

Brazilian Journal of Psychiatry

bjp

Revista Brasileira de Psiquiatria



Brazilian
Psychiatric
Association

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BJP PRE-PROOF
(article published as accepted)

Editorial

**Prof. Dr Raphael Mechoulam, Cannabis and Cannabinoids
Research Pioneer (November 05, 1930–March 09, 2023) and his
legacy for the Brazilian Pharmacology**

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<http://doi.org/10.47626/1516-4446-2023-0047>

Submitted: 24-Mar-2023

Accepted: 25-Mar-2023

This is a preliminary, unedited version of a manuscript that has been accepted for publication in the Brazilian Journal of Psychiatry. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form. The final version may present slight differences in relation to the present version.

Prof. Dr Raphael Mechoulam, Cannabis and Cannabinoids Research Pioneer (November 05, 1930–March 09, 2023) and his legacy for the Brazilian Pharmacology

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The Israeli researcher Raphael Mechoulam, the father of cannabis research, passed away on March 10, 2023, at 92. In early 1960, he was the first to reveal the structure of cannabidiol (CBD) and THC (delta9-tetrahydrocannabinol), molecules now used as medicine worldwide^{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 recognized now that this system regulates various cognitive, physiological and pathophysiological processes, including immune system activity, memory, mood, pain and psychosis, among many others. It also mediates the pharmacological effects of the cannabis plant.

At the time Professor Mechoulam was elucidating the chemical structure and synthesis of the most significant plant cannabinoids, he established an extremely fruitful partnership and a lifetime friendship with the Brazilian researcher Elisaldo Araujo Carlini from Escola Paulista de Medicina (now Unifesp), who was born in the same year (1930) and passed away on September 16, 2020, at 90. 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 of a CBD effect that, at the time, 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 parents of children with severe refractory epilepsy and decided to use CBD with their kids with positive results.

Professor Mechoulam once mentioned that he used to supply cannabinoids (THC, CBD, CBG, CBN, and others) to Professor Carlini for their studies in Brazil by smuggling them by mail inside books or magazines. Using the cannabinoids supplied by Mechoulam, a few years later, Professor Carlini, with his colleagues Isaac Karniol and Antonio Zuardi, observed that Brazilian marijuana samples' THC content did not explain all of its biological activities^{5,6}. This observation highlighted that other cannabinoids might also induce pharmacological effects that, as in the case of CBD, could be opposite to those observed with THC. The studies derived from these ideas were fundamental to the subsequent discovery in Brazil of CBD's anxiolytic and antipsychotic properties, setting the basis for the recent new therapeutic approaches and commercial medicines, such as Epidiolex and Sativex from GW-Jazz Pharm. Furthermore, in 1995, he collaborated with Professor Zuardi and Professor Francisco Guimarães in a first publication of a case of a schizophrenia patient 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 role as a target for treating epilepsy, Parkinson's, post-traumatic stress disorder, chronic pain, schizophrenia, cancer, and diverse other clinical conditions.

Professor Mechoulam also developed several synthetic compounds. Recently he synthesized fluorinated CBD derivatives (HU474, HU475, HU485, CBD-DMH) with the perspective of finding new compounds with properties similar to those of CBD but more potent, with a stable composition and with a profile of equal safety and absence of toxicity. The pre-clinical studies we have carried out so far, in partnership with our group at the University of São Paulo, Federal University of Rio Grande do Sul, and the Hebrew University of Israel, were encouraging. The new compounds demonstrated the same clinical and pharmacological profile of CBD in anxiety, depression and psychosis models but with greater potency and stability. In this way, in 2014 the group filed an international patent (US No. Reg. 61750043; Jan/2014). With the collaboration

of innovation agencies from the Brazilian Universities and the Hebrew University of Israel (Yissum), discussions are going on with the Industry for further development of the fluorinated CBD derivatives. This fact reflects the vision of Professor Mechoulam to expand the development of new compounds with transferring potential for the productive sector, targeting the benefice of patients for a broad range of disorders.

In 2015, during the hearings and collegiate discussion on the reclassification of CBD by the Brazilian regulatory agency ANVISA, Professor Mechoulam collaborated in an article published under the title Joseph Kannabidiol in the newspaper "O Estado de São Paulo", in which we defended the removal of this cannabinoid from the list of pathogenic substances and its inclusion in the list of controlled substances for use. This article was published that same year, which meant the release of cannabidiol for therapeutic use. His role here aligned with his long last position to promote cannabinoids in treating various conditions.

Even after his retirement, Mechoulam remained active as a researcher until a few weeks before he died, mainly collaborating with diverse groups, presenting conferences, giving interviews to the media, struggling to defend cannabinoids as medicine and writing papers. The last papers with our Brazilian group were the clinical trial of CBD in treating burnout in frontline workers during the Covid-19 pandemic, published in JAMA⁷ and Frontiers⁸, respectively. Finally, the preface of our ongoing yet-to-be-published book "*Canabidiol na Medicina: da pesquisa à prática clínica*" was kindly written by him just before he passed away.

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

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