



Opinion note

Cannabis a "new" old medicine? - The challenges of its medical use in the XXI century

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ABSTRACT

Cannabis sativa L. is an ancient plant, that has been used during centuries as rope, cloth, paper, oil and birdfeed and also a well-known psychoactive drug included in the lists of UN 1961 Convention and the following documents related. Likewise, it has remarkable pharmacological properties recognized by tradition that now object of scientific research. This plant produces a unique series of secondary metabolites called cannabinoids which exhibit a typical C₂₁ terpenophenolic skeleton, responsible for its pharmacological profile. These cannabinoids interact with the endogenous endocannabinoid system, involved in the regulation of a variety of physiological and cognitive processes including fertility, pregnancy, during pre- and postnatal development, appetite, pain-sensation, mood and memory. Some of these pharmacological activities are so novel and interesting that justify the scientific research in these areas which is performing now. This process is expensive and takes a lot of time, and in the meantime, millions of people use cannabis herb, for medical treatments based in traditional use. Taking into consideration this fact, there are some countries have approved the medical use of cannabis, creating specific regulations. Also, the Expert Committee on Drug Dependencies, of the World Health Organization (WHO) held in June 2018 a report about the medical use of cannabis. This report recommends that a critical review of the scientific literature on the cannabis plant and its resin, extracts or tinctures should be performed and that Cannabidiol (CBD) should not be included in the lists of prohibited substances.

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INTRODUCTION

Cannabis sativa L. (Cannabaceae) is an ancient plant, native of Asia that has been used during centuries as rope, cloth, paper, etc. Its seeds produce oil and birdfeed. It is a well-known psychoactive drug and for that reason, it is included in the lists of UN 1961 Convention and the following documents related. The legality or the legal regulation of cannabis, considering that it is a psychoactive and addictive substance has been a topic of debate during the last century. Nowadays, almost all countries have laws regarding the cultivation, sale, consumption and possession of this herb (Fig. 1).

The no-psychoactive products of cannabis, as fibre and seeds (they cannot pass the limit of 0.5% of TCH) are legal in a lot of countries, in which the



Fig. 1. Cannabis herb

National Authorities give licenses for the farm the cannabis plants intended for this use. But what about the medicinal use of this millenary plant? There are remarkable pharmacological properties recognized by tradition that now are the object of scientific research.

TRADITIONAL USES OF CANNABIS

Considering the traditional use, different parts of this plant has been used in ancient China, Egypt, Sumerian and Acadia, India and Arabia, inter alia, for at least 5000 years. Also, we have references in the medical notes of Galeno in the Roman Imperium, in European medical books of the middle age and in the Secession War of the United States. The relevant traditional uses are analgesia for all type of pain (including acute, oncological, neuropathic and chronic pain), epilepsy, ophthalmic conditions, cancer and appetite' stimulation (Pertwee, 2014).

PHYTOCHEMICAL PROFILE OF CANNABIS

Cannabis sativa produces a unique series of secondary metabolites called cannabinoids which exhibit a typical C₂₁ terpenophenolic skeleton, responsible for its pharmacological profile. Today the term cannabinoid refers not only the chemical substances isolated from *C. sativa* but also their derivatives and transformation products. These cannabinoids interact with the endogenous endocannabinoid system (ECS) which is a biological system composed of neurotransmitters and receptors (Fride, 2004).

These neurotransmitters are endogenous lipid-based molecules that bind to cannabinoid receptors, which are proteins that are expressed throughout the mammalian central nervous system and peripheral nervous system. The endocannabinoid system is involved in the regulation of a variety of physiological and cognitive processes including fertility, pregnancy, during pre- and postnatal development, appetite, pain-sensation, mood and memory (Klein et al., 2012; Wang et al., 2006).

Two primary endocannabinoid receptors have been identified as CB₁ and CB₂. CB₁ was first cloned in 1990 whereas CB₂ was cloned in 1993. CB₁ receptors are found predominantly in the brain and nervous system, as well as in peripheral organs and tissues, and are the main molecular target of the endocannabinoid anandamide, as well as its mimetic phytocannabinoid, phytocannabinoid tetrahydrocannabinol (THC).

Another main endocannabinoid is 2-arachidonoylglycerol (2-AG) which is active at both cannabinoid receptors, as its mimetic phytocannabinoid, cannabidiol (CBD). It is proved that 2-AG and CBD are involved in the regulation of appetite, functions of immune system and pain management.

PHARMACOLOGICAL RELEVANCE

Due to its legal conditions, there is an enormous difficulty for the scientific research in pharmacology and toxicity of this plant. There are not enough well-controlled clinical trials in order to establish the pharmacological and safety profile as well as characterized the medical potential of the plant and its secondary metabolites.

There is a reasonable amount of evidence regarding preclinical studies and also anecdotal clinical evidence of the usefulness of cannabis for medicinal use. Also, there are substantial traditional and historical references. But all of this is not sufficient to support its use as a medicine according to current sanitary concepts. There is a totally understandable concern in National Health Authorities regarding the approval of miscellaneous medical uses related to this plant. Moreover, most of the physicians are not prepared to indicate this kind of medicine because, unlike opioids which are well studied in medical schools, cannabis products are associated with recreational use and have not been studied in depth to assess its medical potential.

But there are some pharmacological activities of cannabis and cannabinoids that promise to be novel and interesting because of the act in situations that other drugs are ineffective. The research in those areas is in progress but it is expensive and takes a lot of time. In the meantime, millions of people use cannabis herb for the treatment of illness that not have a good response from the pharmaceutical industry. And this is one of the main problems that Health Authorities must recognize and act in consequence. The prohibitionist policies regarding the treatment for refractory epilepsy, cancer and pain among others are not effective.

CURRENT STATUS AND PERSPECTIVES

There are some countries that have approved the medical use. One country in South America, Uruguay has created specific regulation for the recreational use but also for medical and research purposes. Paradoxically, in Uruguay is easier to access to recreational marijuana, with quality certified by the government, than Cannabis for medical use. But this country has an active attitude in order to give its people some kind of solutions.

First of all, it is regulated that pharmaceutical preparations with less than 1% of THC must not be considered controlled drugs, but prescription medicines with mandatory pharmacovigilance. There are now two industrial pharmaceutical preparations made in Uruguay, properly registered as medicines for the treatment of refractory epilepsy based on cannabis extract. Also, there are rules and regulations for the culture of cannabis plants for medical purposes. In addition, this regulation considers the prevention

of drug trafficking and money laundering, creating specific mechanisms to ensure that the funds used are clean money.

In the same line of thinking, the Expert Committee on Drug Dependencies, of the World Health Organization (WHO) held in June 2018, a report about the medical use of cannabis. In this report, it can be remarked the following (Aya, 2018):

1. Cannabidiol (CBD) should not be included in the lists of prohibited substances of the drug control conventions.
2. A critical review of the scientific literature on the cannabis plant and its resin, extracts or tinctures (including extracts rich in CBD, Delta-9-THC and THC isomers) will be carried out.

The next meeting of the Committee of Experts will take place in November 2018 and will continue working in this line.

CONCLUSION

The use of ethnobotanical and traditional knowledge could be an interesting alternative relatively quickly to implement. The ancient recipes should be studied in depth. Botanic specifications, agriculture practices, and ethnomedical preparations in industrial scale should be standardized. All specific indications must be clearly established and pharmacists and physicians would be involved in the rational use of ethnobotanical and traditional knowledge. Accomplishing all of those conditions, this kind of

phytomedicines could offer solutions for some prevalent illness with efficacy, safety and accessibility.

CONFLICTS OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this article.

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