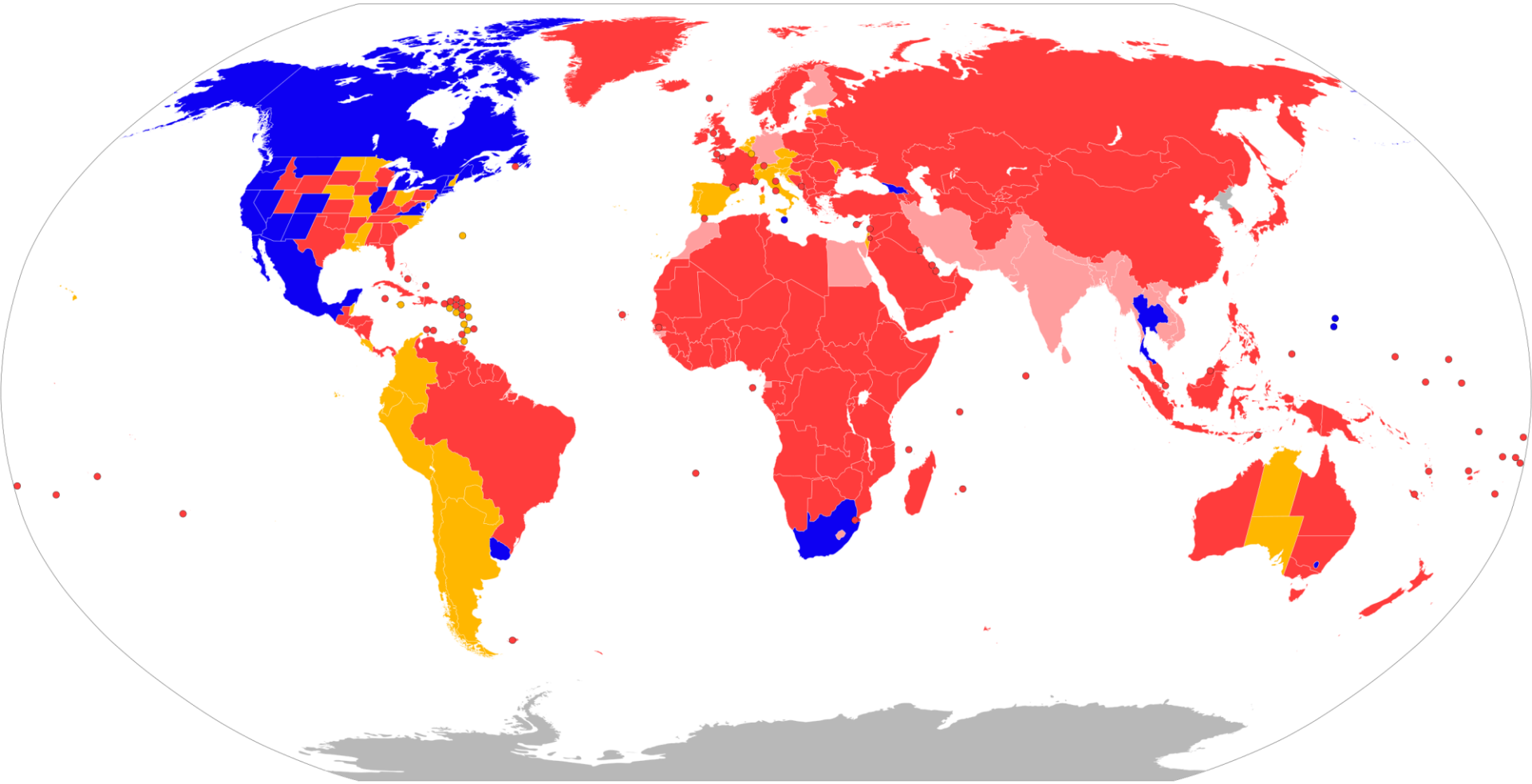
LEGAL FOR ADULT RECREATIONAL USE
LEGAL FOR MEDICAL USE ONLY
NO PROGRAM FOR LEGAL THC
STATUS PENDING

Where in the World is Marijuana Legal?



2022



Legal status of cannabis possession for recreational use Legal | Illegal but decriminalized | Illegal but often unenforced | Illegal | Legality unknown

Conclusion

- For 5 millennia, Cannabis has been used throughout the world medically, recreationally, and spiritually, until the fed goverment impose restrictions on its use
- Cannabis does not have physical dependency property
- Although it’s not complete safe but it Is Less Dangerous Than Alcohol, Other Drugs (Than we thought)
- The science of Cannabinoids /Endocannabinoids is complex
- Pure extract(synthetic) CBD vs Plant with high CBD extract (Entourage effect)
- Public opinions pendulum:- Public approval drives medical marijuana legalization efforts without the scientific data normally required to justify a new medication's introduction.
- Little about cannabis is straightforward