Chapter 270

Real-world data on the therapeutic response in the use of cannabis products in the medical and veterinary clinic

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ABSTRACT
This study aims to use new methodologies to generate evidence through data and requires effort from all stakeholders in the cannabis chain that can potentially use this data for decision-making. With the combination of technologies and scientific advances available today, there has never been a more opportune time to address this issue and verify the potential of Cannabis for scientific socio-environmental evolution in One Health in Brazil. Through the recent discoveries of the Endocannabinoid System and its particularities, the study of the real world becomes of paramount importance to obtain consistent data on the use of medicinal Cannabis, generating social, economic, therapeutic, environmental, and scientific values. The insecurity of health professionals with the lack of consistent information and regulation on the indications, adverse effects, and quality of the available product, demand that new research be implemented. Despite extensive evidence and research that supports the efficacy and safety of use in various therapies, Brazilian regulation is still a problem. 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 therapeutical indications, targeting Cannabis products as a herbal medicine of great value. This study aims to obtain, through forms on a commercial digital platform, focused on integrative and interdisciplinary therapies, Real World Data (RWD) for Real World Evidence (RWE), in the medical, social, and environmental context to promote human, veterinary, and environmental health. Absolute secrecy is guaranteed for the safety and integrity of research participants, through the general data protection law. The study has been approved by the ethics council. Free informed consent term will be applied and the answers to the interdisciplinary forms will be automatically analyzed, in percentage form, on the use of Cannabis products, promoting a social project created to assess social, educational, and environmental impact, with resources generated from the commercial platform.

Keywords: Real World Study, Medical cannabis, One Health.

1 INTRODUCTION

Investigational Product

In 1964, Dr. Raphael Mechoulam discovered THC, which was the first cannabinoid identified. 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-araquidonoilglicerol (2-AG) are considered the main endogenous mediators in high-order mammals, including humans. Both anandamide and 2-AG regulate the transmission mediated by serotonin, dopamine, gamma-aminobutyric acid (GABA), and glutamate in the central nervous system (CNS), thus demonstrating how these endogenous cannabinoids regulate many physiological and pathological processes such as pain, immune response, appetite, thermoregulation, energy, metabolism, depression, and fertility, among others (Zaid, Shingo, Mourad, & Jason, 2020).

A multitude of studies has demonstrated that phytocannabinoids, molecules present in cannabis, mediate their pharmacological actions by binding to cannabinoid receptors CB1 and CB2, as well as by 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 have a high level of expression in areas of the brain that are implicated in nociceptive perception, such as the thalamus and amygdala (Zaid, Shingo, Mourad, Jason, 2020).

The presynaptic localization 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, an increase of anti-inflammatory cytokines, and induction of regulatory T cells (Rossi, Tortora, Argenziano, Di Paola, & Punzo, 2020).

And CB2 agonists have been shown to inhibit TNF-α CD14+ monocytes and M1 macrophages and increase the expression of the anti-inflammatory cytokine IL-10 (Gertsch, 2016). CB2 agonists also induce anti-inflammatory FoxP3+ (Tregs) regulatory T cells 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. Foram reported 565 natural constituents, of which 120 correspond to the cannabinoid class. The rest of the phytochemicals in cannabis include secondary metabolites such as terpenoids, flavon terpenoids, flavonoids, ethylbenoids, lignins, and alkaloids, among others. The term

cannabinoid includes the compounds isolated from the cannabis plant, the pharmacologically analogous synthetic cannabinoids, and the endogenous receptor ligands called endocannabinoids (Schofs, Sparo, & Bruni, 2021).

Cannabinoids are phenolic compounds, including their analogs and transformation products, predominantly produced by Cannabis sativa. They were detected in various parts of the plant; However, they accumulate largely in the secret cavity of the glandular trichomes of female flowers. They can be divided into 10- main structural types: Δ 9-tetrad r cannabinol (Δ 9-THC), Δ 8-tetrahydrocannabinol (Δ8-THC), cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabidiol (CBND), cannabielsoin (CBE), cannabiclol (CBL), cannabinol (CBN) and cannabitriol (CBT) (Schofs, Sparo, & Bruni, 2021).

Δ9-THC, CBN, CBD, and CBC are the most abundant phytocannabinoids in the plant. There are also acidic s-forms, such as CBG, and gerolic cannabi 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 profile of phytocannabinoids, the plant is divided into different chemical phenotypes. Δ9-THC is the predominant cannabinoid in adult 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 the product of the oxidation of Δ9-THC, so it is a minor component of fresh cannabis and exerts a weak partial agonism on the CB1 and CB2 receptors. Higher concentrations of BCC have been found in the vegetative stages of cannabis and its presence is related to the presence of Δ 9-THC. CBC has shown anti-inflammatory and anti-nociceptive activity and exerts an agonism of no CB2 (Schofs, Sparo, & Bruni, 2021).

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

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

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

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

Although limited to preclinical studies, evidence also points to the possible use of cannabidiol in viral infections. 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 antimicrobial activity, and by acting synergistically, the plant's complex blend of chemical compounds makes it difficult to recognize what 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.

2 METHODOLOGY

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

3 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, percentage-ally, 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 various types of products derived from Cannabis. The questionnaire and follow-up of the research will be carried out virtually by the technical analysis of the principal investigator and advisors, potentially benefiting all stakeholders in the cannabis chain, who can use this data for decision-making.

4 CONCLUSIONS

Real-world studies have been considered a tool to complement information from clinical trials in contexts where they are restricted, such as in generalizations to broader, heterogeneous populations, long-term assessments, rare diseases, and adverse events. We intend to innovate, through interfaces with social projects, developing medicinal, social, educational, and environmental impact from resources generated with the commercial platform. Real World Data (RWD) data to generate Real World Evidence (RWE) in the medicinal, social, and environmental context for human health, veterinary, and environmental health promotion through the cannabis plant.

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