Saúde e Pesquisa
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Use of Cannabidiol in Terminal Patients with Refractory Pain: Knowledge Among Students in Maringá

Uso de Canabidiol em pacientes terminais com dor refratária: conhecimento entre estudantes de Maringá

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ABSTRACT
Cannabis has emerged as an alternative in the treatment of chronic conditions, especially in cases of pain refractory to conventional medications. Its use in conjunction with opioids allows for reducing opioid doses while preserving efficacy and minimizing side effects. Despite scientific support, the coverage of this topic in medical education is limited. Therefore, an exploratory-descriptive survey was conducted at UniCesumar (Cesumar University), Maringá-PR, aiming to identify knowledge gaps among students regarding the use of cannabis in treating terminal patients with refractory pain. The results revealed knowledge deficits, highlighting the need for deeper engagement during medical education. Among the expected findings, a lack of information about benefits, adverse effects, and the use of cannabidiol was noted. This study emphasizes the importance of a more comprehensive approach in medical training to demystify prejudices and stigmas about the subject, ensuring humane care and improved quality of life for patients.

Keywords: Cannabis; Chronic Pain; Surveys and Questionnaires.

RESUMO
A cannabis surge como alternativa no tratamento de condições crônicas, especialmente em casos de dor refratária aos medicamentos convencionais. Seu uso em conjunto com opióides possibilita a redução das doses do mesmo, preservando a eficácia e minimizando efeitos colaterais. Apesar do respaldo científico, a abordagem desse tema na graduação em medicina é limitada. Diante disso, foi realizada uma pesquisa exploratório-descritiva na UniCesumar (Universidade Cesumar), Maringá-PR, com o objetivo de identificar lacunas no conhecimento dos estudantes sobre o uso da cannabis no tratamento de pacientes terminais com dor refratária. Os resultados revelaram déficits de conhecimento, evidenciando a necessidade de maior aprofundamento durante a graduação. Dentre os resultados esperados, destaca-se a falta de informação sobre benefícios, efeitos adversos e uso do canabidiol. Este estudo enfatiza a importância de uma abordagem mais abrangente na formação médica com o intuito de desmistificar preconceitos e estigmas acerca do tema, assegurando um atendimento humanizado e melhor qualidade de vida aos pacientes.

Palavras-chave: Cannabis Sativa; Dor crônica; Levantamento e questionários.

INTRODUCTION

Updated data from the World Health Organization (WHO) in 2022 show that approximately three-quarters of deaths worldwide are caused by non-communicable chronic diseases (NCDs), such as cardiovascular diseases, diabetes, and cancer[1]. In Brazil, according to the National Cancer Institute (INCA), it is estimated that about 704,000 new cases of various types of cancer will occur between 2023 and 2025, responsible for causing acute and chronic pain, consequently reducing the quality of life of patients[2].

According to Lima et al., 2013, the most common types of pain found in cancer were visceral, nociceptive, and neuropathic, which in most cases are exacerbated by metastases and treatment with radio and chemotherapy[3]. Therefore, the use of opioids, which are strong analgesics, has been increasingly widespread in the treatment of pain. A limitation in this use is associated with the capacity to cause dependence, in addition to numerous side effects such as sedation, lack of motor coordination, and decreased concentration. Despite all pharmacological approaches, 25% of neuropathic pains are not controlled even in centers of excellence.

Undoubtedly, promoting health and enhancing the quality of life for terminal cancer patients suffering from refractory pain, that is, where conventional medications are insufficient or ineffective in relieving the patient's pain, is essential. In this context, cannabis emerges as a potential alternative to help minimize suffering. Cannabis is a controversial plant that divides opinions and has been gaining visibility among these patients due to its analgesic and antiemetic properties related to its modulating role in neurotransmission[4]. Additionally, there is a synergistic effect with opioids, allowing for reducing these analgesics without loss of efficacy. Within such context, this leads to the decrease of unwanted adverse effects and mortality from opioid overdose in a hospital setting[5].

Cannabis is the most consumed illicit drug worldwide, according to the 2022 World Drug Report presented by the United Nations Office on Drugs and Crime (UNODC), having been used by humanity for thousands of years[6]. Cannabis can be classified into three varieties: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*, all of which produce different amounts of psychoactive cannabinoids. Among all the species, *Cannabis sativa* is the most versatile - popularly known as "marijuana" for containing cannabinoids[7]. There are over 400 chemical substances in its composition; however, regarding pharmacodynamics, the main constituents of *Cannabis sativa* are 9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), which are the compounds in the highest concentrations in the plants[8].

For cannabidiol to act, it relies on the so-called endocannabinoid system, which is linked to the hypothalamus-pituitary-adrenal axis, thereby modulating effects related to appetite, energy balance, and fertility9. This system is composed of two types of receptors to which the aforementioned cannabis compounds bind: endocannabinoid receptors 1 (CB1), in the basal ganglia, cerebellum, hippocampus, cortex, spinal cord, and peripheral nerves; and endocannabinoid receptors 2 (CB2), found in immune system defense cells, playing a significant role in pain physiopathology control by regulating various signaling pathways involved in this process[10].

Besides its analgesic action, there are other beneficial effects of cannabis use, including alterations in the pathways of tumor vascularization due to overexpressed cannabinoid receptors on the surface, which allow the inhibition of angiogenesis, thus slowing down or even halting the formation and dissemination of metastases[11]. Moreover, CBD can act on several endogenous targets, enabling actions beyond

pain attenuation, including combating factors such as depression and anxiety; it may have anti-inflammatory effects, enable the prevention of nausea caused by chemotherapy treatment, and even induce apoptosis in certain types of cancer cells[12].

The localization of these receptors justifies the action of THC in producing the well-known psychoactive symptoms of euphoria, but it also relieves pain and inflammation and is an antispasmodic and muscle relaxant since it distorts sensory perception. However, this compound can also generate adverse effects such as tachycardia, anxiety, and sedation, varying with the duration of use and amount, which can cause serious consequences with chronic use[5]. On the other hand, CBD does not have psychoactive effects and is considered an inverse agonist of CB2 receptors, thus generating an anti-inflammatory response[8]. Additionally, unlike THC, the side effects of CBD are reduced, which enhances its safety profile and justifies the fact that it is increasingly studied in pharmacology for various pathologies[8].

Finally, there is a lack of knowledge among students and professionals about the use of cannabis, its properties, and its benefits for clinical practice, leading to health professionals and students being unfamiliar with the topic. Thus, this study aimed to evaluate medical students' knowledge regarding *Cannabis sativa* in the treatment of terminal cancer patients suffering from refractory pain, a need that transcends ideological debates and drug regulations, prioritizing the quality of life and humanization of the patients in question.

OBJECTIVE

Identify possible gaps in medical students' knowledge about the use, benefits, adverse effects, and legalization of cannabis to treat terminally ill cancer patients with pain refractory to conventional drugs.

METHODOLOGY

TYPE OF STUDY

The current research project is based on a quantitative approach, characterized as exploratory-descriptive, to identify the level of knowledge among students regarding the use of cannabis for refractory pain in terminally ill cancer patients.

INCLUSION AND EXCLUSION CRITERIA

The selected population consists of medical students from the University Center of Maringá, in the state of Paraná, Brazil, from the first to the sixth year, of both sexes, and over 17 years old. As this is research involving human beings, the Research Ethics Committee of UniCesumar approved the work with opinion number 6.108.926, respecting Resolution number 466 of 2012 from the National Health Council (CNS) of the Ministry of Health (MS). The study treated the participants' data with confidentiality and anonymity.

DATA COLLECTION AND ANALYSIS

To achieve the objective of the study, an online questionnaire was applied. This is a modified instrument derived from the research by Graças et al., 202113. The original instrument, published in English, was translated into the local language and made available through Google Forms. The form was available in August 2023. Before accessing the questionnaire, participants had to agree to the Informed Consent Term (ICF), which establishes the objectives, risks, and benefits of the research, and only after agreement was the questionnaire opened for responses. A series of variables were queried, including age, sex, current year in the medical courses, differences in the components of *Cannabis sativa*, the therapeutic potential of cannabis,

beneficial effects in treating chronic pain in terminally ill cancer patients, adverse drug effects, pharmacodynamics, pharmacokinetics, and legal aspects regarding the use of the drug in Brazil.

Responses were automatically received through the Google Forms platform and organized in an Excel spreadsheet. To synthesize and group individual responses, they were organized, and the frequencies (%) were displayed in tables and charts.

RESULTS

The study sample consisted of 123 students from the medicine course at Unicesumar, Maringá campus. The predominant frequency of respondents was female, accounting for 92 women (74.8%) and 31 men (25.2%). This frequency corresponds with the patterns described in the "Demografia Médica no Brasil 2023" study14. Regarding the age of the students, the minimum was 17 years with a maximum of 34 years, the majority being 20 years old (20.3%), followed by 17 years old (13.8%). Furthermore, 23.6% of the respondents are in the basic cycle, which corresponds to the 1st and 2nd year, and the vast majority (69.9%) are in the clinical cycle, equivalent to the 3rd and 4th year, while 6.5% of the students are in the internship phase (Table 1).

Table 1. Sample characterization (n=123)

Variables	**%(n)**
Sex	
Female	74.8% (92)
Male	25.2% (31)
Curricular Year	
Basic Cycle	23.6% (29)
Clinical Cycle	69.9% (86)
Internship	6.5% (8)
Age	
17 to 22 years	58.5% (72)
23 to 27 years	37.3 (46)
28 to 32 years	2.4% (3)
33 to 37 years	1.6% (2)

Source: Results obtained through the applied questionnaire.

Regarding the use of cannabis, it was found that 76.4% (94) of the participants denied consumption, and 23.6% (29) affirmed their use, with 23.2% (26) using it for recreational purposes, and only 2.4% (3) for therapeutic use (Figure 1).

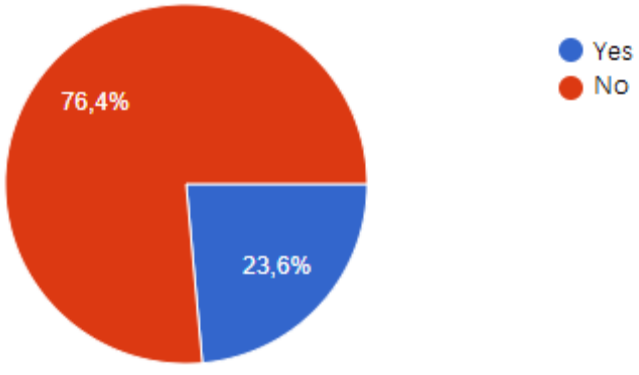

FIGURE 1. Percentage of students who use marijuana
Source: Results obtained through the applied questionnaire.

In Figure 2A, it can be observed that 84.6% of the students know how to differentiate cannabis from marijuana, and 15.4% claim the opposite, while in 2B, it is noted that 61% of the participants claim to know how to differentiate the compounds present in the substance, such as THC and CBD, and 39% are unable to differentiate.

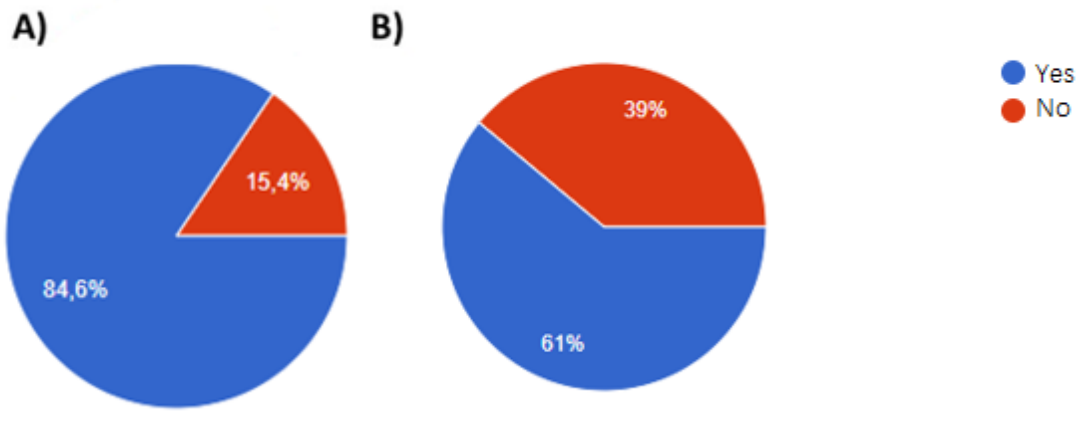

FIGURE 2. Percentage of students who claim to know how to differentiate marijuana from cannabis (A) and those who claim to know how to differentiate cannabis from THC and CBD (B)
Source: Results obtained through the applied questionnaire.

Figure 3 demonstrates the students' knowledge about some of the possible therapeutic applications of cannabis. Among the options, the most cited and recurrent by the students were chronic pain (87%), epilepsy (78%), and Parkinson's disease (76.4%).

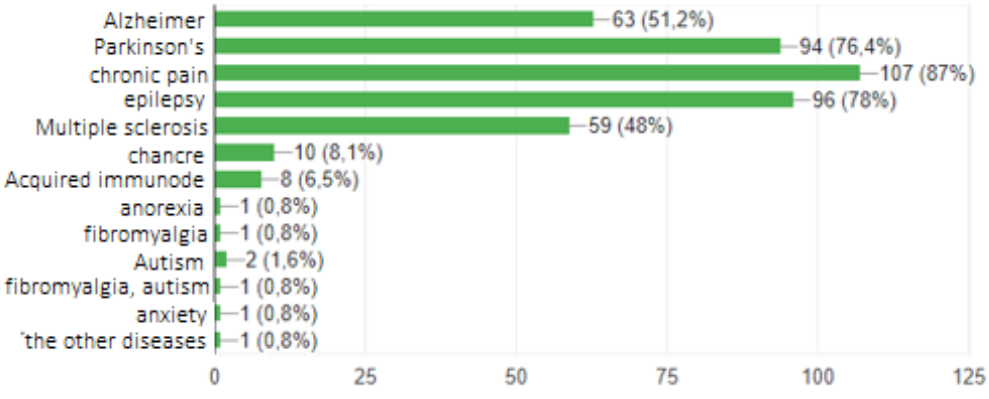

FIGURE 3. Therapeutic use of cannabis according to students
Source: Results obtained through the applied questionnaire.

As for the action of cannabis in treating chronic pain in oncological patients, most of the respondents, i.e., 102 (82.9%), believe that cannabis is effective in analgesia, followed by efficacy in anxiety, depression, and alleviating side effects of chemotherapy (65.9%). Among the possible options, the least selected were that the compound minimizes the chance of metastasis (1.6%) and that it reduces angiogenesis (2.4%), despite being correct.

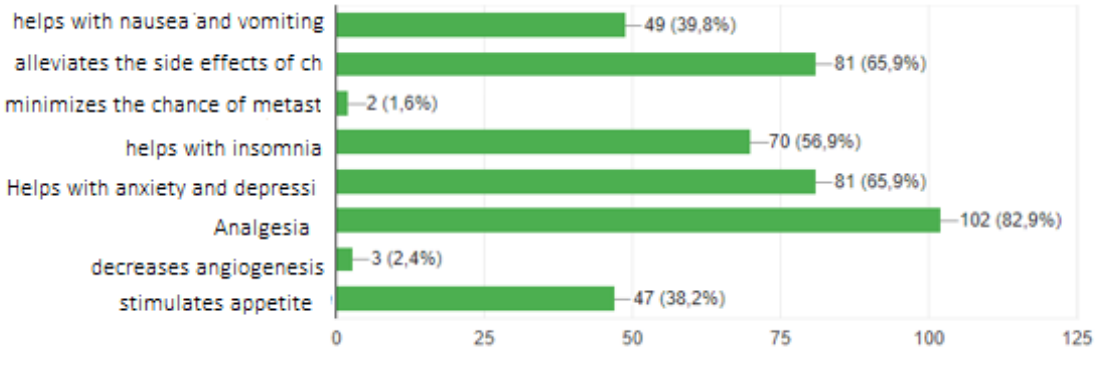

FIGURE 4. Students' perception of the action of cannabis in treating chronic pain in terminal oncological patients
Source: Results obtained through the applied questionnaire.

According to Figure 5, 73 participants (59.3%) stated they were aware of the legalization of cannabis for therapeutic purposes in Brazil, with 105 (85.4%) in favor of legalization, 16 (13%) unsure, and 2 (1.6%) not in favor. Among the reasons presented for opposing legalization, the most voted were side effects with 10 (9.8%) votes, followed by 7 (6.9%) due to dependency caused, and 4 (3.9%) due to lack of scientific evidence on the topic.

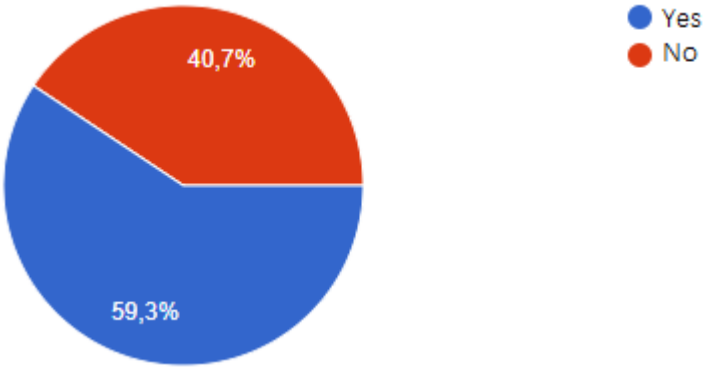

FIGURE 5. Students' knowledge about legal aspects of cannabis in Brazil
Source: Results obtained through the applied questionnaire.

Figure 6 highlights that when asked about the need for further depth on the topic during the course, 96.7%, i.e., the vast majority, believe it is necessary since it is not a topic widely discussed during graduation but has great relevance in the field.

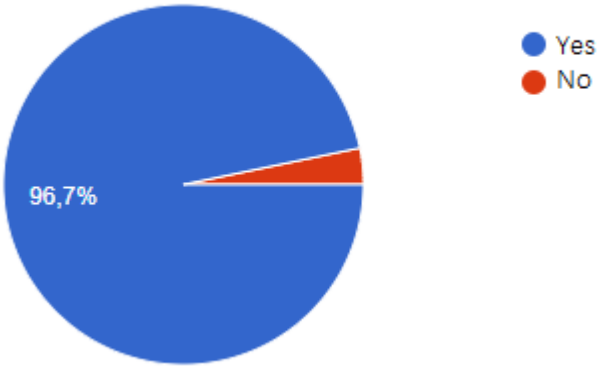

FIGURE 6. Students' view on the need to delve deeper into the topic during the medical course
Source: Results obtained through the applied questionnaire.

DISCUSSION

After analyzing the data from the sample, it can be observed that regarding the use of cannabis, most university students reported using it for recreational purposes. Thus, highlighting a higher consumption among university students than in the general Brazilian population—according to data from the Oswaldo Cruz Foundation (FIOCRUZ) in 2019, 3.2% of Brazilians consumed illicit drugs[15]. Considering the large number of students who use cannabis, it can be hypothesized a relationship between its use and the exhaustive profile of a career like medicine because of greater vulnerability related to changes and anxieties in the lives of new students, excessive workload, and the direct contact of medical students with patients and the pain faced by them[16].

Given the results, it can be observed that 84.6% of the students know how to differentiate cannabidiol from marijuana, while 61% of the

participants claim to know how to differentiate the compounds present in cannabis, such as THC and CBD. Therefore, this distinction between the various compounds is fundamental since, in the therapeutic use of cannabis, CBD is predominantly used, unlike THC, which is a substance associated with psychoactive effects of euphoria and distortion of social perception commonly related to recreational and illicit drug use[4].

THC is considered the main active compound present in *Cannabis sativa*; this substance is primarily responsible for generating the effects of euphoria and hallucinations popularly known with the indiscriminate use of marijuana. Its effect is due to its tropism for CB1 and CB2 receptors but mainly of type 1 located in the basal ganglia (striatum, substantia nigra, and subthalamic nucleus), cerebellum, hippocampus, cortex, spinal cord, and in peripheral nerves[16]. After interaction with these receptors, behavioral changes occur, changes in the level of consciousness, in addition to tachycardia, intoxication, and sedation[3].

However, about 40% of the composition of cannabis is the compound CBD, which can be used for many purposes because of its wide range of reported therapeutic effects, notably its antipsychotic character due to exerting divergent effects from THC, thereby contributing to its high safety profile[16]. The compound acts on several receptors spread throughout the central nervous system and has a low affinity for CB1 and CB2 receptors, aiding in explaining the absence of psychotic effects in CBD. Its effects are related to the activation of type 1 vanilloid receptors that integrate multiple nociceptive effects, highlighting its modulation of pain through its antiinflammatory effects. Moreover, the compound has a serotonergic agonist character, modifying the release of the neurotransmitter, thereby justifying its anxiolytic and antiemetic effects[17].

In addition, some medications based on cannabis components are available. These can include isolated or combined compositions of CBD and THC and can be used through various routes such as oral, transdermal, intranasal, and inhaled, having modifications in their speed of action and availability according to the chosen route of introduction[13]. Moreover, the main form known and disseminated within the field of medicine would be in the format of cannabidiol oils, but they can also be available in capsules and other formats.

Furthermore, Figure 3 demonstrates the knowledge of the interviewed students about some of the possible therapeutic applications of cannabis, where all the alternatives were correct despite some responses like chronic pain and epilepsy being selected in larger quantities[13]. However, contrary to the results found in the current research, there are different articles[18,13] in which other diseases were more prevalent, such as cancer or even epilepsy as the main therapeutic application. However, in all studies, a common finding is the lack of correlation among students regarding the treatment with cannabis for diseases like AIDS or neuropathic pain related to diabetes.

Concerning epilepsy, treatment with cannabinoids has proven to be effective and safe, especially in patients who are resistant and cannot control seizures with conventional medication, which corresponds to 15% of cases[18]. This can be corroborated by various research, such as that of Devinsky in 2016[19], which compared the efficacy of CBD-based medications with antiepileptics and demonstrated a reduction of 36.5% in the frequency of seizures per month. However, other publications by the Federal Council of Medicine[20] (CFM) state that the available studies are not sufficient to prove their safety, precisely because they involve a limited number of participants. Despite this, the CFM considers that further exploration is necessary for developing new treatments for epilepsy that cause fewer side effects and alter the natural history of the disease [20].

Moreover, efforts have been made to demonstrate the efficacy of cannabinoids in treating neurodegenerative diseases such as Parkinson's. This information aligns with the study by HAMPSON AJ from 2000[21], which demonstrates through studies with rats that cannabidiol possesses antioxidant and neuroprotective properties, delaying the degeneration of dopaminergic neurons in the nigrostriatal region[22].

Regarding chronic pain[23,24], this is a condition that, according to the World Health Organization (WHO), affects about 30% of the global population and causes numerous impacts on the daily lives of patients because of its association with loss of autonomy, thus being linked with high rates of anxiety, depression, and sleep disorders[1]. Given the high prevalence and the damage caused by it, patients resort to several pharmacological treatments for pain relief. The WHO has established the Analgesic Ladder, where the first level uses non-steroidal anti-inflammatory drugs (NSAIDs), the second level for moderate pain uses weak opioids like tramadol, and as a last resort for treating pain, strong opioids such as morphine are used[25]. Therefore, due to the high intensity of neuropathic pains experienced by oncological patients, the abuse of strong opioids is common, and even with their use, about 25% of patients do not achieve the desired result even when treated in centers of excellence[3].

The patient's history must be thoroughly analyzed, as well as the risks of dependence, increased tolerance, and the multiple side effects of the drug must be considered before prescribing opioids since the abuse of these medications can lead to fatality by overdose. Therefore, the concurrent use of cannabis is an alternative to decrease the abuse of analgesic drugs. A plausible justification for the reduction in opioid use is because of the synergism between cannabis components and opioid receptors. Such synergism maintains analgesia, reducing side effects, and mortality due to abusive use.[5]

When participants of this study were questioned about some effects of cannabis on the body, the most frequent response was the lack of sufficient knowledge to discuss the subject. Following this response, the second most frequent was related to dependency, followed by schizophrenia, neuronal alterations, cognitive deficit, psychosis, hallucinations, lethargy, depression, anxiety, tachycardia, nausea, mental retardation, withdrawal, drug tolerance, drug interaction, insomnia, loss of appetite, diarrhea. This can be correlated with the article by Bar-Lev Schleider L in Israel in 2018[26], wherein a six-month follow-up with oncological patients, the most prevalent side effects were vertigo (8%), dry mouth (7.3%), increased appetite (3.6%), sleep deprivation (3.3%), and psychoactive effects (2.8%), showing a significant divergence from the responses provided by the medical students.

Despite the potential side effects, many studies show promising results for treating chronic pain. An example is the article by Schleider et al., 2018[26]: during an *in vivo* study with over 3,000 cancer patients, about 50% experienced high-level chronic pain (8-10 on the pain scale), but after six months of treatment with cannabis compounds, only 5% of the patients still suffered from such high-intensity pain. Moreover, a significant improvement in the symptoms that hindered the wellbeing of these patients was also reported. Among the complaints with major changes were the improvement of nausea and vomiting reported by 91% of the patients, improvement in sleep quality (87.5%), anxiety and depression (84.2%), and headache (81%). Moreover, when comparing the side effects of cannabis use for medium and long-term treatment, they are still scarce when compared with other prescription medications usually prescribed as conventional treatments for the symptoms, such as opioids.

Regarding Brazilian laws on the subject, according to resolution 2.324/2022 approved by the CFM27, the prescription of cannabidiol (CBD) is authorized for cases of epilepsy in childhood and

adolescence that are refractory to conventional therapies in Dravet Syndrome (severe and treatment-resistant epilepsy), Lennox-Gastaut Syndrome (severe epileptic encephalopathy of childhood), and in the tuberous sclerosis complex (a rare genetic disorder characterized by abnormal tumor growth in multiple organs, including the brain). Furthermore, the patient must be informed about the potential risks and benefits of the treatment along with the signature of the informed consent form by the interested parties. Additionally, the prescription of cannabis *in natura* and any other derivatives other than cannabidiol for medicinal use is prohibited.

The article by Caetano 202328 mentions that legalizing cultivation would allow for greater development of research, resulting in new medications on the market that would be of national production, thus reducing costs by eliminating the need for importation and facilitating access by not requiring judicial authorization for acquisition. Moreover, there are several bills addressing this issue, such as BILL No. 89 of 202329, authored by Senator Paulo Paim, which establishes the free provision of medications derived from cannabidiol combined with other cannabinoid substances, including tetrahydrocannabinol, at health units affiliated with the Unified Health System - SUS. Thus, it allows the medication to be available to people with lower financial conditions, for example, since it is highly priced, thereby ensuring broader access to health.

Another point raised was that national production would allow for greater quality control and safety of the product, and regulation would also enable an educational process about cannabis for the population. On the other hand, among the negative points mentioned, concerns about side effects such as hyperemesis, acute psychosis, impairment in learning and memory, as well as the risk of dependence, stand out[30].

It is important to emphasize that although the majority of students showed support for legalizing cannabidiol in Brazil, most of them do not fully understand its therapeutic indications, benefits, and the difference between CBD and THC compounds, for example, which is evidenced by the results presented in Figures 2, 3, and 4. These findings highlight a paradox, as understanding the clinical applicability of cannabidiol is necessary to form an opinion on its legalization, and this inconsistency may be attributed to a lack of information and knowledge on the topic.

According to Valber da Silva Frutuoso, advisor at the Oswaldo Cruz Foundation in 2013[15], there is a significant amount of research showing the therapeutic benefits of cannabidiol. Moreover, there is a need to expand the training of professionals so that they feel confident in prescribing and treating, as many feel insecure due to the lack of appropriate clinical protocol, including the effects of long-term therapy.

Finally, this aligns with the results presented in Figure 6, where almost all students, 119 (96.7%), confirmed the need for deeper exploration of the topic during the medical course, reinforcing the central idea of the project that there is a knowledge gap among students about the topic, leading to health professionals and students being unfamiliar with the subject. Thus, the study aims to highlight to healthcare universities the need for curriculum enhancement in medical course by adding more classes and discussions on the therapeutic use of cannabis. This approach aims to provide oncological patients with refractory pain to conventional medications with alternatives for their treatment, aiming at health promotion through comprehensiveness, universality, and equity.

CONCLUSION

Given the discussed results, it can be observed that there is a lack of depth in the knowledge of medical students from Maringá,

Paraná, regarding the use of cannabis in refractory pain treatment, particularly concerning its effects and side effects. Furthermore, it is worth noting that the medicinal use of cannabis and its derivatives can lead to a reduction in opioid use and significantly decrease the pain reported by oncological patients, thus improving quality of life and making the terminal process more comfortable and humanized. Therefore, the need for a more comprehensive approach to the topic during the course is undeniable, to ensure the provision of the best possible care.

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