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REAL WORLD DATA ON THE THERAPEUTIC RESPONSE TO THE USE OF *CANNABIS* PRODUCTS IN MEDICAL AND VETERINARY CLINICS

Telma Florio
Master Student, Universidade Federal de São Paulo (Unifesp), Department of Neurosciences and Behavior - PPGICS-Santos - SP

Luiza Ramos
Doctor - UNESA, CANAPSE National Consortium – Student of Cannabinology, Research and Service, Rio de Janeiro – RJ

Jomênica de Bortoli
PhD in Neurosciences - UNIFESP, Specialist in Clinical Research - - Harvard University - Boston, MA, Vice- President of the Research Ethics Committee of: ``Fundação Rocha Brito``, Núcleo de Pesquisa Herbarium Laboratório Botânico, Colombo, Paraná

Camila Abreu
Master in Research, Management and Development in the pharmaceutical industry by: Fiocruz

Jackeline Barbosa
PhD in Medical Sciences - UFRJ, Master in Neurology - – FMUSP-RP, CANAPSE - National Consortium - Academic of Cannabinology, Research and Service, ``Núcleo de Pesquisa``: Herbarium Laboratório Botânico``, Colombo, Paraná

Abstract: This study aims to use new methodologies for generating evidence through electronic data, and requires effort from all *stakeholders* in the cannabis chain who will be able to use this data for decision-making. With the combination of technologies and scientific advances available today, there has never been a more opportune moment to address this issue and verify the potential of Cannabis for socio-environmental and scientific evolution in the One Health in Brazil. Through the recent discoveries of the Endocannabinoid System and its particularities, the Real-World Study becomes extremely important to obtain consistent data on the use of medicinal Cannabis, which can generate social, economic, therapeutic, environmental and scientific values. The scenario of insecurity of health professionals with the lack of consistent information and regulation on the indications, adverse effects and quality of the available product, requires that new research be implemented. Despite extensive evidence and research supporting efficacy and safety in use in various therapies, Brazilian regulation is still problematic. The use of Cannabis by humans and animals, for thousands of years, to relieve physical, mental, emotional and spiritual pain, is contextualized through traditional medicine, and its use today can bring us essential and complementary data for safety, effectiveness and therapeutic indications, characterizing Cannabis products as a highly valuable herbal medicine. Through forms on a digital platform focused on integrative and interdisciplinary therapies, this study aims to obtain Real World Data (DMR), to generate Real World Evidence (EMR), in the medical, social and environmental context for the promotion of human health, veterinary and environmental. Absolute secrecy is guaranteed for the safety and integrity of research participants, through the General Data Protection Law. The study was approved by the Ethics Committee. The Free and Informed Consent Term will be applied and the answers in the interdisciplinary forms will be automatically analyzed, in percentage form, on the use of Cannabis products, also promoting a social project created to evaluate the social, educational and environmental impact, from resources generated with the commercial platform.

Keywords: Real World Study; medical cannabis; Unique Health; Social Impact.

INTRODUCTION

INVESTIGATIONAL PRODUCT

In 1964, Dr. Raphael Mechoulam discovered THC, which was the first identified cannabinoid. Cannabinoids are components found in plants of the genus Cannabis. This finding paved the way for the discovery of the endogenous cannabinoid system (ECS) of which anandamide and 2-arachidonoylglycerol (2-AG) are considered the main endogenous mediators in high-order mammals, including humans. Both anandamide and 2-AG regulate serotonin, dopamine, gamma-aminobutyric acid (GABA) and glutamate-mediated transmission in the central nervous system (CNS), thereby demonstrating how these endogenous cannabinoids regulate many physiological and pathological processes such as pain, immune system, appetite, thermoregulation, energy, metabolism, depression and fertility, among others (Zaid, Shingo, Mourad, & Jason, 2020).

A plethora of studies have shown that phytocannabinoids, molecules present in cannabis, mediate their pharmacological actions through binding to CB1 and CB2 cannabinoid receptors, as well as regulating the production and degradation of endogenous endocannabinoids. CB1 receptors are abundant and widely expressed throughout the CNS and are responsible for the psychopharmacological and analgesic effects

of THC. Of particular interest, CB1 receptors are highly expressed in areas of the brain that are implicated in nociceptive perception, such as the thalamus and amygdala (Zaid, Shingo, Mourad, & Jason, 2020).

The presynaptic location of CB1 receptors allows cannabinoids to modulate the release of neurotransmitters such as dopamine, noradrenaline, glutamate, GABA, serotonin and acetylcholine. Among their actions, they regulate nociceptive thresholds and produce multiple biological effects through the balance between excitatory and inhibitory neurotransmitters. Although CB2 receptors have limited expression in sensory cells in the CNS, they are mainly distributed in peripheral tissues (Zaid, Shingo, Mourad, & Jason, 2020).

CB2 is widely known for its immunomodulatory role, which is related to the main events: induction of apoptosis, suppression of cell proliferation, inhibition of pro-inflammatory cytokine production, increase of anti-inflammatory cytokines and induction of regulatory T cells (Rossi, Tortora, Argenziano, Di Paola, & Punzo, 2020).

CB2 agonists have been shown to inhibit TNF-α on CD14+ monocytes and M1 macrophages and increase the expression of the anti-inflammatory cytokine IL-10 (Gertsch, 2016). CB2 agonists also induce FoxP3+ anti-inflammatory regulatory T cells (Tregs) that produce TGF-β and IL-10 (Gentili, et al, 2019).

Consistent with the wide range of physiological actions of endocannabinoids, phytocannabinoids have demonstrated applicability in various clinical conditions. *Cannabis sativa* is a dioecious plant with a complex chemical composition. 565 natural constituents were reported, of which 120 correspond to the cannabinoid class. The rest of the *Cannabis* phytochemicals include secondary metabolites such as terpenoids, flavonoids, ethylbenoids, lignins and alkaloids, among others. The term cannabinoid includes compounds isolated from the *Cannabis* plant, pharmacologically analogous synthetic cannabinoids, and endogenous receptor ligands called endocannabinoids (Schofs, Sparo, & Bruni, 2021).

Cannabinoids are phenolic compounds, including their analogues and transformation products, predominantly produced by *Cannabis sativa*. They were detected in various parts of the plant; however, they largely accumulate in the secret cavity of the glandular trichomes of female flowers. They can be divided into 10 main structural types: Δ9-tetrahidrocanabinol (Δ9-THC), Δ8-tetrahidrocanabinol (Δ8-THC), canabigerol (CBG), canabicromeno (CBC), canabidiol (CBD), canabinodiol (CBND), canabielsoin (CBE), canabiclol (CBL), canabinol (CBN) e canabitriol (CBT) (Schofs, Sparo, & Bruni, 2021).

Δ9-THC, CBN, CBD and CBC are the most abundant phytocannabinoids in the plant. There are also acidic forms, such as CBG, cannabigerolic acid (CBGA). CBG appears as an intermediate cannabinoid, of relatively low concentration in the Cannabis plant, and among its suggested properties are antiproliferative, muscle relaxant, antidepressant and analgesic effects. Δ9-THC is the main psychoactive component of *Cannabis sativa.* According to the phytocannabinoid profile, the plant is divided into different chemical phenotypes. Δ9-THC is the predominant cannabinoid in adult use chemotypes. Δ9-THC interacts with endogenous cannabinoid receptors types 1 and 2 (CB1 and CB2) and produces psychoactivity, analgesia, muscle relaxation and antispasmodic effects. CBN is a product of Δ9-THC oxidation, therefore it is a minor component of fresh *Cannabis*, and exerts a weak partial agonism on CB1 and CB2 receptors. Higher concentrations of CBC were found in the vegetative stages of *Cannabis*

and its presence is related to the presence of Δ9-THC. CBC has shown anti-inflammatory and anti-nociceptive activity and exerts an agonism on CB2 (Schofs, Sparo, & Bruni, 2021).

Meanwhile, CBD is the main non-psychoactive constituent of hemp-type Cannabis strains. Within the applications of CBD are inflammatory and neurodegenerative diseases, epilepsy, pain, anxiety, multiple sclerosis, cancer, among others (Schofs, Sparo, & Bruni, 2021).

The aforementioned multidirectional properties of CBD stem from its complex mechanism of action. CBD has an affinity for cannabinoid receptors (CB-Rs); acts as a negative allosteric modulator of CB1 and as an inverse agonist of CB2. In addition, CBD acts through many other molecular targets, including G protein-coupled receptors such as peroxisome proliferator activating receptor γ (PPAR-γ), serotonin receptors (5-HT1A and 5-HT2A), and inotropic receptors, for example, activating vanilloid TRPV1, and inhibiting serotonin 5-HT3 receptors (Malinowska, Baranowska-Kuczko, Kicman, & Schlicker, 2021).

In addition, CBD inhibits the activity of several transport proteins (eg adenosine uptake) and enzymes such as fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of endocannabinoid anandamide. Its effect against oxidative stress, acting on mitochondria, has been considered as an additional molecular mechanism (Malinowska, Baranowska-Kuczko, Kicman, & Schlicker, 2021).

Several studies have described cannabinoids as multi-target molecules, acting as adapters and modulators, in different ways, depending on the type and location of the imbalance in the brain and body, interacting mainly with the specific receptor proteins CB1 and CB2 (Malinowska, Baranowska-Kuczko, Kicman, & Schlicker, 2021).

Although limited to preclinical studies, evidence also points to a possible use of cannabidiol in viral infections. Indeed, several plant-derived compounds have evolved to exhibit antiviral activity, including many phenol-based compounds such as terpenoids. Cannabinoids exert their activity through interaction with nuclear peroxisome proliferator-activated receptors, known as Peroxisome Proliferator-Activated Receptors - PPARs (O'Sullivan & Kendall, 2010), and their activity is regulated by steroids and lipid metabolites. There are three isoforms of PPARs: PPAR-α, PPAR-β and PPAR-γ. They have been identified and have been shown to regulate the expression of genes related to lipid homeostasis, in addition to glucose and inflammatory responses (Gentili, et al, 2019; Esposito, et al, 2020).

Many compounds present in *Cannabis* extracts could contribute to the antimicrobial activity, in addition to the fact that, acting synergistically, the plant's complex mix of chemical compounds makes it difficult to recognize which is the main component behind the antimicrobial and antiviral effects (Schofs, Sparo, & Bruni, 2021).

To date, tetrahydrocannabinol and cannabidiol, alone or in combination with other phytocannabinoids, have been extensively examined in many clinical trials for the treatment of numerous health conditions, including pain and inflammation. However, few studies have investigated the biological benefits of full-spectrum *Cannabis* plant extract. Given that Cannabis is known to generate a large number of cannabinoids, along with numerous other biologically relevant products, including terpenes and flavonoids, studies involving tetrahydrocannabinol and/or cannabidiol alone do not consider the potential biological benefits of full-spectrum *Cannabis* extracts.

METHODOLOGY

The research participant using cannabis products will be directed to the questionnaire anonymously, individually, in partnership with health professionals, industries, associations and cannabis research institutions. Research data will be obtained through questionnaires previously developed for this study, generating automated percentage results every 2 months for 6 months. After acceptance of the TCLE, available on a virtual platform (www.caonabico.com), we will verify the evolution and clinical routine based on the responses to the questionnaire on cannabis therapy in animals and humans. The questions will be developed in multiple choice format so that the results are obtained in percentage form, automatically, mitigating the risks of errors and data manipulation.

RESULTS AND DISCUSSION

The results will be analyzed by the researchers in each round of questionnaires. The clinical evolutions will be evaluated, within each pathology or symptomatic condition, in percentage, systematizing them and compiling them for future scientific publications. Thus, after knowing the responses of the participants, we have the opportunity to obtain clinical data on the effectiveness and safety of the different types of products derived of *Cannabis*. The questionnaire and survey follow-up will be carried out virtually by the technical analysis of the responsible investigator and advisors, potentially benefiting all stakeholders in the cannabis chain, who will be able to use this data for decision-making.

CONCLUSIONS

Real-world studies have been considered a tool to complement information from clinical trials in contexts where these are restricted, such as generalizations to broader and heterogeneous populations, long-term evaluations, diseases and rare adverse events. We intend to innovate, through interfaces with social projects, developing medical, social, educational and environmental impact from resources generated with the commercial platform. Collect Real World Data (DMR) to generate Real World Evidence (EMR) in the medical, social and environmental context for promoting human, veterinary and environmental health throughout the plant *Cannabis*.

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