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EDITORIAL

Fifty years of research on cannabidiol as an anticonvulsant: the legacy of Brazilian groups

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Fifty years ago, a group of Brazilian researchers led by Professor Elisaldo Carlini first demonstrated preclinical evidence that cannabidiol (CBD) could be an anticonvulsant. Until that point, CBD had been considered inactive because it did not cause the same effects observed with tetrahydrocannabinol (THC), the main active constituent of Cannabis sativa. Early evidence indicated that CBD protected mice from seizures and lethal effects induced by leptazole,[1] blocked audiogenic seizures in rats,[1] and reduced the susceptibility of the rat hippocampus to seizure discharges induced by afferent stimuli.[2]

In the following years, other research groups confirmed these groundbreaking findings; thus, Professor Carlini's group conducted a double-blind, placebo-controlled clinical trial to confirm the safety of CBD for human use in health volunteers and to assess the effects of chronic cannabidiol use in participants with epilepsy. Over four and a half months, 15 adult individuals with refractory (i.e., drug-resistant) epilepsy received CBD or placebo plus the usual drugs they were already taking. Partial results of the study were published in 1978 and the full study was published in 1980.[3] At the end of treatment, only 10% of the participants who received CBD still experienced generalized epileptic seizures; conversely, in the placebo group, 90% of the patients continued to have seizures.

Although these initial results were entirely consistent, they were ignored by the scientific literature during the next 40 years. Professor Rafael Mechoulam, a pioneer in cannabis and endocannabinoid research, commented on the early observations of the effects of CBD on epilepsy saying that "it seemed a very promising approach, but unfortunately, nothing has been done ever since. To the best of my knowledge, nobody has done any work on cannabidiol in the clinic on epilepsy, and I just wonder why."[4]

Interest in the topic was finally reawakened due to the effort of parents who added CBD to the medication of their children with refractory epilepsy in a desperate attempt to relieve symptoms, with encouraging results reported. These initiatives were recorded in a retrospective study organized by Stanford University and published in 2013. In that study, questionnaires were administered to the parents of 19 children with refractory epilepsy who received CBD. The results showed a reduction in seizures of more than 80% in 52% of the children.

This renewed interest has led to multicenter, double-blind, placebo-controlled clinical trials. The first study, published in 2017, included 120 children with Dravet syndrome who were refractory to four antiepileptic drugs and received CBD for 14 weeks alongside their usual medications.[5] The study showed a significant reduction in the median frequency of monthly seizures with the use of CBD, which is consistent with the original results that had been obtained in adults with refractory epilepsy by the Brazilian group 37 years earlier. In 2018, a new study including 171 patients with Lennox-Gastaut syndrome showed a significant reduction in seizure frequency with CBD compared to the placebo group.[6] These two studies supported the US Food and Drug Administration's (FDA) decision to approve a CBD drug for these two indications in June 2018.

In Brazil, an agreement signed in 2016 between the Universidade de São Paulo (USP) and a Brazilian pharmaceutical company made it possible to conduct a multicenter, placebo-controlled clinical trial in children with refractory epilepsy. The results of this study are currently being evaluated by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA]); however, a partial analysis contributed to the market approval by ANVISA of the first phytopharmaceutical containing pure CBD in April 2020.

We hope that more regulated clinical trials for various neuropsychiatric disorders will support the translation of research findings into clinical therapeutic utility without the delays seen in the last few decades, as has happened with CBD in the treatment of epilepsy.

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and personal fees from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Disclosure

AWZ is a co-owner of a patent for fluorinated CBD compounds (licensed to Phytecs) and has a patent pending for a cannabinoid-containing oral pharmaceutical composition outside the submitted work. JAC was a consultant and/or has received speaker fees and/or sits on the advisory board and/or receives research funding and/or receives speaker fees from Janssen-Cilag, Torrent Pharm, Ease Labs Pharm, Prati-Donaduzzi, Mantecorp, ArtMed, PurMed Global, and BSPG Pharm over the past 3 years. JAC is the coinventor of the patent ''Fluorinated CBD compounds, compositions, and uses thereof, Pub. No.: WO/2014/108899, International Application No.: PCT/IL2014/050023,'' Def. US number Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR1120150 164927; Mechoulam R, Zuardi AW, Kapczinski F, Hallak JEC, Guimarães FS, Crippa JAS, Breuer A). Universidade de São Paulo (USP) has licensed this patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1). It has an agreement with Prati-Donaduzzi to ''develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders.'' JAC is the coinventor of the patent ''Cannabinoid-containing oral pharmaceutical composition, method for preparing and using the same,'' INPI on September 16, 2016 (BR 112018005423-2).

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