Cannabis sativa: the plant that can induce unwanted effects and also treat them

Cannabis sativa: a planta que pode produzir efeitos indesejáveis e também tratá-los

"Ce qui est aujourd'hui un paradoxe pour nous sera pour la postérité une vérité démontrée" (That which today is a paradox to us will be tomorrow's truth).
Denis Diderot

Before the Christian Era, references to *Cannabis sativa* (*cannabis*) can be found in Chinese writings stating that, if "taken in excess, it can lead to seeing devils", and "if taken for a long period of time, it can make people communicate with spirits" (Pen Ts'ao Ching, the earliest pharmacopeia), whereas current evidence suggests that one of the components of *cannabis*, cannabidiol (CBD), has antipsychotic effects.[1,2] In the same direction, a number of studies show that *cannabis* users justify the use of the substance as a way to relax, to deal with stress, and to reduce anxiety. However, the main adverse effect of *cannabis* is an acute and intense anxiety reaction that often resembles panic attacks.[3] How can this plant, which is among the earliest ones cultivated by Man, induce such antagonistic effects?

This question began to be answered in the first half of the 1960s by the group of Professor Raphael Mechoulam, with the discovery of the chemical structure of *cannabis*' major components, such as Δ^9-tetrahidrocanabinol (Δ^9-THC), accountable for the psychoactive effects of the plant, and CBD, the best known non-psychotropic cannabinoid. Over 80 cannabinoids are known today, secreted by glands located in the head of hairs that cover the plant's flowers and leaves. The availability of these components in pure form stimulated the interest for the study of *cannabis*, with publications reaching their peak in the mid-1970s.

In this period, a group of Brazilian researchers led by Elisaldo Luiz de Araújo Carlini made significant progress in the study of the plant, especially in regard to the interactions among cannabinoids, demonstrating that the effects of cannabis could not be fully explained by the action of Δ^9-THC.

In one of such interaction studies involving healthy volunteers, CBD was shown to attenuate the anxiety and psychotomimetic actions of elevated doses of Δ^9-THC, suggesting that CBD could have anxiolytic and/or antipsychotic properties. That was the beginning of a line of investigation followed by our research group until today[4] and that is described in the article entitled *Therapeutical use of cannabinoids in psychiatry*, included in this supplement.[5] The contradictory actions of cannabinoids on mental disorders are discussed in this supplement by two other articles, one dealing with the effects of cannabinoids in psychoses and the other with the abuse of *cannabis* by patients with mental disorders.

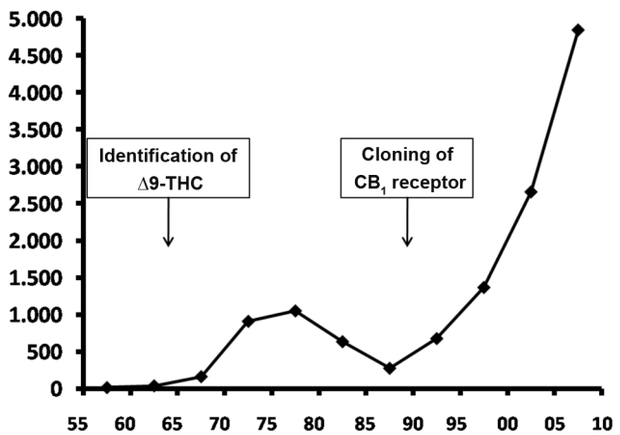

Figure 1 – Each point represents the number of publications related to *Cannabis sativa* in five-year periods between 1955 and 2010. The data were obtained from a search performed on the ISI Web of Science online database using the keywords *cannabis*, *cannabinoids*, *marihuana*, and *marijuana*.

After the peak in the 1970s, the number of articles published in the area decreased for over a decade. However, in the end of the 1980s and beginning of the 1990s, the interest for the study of *cannabis* was renewed with the description and cloning of cannabinoid-specific receptors in the nervous system and the ensuing identification of endogenous ligands bound to these receptors. This subject is analyzed in detail in the article *Pharmacological exploitation of the endocannabinoid system: new perspectives for the treatment of depression and anxiety disorders?*.[6] After these findings, the number of publications related to *cannabis* has increased almost tenfold from the 1980s to the current decade (ISI Web of Science – Figure 1).

The amount of knowledge gathered by these investigations has contributed for the clarification of polemic questions related to *cannabis*, such as its effects on cognition and its potential to cause dependence and abstinence symptoms. These issues are approached in this supplement by the articles *Cognitive abnormalities and*

cannabis *use*[7] and *Pharmacological and psychosocial interventions for* cannabis *use disorders.*[8]

Today, we are closer to understanding how cannabinoids act, and this understanding has unveiled the functioning of a modulating neurotransmission system whose existence was unsuspected of 20 years ago. These advances might be able to reconcile the apparently contradictory findings related to *cannabis*, to further our knowledge concerning psychiatric disorders, and to support the design of novel treatment possibilities in psychiatry.

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**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.
For more information, see Instructions for authors.

References

1. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39(4):421-9.

2. Zuardi AW. History of cannabis as a medicine: a review. *Rev Bras Psiquiatr*. 2006;28(2):153-7.

3. Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli P. Cannabis and anxiety: a critical review of the evidence. *Hum Psychopharmacol*. 2009;24(7):515-23.

4. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*. 2008;30(3):271-80.

5. Crippa JAS, Zuardi AW, Hallak JEC. Therapeutical use of the cannabinoids in psychiatry. *Rev Bras Psiquiatr*. 2010;32(Suppl I):S56-66.

6. Saito VM, Wotjak CT, Moreira FA. Pharmacological exploitation of the endocannabinoid system: new perspectives for the treatment of depression and anxiety disorders? *Rev Bras Psiquiatr*. 2010;32(Suppl I):S7-14.

7. Solowij N, Pesa N. Cognitive abnormalities and cannabis use. *Rev Bras Psiquiatr*. 2010;32(Suppl I):S31-40

8. Budney AJ, Vandrey RG, Stanger C. Pharmacological and psychosocial interventions for cannabis use disorders. *Rev Bras Psiquiatr*. 2010;32(Suppl I):S46-55.