

EDITORIAL

Dr. Raphael Mechoulam, cannabis and cannabinoids research pioneer (November 5, 1930–March 9, 2023) and his legacy for Brazilian pharmacology

José Alexandre S. Crippa,^{1,2}  Francisco S. Guimarães,^{2,3}  Antonio Waldo Zuardi,^{1,2} 
Jaime E.C. Hallak^{1,2} 

¹Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil. ²Instituto Nacional de Ciência e Tecnologia, Medicina Translacional (INCT-TM), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Ribeirão Preto, SP, Brazil. ³Departamento de Farmacologia, FMRP, USP, Ribeirão Preto, SP, Brazil.

Israeli researcher Raphael Mechoulam, the father of cannabis research, passed away on March 10, 2023, at 92 years of age. In early 1960, he was the first to reveal the structure of cannabidiol (CBD) and delta 9-tetrahydrocannabinol (THC), molecules now used worldwide as medicine.^{1,2} In addition, Professor Mechoulam and his research group identified the endocannabinoid system, a biological system with endogenous neurotransmitters that bind to specific receptors and are synthesized and metabolized by specific enzymes. It is now recognized that this system regulates various cognitive, physiological and pathophysiological processes, including immune system activity, memory, mood, pain, psychosis, etc. It also mediates the pharmacological effects of the cannabis plant.

While Professor Mechoulam was elucidating the chemical structure and synthesis of the most significant plant cannabinoids, he established an extremely fruitful partnership and a lifelong friendship with Brazilian researcher Elisaldo Araujo Carlini of the Escola Paulista de Medicina (now UNIFESP), who was born in the same year (1930) and passed away on September 16, 2020, at 90 years of age. In another seminal work, they suggested for the first time that CBD presented anticonvulsant properties in animals (1973)³ and, later, in humans (1980).⁴ This finding was the very first evidence that CBD had any effects, since at the time it was considered an inactive cannabinoid. In 2009, Professor Mechoulam stated, “Nobody has done any work on cannabidiol in the clinic in epilepsy, and I just wonder why.” Accordingly, this finding remained almost unnoticed for 35 years until the media covered the parents of children with severe refractory epilepsy, who decided to treat their children with CBD, finding positive results.

Professor Mechoulam once mentioned that he used to smuggle cannabinoids (THC, CBD, cannabigerol, cannabinol, etc.) to Professor Carlini in Brazil through the mail inside books or journals. A few years later, using

cannabinoids supplied by Dr. Mechoulam, Professor Carlini, with his colleagues Isaac Karniol and Antonio Zuardi, observed that the THC content of Brazilian marijuana samples did not explain all of their biological activity.^{5,6} This observation indicated that other cannabinoids might also have pharmacological effects, which, in the case of CBD, could be the opposite of those observed in THC. Studies based on these ideas were fundamental to the subsequent discovery of CBD’s anxiolytic and antipsychotic properties in Brazil, setting the stage for recent new therapeutic approaches and commercial medicines, such as Epidiolex and Sativex from GW/Jazz Pharma. In 1995, he collaborated with Professor Zuardi and Professor Francisco Guimarães on the first report of a schizophrenia case successfully treated with CBD. Therefore, Professor Mechoulam’s groundbreaking work led to the development of new therapeutic molecules and shed light on the endocannabinoid system’s role in treating epilepsy, Parkinson’s, post-traumatic stress disorder, chronic pain, schizophrenia, cancer, and several other clinical conditions.

Professor Mechoulam also developed several synthetic compounds. Recently, he synthesized fluorinated CBD derivatives (HU474, HU475, HU485, CBD-DMH) in search of new compounds with similar, but more potent, properties than CBD, having a stable composition and equivalent safety and non-toxicity profiles. The pre-clinical studies we have carried out so far, in partnership with our group at the Universidade de São Paulo, Universidade Federal do Rio Grande do Sul, and the Hebrew University of Israel, have been encouraging. The new compounds showed the same clinical and pharmacological profile of CBD in anxiety, depression, and psychosis models, but with greater potency and stability. Thus, in 2014 our group filed for an international patent on these compounds (US No. Reg. 61750043; Jan/2014). With the collaboration of innovation agencies from Brazilian universities and the

Correspondence: Jaime E. C. Hallak, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes, 3º andar, CEP 14048-900, Ribeirão Preto, SP, Brazil.

E-mail: jhallak@fmrp.usp.br

Submitted Mar 24 2023, accepted Mar 25 2023.

How to cite this article: Crippa JAS, Guimarães FS, Zuardi AW, Hallak JEC. Dr. Raphael Mechoulam, cannabis and cannabinoids research pioneer (November 5, 1930–March 9, 2023) and his legacy for Brazilian pharmacology. *Braz J Psychiatry*. 2023;45:201-202. <http://doi.org/10.47626/1516-4446-2023-0047>

Hebrew University of Israel (Yissum), discussion is ongoing with the pharmaceutical industry regarding further development of fluorinated CBD derivatives. This highlights Professor Mechoulam's vision for developing new compounds whose potential can be translated to industry and, thus, help patients with a broad range of disorders.

In 2015, during ANVISA (the Brazilian regulatory agency) hearings to reclassify CBD, Professor Mechoulam contributed to a newspaper article titled "Joseph Kanabidiol" in *O Estado de São Paulo*,⁷ which defended the removal of this cannabinoid from the list of pathogenic substances and its inclusion in the list of controlled substances. CBD was approved for therapeutic use that same year. His role here aligned with his longstanding interest in promoting the use of cannabinoids to treat various conditions.

Even after his retirement, Mechoulam remained active as a researcher until just a few weeks before he died, mainly collaborating with diverse groups, speaking at conferences, giving media interviews, struggling to defend cannabinoids as medicine, and writing articles. His final collaboration with our group was a clinical trial of CBD for treating burnout in frontline workers during the COVID-19 pandemic, with subsequent articles published in *JAMA*⁸ and *Frontiers*.⁹ Finally, the preface of our upcoming book, *Canabidiol na medicina: da pesquisa à prática clínica*, was kindly written by him just before he passed away.

Thus, Dr. Mechoulam's academic and scientific legacy is immense and includes collaboration with Brazilian researchers at all levels. As a scientist who was always engaged in translating his knowledge to society, he helped transform Brazil into an epicenter of research on cannabis in general and CBD in particular. Dr. Mechoulam is survived by his wife, Dalia, his son, Roy, and his daughters, Dafna and Hadas.

Disclosure

AWZ, JECH, FSG and JAC are coinventors of the patent "Fluorinated CBD compounds, compositions and uses

thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023" Def. US no. Reg. 62193296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). Universidade de São Paulo has licensed this patent to Phytects Pharm (USP Resolution No. 15.1.130002.1.1) and has an agreement with Prati-Donaduzzi (Toledo, Brazil) to "develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders."

References

- 1 Mechoulam R, Shvo Y, Hashish. I. The structure of cannabidiol. *Tetrahedron*. 1963;19:2073-8.
- 2 Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. *Science*. 1970;169:611-2.
- 3 Carlini EA, Leite JR, Tannhauser M, Berardi AC. Letter: Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents. *J Pharm Pharmacol*. 1973;25:664-5.
- 4 Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*. 1980;21:175-85.
- 5 Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol*. 1974;28:172-7.
- 6 Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by Δ 9-THC in normal subjects. *Psychopharmacology (Berl)*. 1982;76:245-50.
- 7 Redação. Estadão [Internet]. Joseph Kanabidiol. 2014 Jun 14. <https://www.estadao.com.br/alias/joseph-kanabidiol/>
- 8 Souza JDS, Zuardi AW, Guimarães FS, Osório FL, Loureiro SR, Campos AC, et al. Maintained anxiolytic effects of cannabidiol after treatment discontinuation in healthcare workers during the COVID-19 pandemic. *Front Pharmacol*. 2022;13:856846.
- 9 Crippa JAS, Zuardi AW, Guimarães FS, Campos AC, Osório FL, Loureiro SR, et al. Efficacy and safety of cannabidiol plus standard care vs standard care alone for the treatment of emotional exhaustion and burnout among frontline health care workers during the COVID-19 pandemic: a randomized clinical trial. *JAMA Netw Open*. 2021;4:e2120603.