

# A Systematic Review of Therapeutic Potential of Illicit Drugs: A Narrative Overview of How Cannabinoids and Psychedelics Can be used in Medicine

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**ABSTRACT:** *To aid the therapeutic process, illicit chemical substances and drugs are used in drug therapy. Various cultures have used illegal substances for thousands of years in medicine and various practices. The present study is a general approach to pharmaceutical science and attempts to contextualize drug-assisted therapy through an integrative literature review. All related articles were found through the electronic databases Medical Publications (Pubmed) and Scopus. The research question was related to articles written in English within the last 20 years. The database research found 77 articles on psychedelics between Jan 2000 and Oct 2021. Twenty-two articles were selected for analysis according to the inclusion criteria. In analyzing the texts, we have been able to correlate several aspects. We conclude that psychedelic therapy has great potential and that its rebirth occurs in the context of social transformations and demands in psychotherapy that are unmissable. Database searches between Jan. 2000 and Oct. 2021 found 1164 articles about cannabinoids. According to the inclusion criteria, only 235 articles were selected for analysis. The United States produced the most publications, followed by Canada and Australia; evidence has steadily increased between 2000 and 2021. The contents of the publications deal with beneficial and adverse health effects, the consequences of cannabis legislation, and its association with various variables. There is a lack of research on cannabis' medicinal use regarding treatments and diseases, its standardization, routes of administration, and doses, recognizing the need for more research.*

**KEYWORDS:** *Drug Therapy; Psychedelic Therapy; Psychedelic; Psychedelic associated therapy; Psychedelic drugs; Cannabis-based drugs; Cannabinoid therapy; Cannabidiol.*

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## INTRODUCTION

According to William M. Suavé, MD, medical director, Greenbrook TMS NeuroHealth Centers, most studies exploring the therapeutic potential of marijuana, classic hallucinogens, 3,4-methylenedioxymethamphetamine, and ketamine have been small and flawed. Still, promising results suggest that larger studies are warranted. At the 2017 Neuroscience Education Institute (NEI) Congress, William M. Suavé, MD, of Greenbrook TMS NeuroHealth Centers, talked about the potential therapeutic benefits of several illegal drugs. This paper focuses on marijuana as the first drug. According to patient reports, cannabis benefits chronic pain, chemotherapy-induced nausea, and spasticity associated with multiple sclerosis.

Furthermore, there is evidence that cannabis is linked to respiratory symptoms, motor vehicle crashes, low birth weight, and psychosis. According to the literature, there is evidence that some people are replacing conventional pain medications with cannabis. Opioids in patients with chronic pain were reduced by 65% when cannabis was used.

Literature pointed out that both short- and long-term use of cannabis can have adverse effects. As a result of long-term use, tetrahydrocannabinol may cause impaired short-term memory, motor coordination, judgment, paranoid ideation, and psychotic symptoms. If used long-term or heavily, it can lead to altered brain development, chronic bronchitis symptoms, psychosis disorders, and cognitive impairment. Medical marijuana is not a viable prescription option currently because drug approval standards require a consistent, pure, and well-defined chemical formulation; safety data in healthy populations and specific medical disorders; a consistent, well-defined pharmacokinetic profile; efficacy data in specific medical disorders; and warnings regarding all potential side effects. Currently, in the case of medical marijuana, compounds differ from plant to plant, dosing is not well regulated, and there are residual impurities. Other studies have also discussed psychedelics due to the renewed interest in hallucinogens as therapeutic tools. One or two doses would be administered as part of psychotherapy for several disorders, including depression, anxiety, addiction, and alcoholism. Classic hallucinogens contain two types of alkaloids: tryptamines and phenethylamines. There are also non-classic hallucinogens, including 3,4-methylenedioxymethamphetamine (MDMA) and dissociative anesthetics.

Psychedelics as therapeutic tools in treating mental disorders have recently gained attention. The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designations for (±)-3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in severe posttraumatic stress disorder (PTSD) (in 2017) and the adjunctive use of psilocybin with psychotherapy in both Treatment-Resistant Depressions (TRD) (in 2018) and Major Depressive Disorder (MDD) (in 2019). In addition, clinical trials using psychedelics are being conducted for various indications, including eating disorders, cognitive impairment, and Substance Use Disorder (SUD).

These psychoactive substances typically produce perceptual distortions and mind-altering effects, mainly by agonistic action at the serotonin (5-HT) 2A brain receptor. Recent placebo-controlled experimental studies have also shown that LSD and psilocybin increase self-rated positive mood and social behavior, enhance emotional empathy, and reduce the recognition of negative emotional states (e.g., sadness and fear).

Psychedelics are a class of substances scoring relatively high on physiological and psychological safety when used under supervision in a controlled setting. In general, they do not induce dependence or adverse effects that would not be manageable when given in appropriate doses and in the presence of someone who can provide psychological support if needed. Moreover, preliminary findings and anecdotal reports suggest that psychedelics even show therapeutic potential in substance use disorders. In addition, current research is investigating therapeutic applications of these substances in psychiatric disorders, focusing on affective disorders.

Interestingly, Albert Hofmann, the 'discoverer' of LSD and its hallucinogenic effects, stated decades ago that 'very small doses, perhaps 25 micrograms', could be useful as an antidepressant. Classic hallucinogens, their mechanisms of action are primarily mediated by the activation of 5HT<sub>2A</sub> receptors in the prefrontal cortex. In most studies, therapeutic effects correlate with the level of "mystical" experiences. There is a decrease in brain connectivity in the default mode network, establishing new connections. Psychiatric conditions are thought to be caused by disputed neural connections in the brain that healthier ones replace; Psilocybin has been shown to benefit treatment-resistant depression, anxiety, and depression associated with cancer, obsessive-compulsive disorder,

and smoking cessation in small studies. According to a meta-analysis of randomized control trials, in the context of an alcoholism treatment program, lysergic acid diethylamide, aka LSD, may be beneficial for reducing alcohol use. There is a risk of dizziness, weakness, dilated pupils, tremors, and rarely prolonged psychosis when taking these classic hallucinogens. MDMA, also known as "ecstasy," was originally intended as a therapeutic agent. PTSD patients have recently been approved for phase 3 clinical trials testing MDMA. It has been shown that MDMA increases motivation to engage in therapy due to its stimulating effect, reduces hypervigilance associated with PTSD, and allows reflection on traumatic memories during psychotherapy without being overwhelmed.

Marijuana, classic hallucinogens, MDMA, and ketamine have all shown some evidence of therapeutic applications in a wide range of psychiatric and neurological disorders. Still, Schedule I status severely restricts access to research. Even though most studies to date have been small, underpowered, and have other methodological flaws, it appears that larger studies should be conducted.

Many clinical trials have greatly improved our understanding of the therapeutic potential of cannabis [1-5]. During a hearing of the Health Committee of the German Federal Parliament (Bundestag), the German Medical Association, the National Association of Statutory Health Insurance Physicians, and the Drug Commission of the German Medical Association issued the following statement: "The benefit of treating patients with cannabinoids for several medical indications has been established in controlled trials in which standardized and/or synthetic cannabinoid preparations were primarily used. Such preparations may be warranted for patients who are not relieved adequately by conventional treatment of symptoms such as spasticity, pain, nausea, vomiting, or loss of appetite [6]. Current knowledge regarding the therapeutic use of cannabinoid medications is discussed in this article.

Psychedelics, or hallucinogens, as they are sometimes called, are a class of psychoactive substances that induce an altered state of consciousness marked by alterations in visual perception, self-experience, and emotion processing. Serotonin (5-HT) 2A receptors in the brain are responsible for their psychoactive effects [2]. Healing and religious rituals have long made use of psychedelic substances.

In 1943, Albert Hofmann discovered that LSD had psychological effects. This discovery catalyzed the scientific investigation of these substances. LSD and psilocybin to treat various mental illnesses were extensively studied in the 1950s and 1960s. Despite not meeting current methodological standards to investigate clinical efficacy, these first studies demonstrate impressive improvements in depression and alcohol dependence, among other psychiatric symptoms.

It has been about 50 years since studies looked at the effects of illicit substances on addiction, mood disorders, chronic pain, chemotherapy-induced nausea, and spasticity in multiple sclerosis. The first part of this review introduces the beneficial effects of psychoactive drugs. The second part focuses on current research results uncovering the effects of cannabinoids.

Lastly, we discuss the potential of illicit drugs in the future of medicine. This narrative review summarizes the existing evidence regarding potential mechanisms of action and efficacy of psychedelics and cannabis to generate hypotheses and highlight research gaps for future studies. Published modern clinical trials that are testing the efficacy of illicit drugs are discussed in this part to detect knowledge gaps that need to be filled to gain a comprehensive understanding of the clinical potential of those substances.

## METHODOLOGY

In systemic reviews, secondary data is collected and analyzed using repeatable analytical techniques. Systematic reviews are a form of evidence synthesis in which research questions are broad or narrow in scope, and data is identified and synthesized that directly corresponds to the question of the systematic review[1-4]. While some people associate 'systematic review' with 'meta-analysis,' there are multiple kinds of reviews that can be defined as systems that do not involve a meta-analysis. Reviews often provide an exhaustive summary of current evidence relevant to a research question. Systematic reviews evaluate research studies and synthesize findings either qualitatively or quantitatively. Systematic reviews of randomized controlled trials, for example, can inform evidence-based medicine. It is usually quicker and cheaper to review existing studies than start new ones. In addition to biomedical and healthcare contexts, systematic reviews can also assess a precisely defined subject in other areas [5].

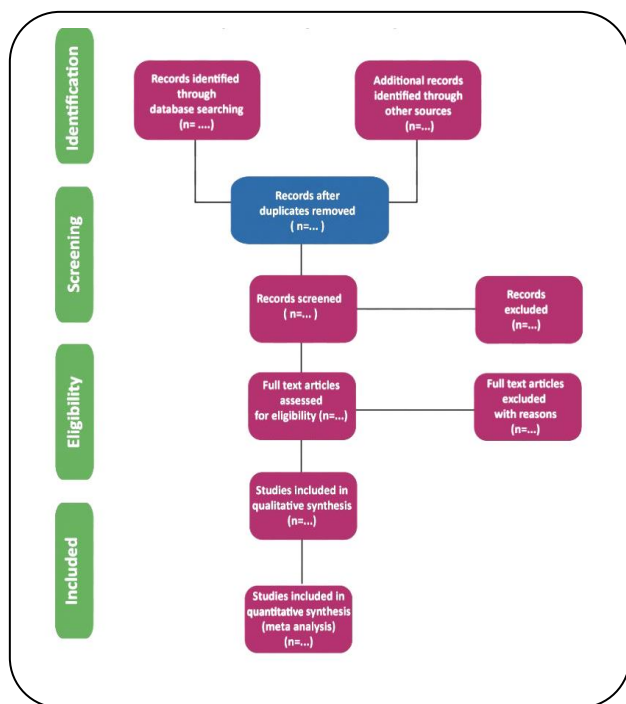


Fig. 1: Flowchart of a systematic review.

Clinical tests, public health interventions, environmental interventions, social interventions, adverse effects, qualitative evidence syntheses, methodological reviews, policy reviews, and economic evaluations [6,7] are some topics of systematic reviews. Professionals involved in health care, public health, and public policy would benefit from understanding systematic reviews and how to implement them in practice.

### A systematic review of the psychedelics

This study is an integrative literature review, a type of study that allows a mapping of the content produced on a specific theme, synthesizing the main results of the studies, assisting the decision-making facing the patient, and identifying gaps in Future Searches [10].

For the elaboration of this integrative review of the literature adopted the following steps: establishment of the guiding question; Integrative review objectives; Establishment of inclusion and exclusion criteria (sample selection); definition of information to be drawn from the selected articles; analysis of results; Discussion and presentation of the results [10].

1- At first, the question of research that guided the research on the databases was: "What is the purpose of

psychedelic therapy in the psychiatric and psychotherapeutic scope?" From this, the other steps were carried out.

2- The objectives of this integrative review were: Show in what form is the rebirth of psychedelic therapy; investigate the causes and boosters of this rebirth; address the purposes of developed therapies and the objective of those involved; Explain how psychedelic therapy resurfaced in the current psychiatric and psychotherapeutic scenario.

3- After that, the inclusion criteria (articles in English) were selected, articles published in the last 20 years directly related to the research question, and the exclusion criteria (repeated articles not related to them and are unavailable for reading). This stage was fundamental for research on Medical Publisher databases (Pubmed) and Scopus. The period that understood the search was between Jan 2020 to Oct 2021.

4- Definition of information to be drawn from the selected articles: Here, read and interpret the main information of the articles chosen to compose the final sample.

5- After that, the next step was analyzing the information found, extracting the information directly related to the research question, and systematizing them in Tables 2, 3, and 4.

6- With this, we proceeded with constructing the argument to defend the research question, and the results were presented and contextualized.

For inclusion criteria, articles published in the last 20 years, with a view to the low quantity of studies related to the research question, were used as a descriptor: "psychedelic therapy," with which 43 articles obtained that, when filtered for the period Jan 2000 to Oct. 2021, resulted in a total of 40. So based on the proposed theme, from the exclusion criteria and research articles directly related to the research issue, 22 articles were selected to cover the guiding question.

The studies found were organized into a worksheet in Excel software with the description of the title of the studies; this tool allowed the removal of duplicates. Then a careful reading of the titles and abstracts was carried out to verify which studies were with the guiding question of this research; from this, its adequacy was analyzed to the other selection criteria of this study described above. Finally, it was performed in full of the final sample, and the desired data was extracted (see Fig. 2).

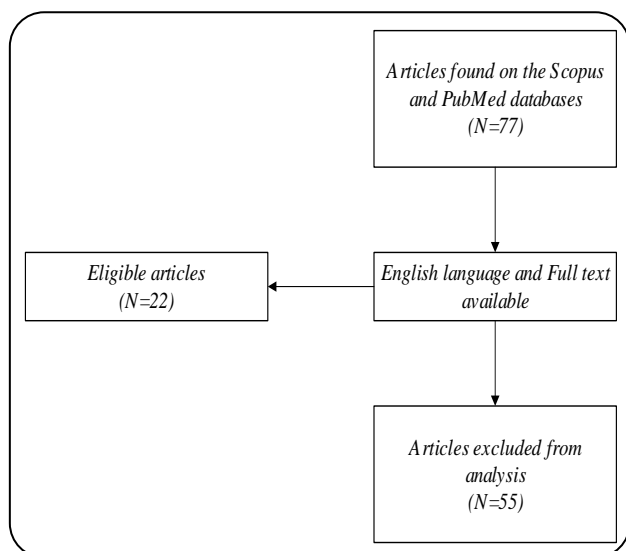


Fig. 2: Flowchart selection of articles.

### A systematic review of the cannabinoids

This systematic review is guided by the prism method that organizes the evidence's exploration, classification, and analysis. The search for information in Scopus included the keywords "Cannabis," "Marijuana," "Medical use," "Medicinal use," and "Therapeutic use," according to the descriptors of the DeCS thesauri (descriptors in Health Sciences) and MeSH (descriptors in Medical Subjects), and the use of the respective Boolean operators (AND, OR). Research and reflection articles, letters, editorials, book chapters, articles in the press, and notes, published from Jan 2000 to Oct 2021 were included in English. Publications not indexed in Scopus, outside the defined age range, duplicate, and unavailable documents, and studies with conflicts of interest were excluded. Thus, the selection procedure was divided into four stages: (1) design of the literature search strategy, (2) selection of publications according to inclusion and exclusion criteria, (3) extraction of data from the studies, and (4) critical analysis of the information according to the quality of the evidence (see Figure 3). The content analysis of the publications was carried out by employing a synthesis of the ideas and relevant conclusions in each one, establishing thematic categories to facilitate the organization of the information obtained.

### A REVIEW ON THE PSYCHEDELICS

In 1938 in Switzerland, Chemist Albert Hofmann looked for medicines for blood circulation and respiratory

apparatus when he first synthesized lysergic acid diethylamide - LSD. He would surface his psychic properties only five years later in a self-experiment by Hofmann [1]. Shortly after the animal experiments, the first systematic test on humans was made in 1947. With the disclosure of the results, it was not long before the psychiatric and therapeutic interest in the substance was described as the most potent and interesting psychoactive so far known [1]. Its deep and mysterious effect also drew the attention of the artistic and intellectual environment, in which the first uses did not hallucinogen medicines. By half of the 1950s, the "sacred mushrooms" and their active principle, psilocybin - a molecule similar to LSD, were isolated. They were used for millennia in religious rituals and sacred contexts in Central America [1]. At the end of the 1950s, these substances were stabilized in the psychiatric and psychotherapeutic scenarios of the United States and, in a smaller part, of Europe [2]. In the 1960s, recreational and non-therapeutic use of these drugs spread among the population [3]. They were mostly used by hippies and pacifists who asked for the end of the Vietnam War [4]. It did not take long for the wave of pacifist protests and the indiscriminate use of these substances carried out in 1970, the LSD illegalization in the United States of America. Like this fact, it also occurred the same with research and psychotherapy in hallucinogens [5].

For more than 20 years, the discrimination against these substances made it impossible for scientific studies on hallucinogens. From the 1990s, with a few special authorizations, neurological studies have returned to these drugs and, above all, what has now been called psychedelic therapies [6]. After two decades of quiescence, clinical psychedelic research was restarted in the 1990s and is rapidly progressive. The first evidence of effectiveness is promising, but understanding the psychological processes of underlying changes to the observed benefits is limited [7]. Assisted psychedelic therapy comprises preparation, psychedelic session, and integration. Preparation is the key to maximizing the potential for the benefit of a psychedelic, being the important experience and integration to prolong improvements. The Psychological Flexibility Model (PFM) seems promising to guide psychedelic preparation and integration. With this in mind, a new model based on acceptance, connection, and incorporation presents the six

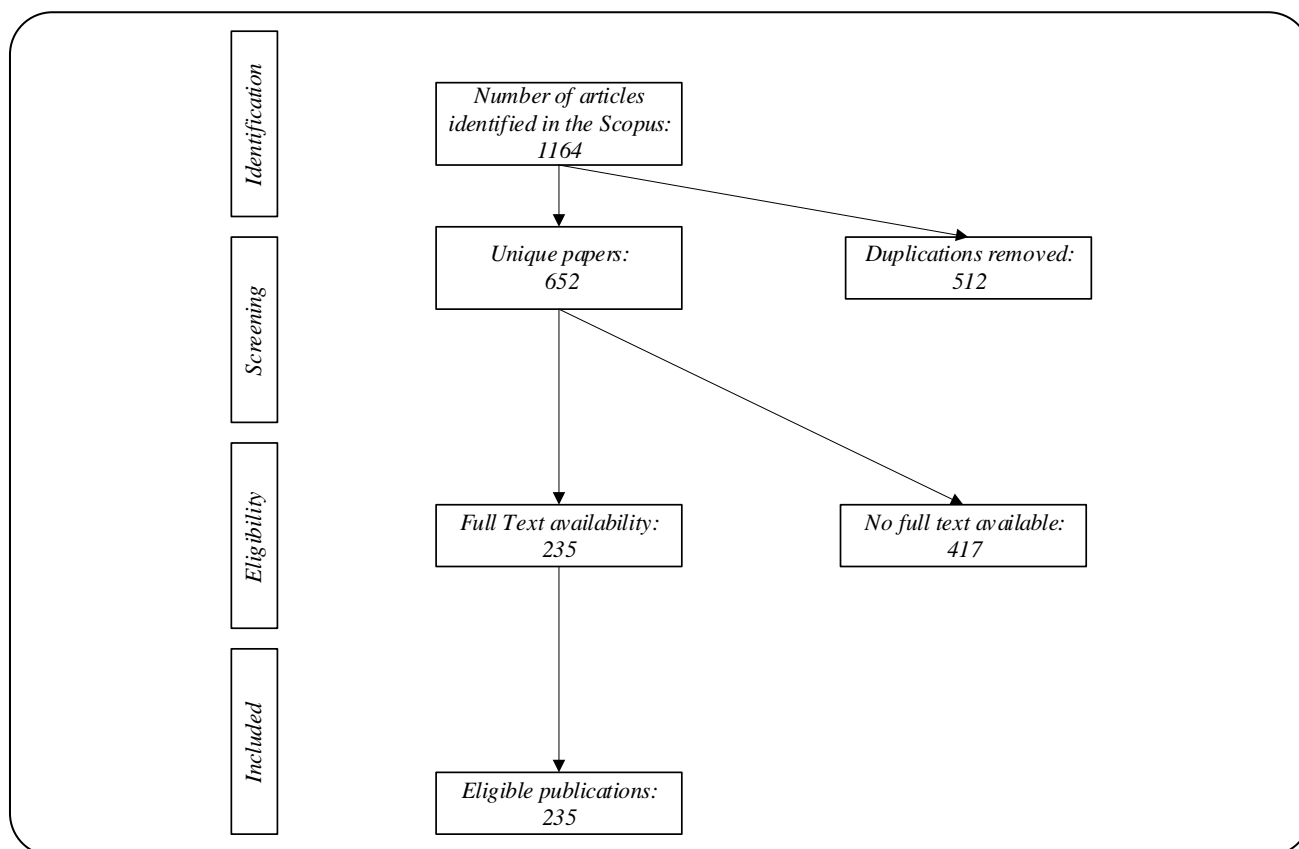


Fig. 3: Flowchart of the publication selection process.

psychological flexibility processes, renamed and reorganized in a triad of acceptance (cognitive desolation, focus on the present, and will) and a triad of connection (the self as context, compromised values, and action) [8]. The confluence of these six processes is psychological flexibility, or the ability to get in touch with the present moment more fully as a conscious human being. Based on what the situation allows, the ability to change or persist in the behavior serves valuable purposes. In addition, several studies have demonstrated that improvements in psychological flexibility are related to better clinical outcomes [8]. This method also incorporates psychotherapy support that normally consists of a period of preparation, followed by a moderate dose of psychedelics in the presence of one or more therapists, followed by one or more integration sessions [7]. Psychedelic therapy offers a path to incorporate awareness, allowing relief and learning to patients. Psychedelics also offer the opportunity for more patients to experience profound psychological changes than only through speech therapy, being a good adjuvant therapy [8].

Humor disorders (e.g., depression, anxiety, post-traumatic stress disorder - TEPT), alcohol, and other disorders caused by drug use represent a great burden for individuals, families, and health systems, with significant public health expenditures. Psychedelics such as LSD and psilocybin can represent new treatment options for mood disorders, alcohol use disorders, and other drugs [9]. The current resurgence of importance on the effectiveness of these compounds is at first. Still, preliminary findings are promising: Some benefits have been demonstrated for indications such as major depressive disorder, post-traumatic stress disorder (TPT), obsessive-compulsive disorder (TOC), anxiety associated with life-risk diseases, alcohol dependence, long-term smoking, being the identified risks of toxicity and dependence considered low [9].

Their therapeutic properties have been studied especially to help patients with psychiatric conditions, psychological distress, or substance use disorders. This article is a systematic review of the literature, which aims to provide an overview of all studies that assessed the efficacy of psychedelics, i.e., psilocybin, ayahuasca,

and Lysergic Acid Diethylamide (LSD), on psychiatric diseases and addictions[6].

Some examples of psychoactive compounds are magic mushrooms (psilocybin and psilocin), MDMA (3,4-methylenedioxymethamphetamine), LSD (lysergic acid diethylamide), DMT (N, N-dimethyltryptamine), Ibogaine, Ketamine and Mescaline (3,4,5- trimethoxyphenethylamine) [4]. Recent studies suggest that serotonergic hallucinogens/psychedelics, including ayahuasca, psilocybin, and lysergic acid diethylamide (LSD), are anxiolytic antidepressive and antiaddictive effects[1]. Psilocybin and LSD reduced anxiety and depression in cancer patients and alcohol and tobacco dependence symptoms, and ayahuasca reduced depression in treatment-resistant depression[3].

The “classical” psychedelics, consisting of indoleamine (psilocybin), alkaloids (N, N-dimethyltryptamine [DMT], the active constituent contained in ayahuasca), and ergolines (LSD), act primarily via serotonin 5-HT<sub>2A</sub> receptor agonism. MDMA, a phenethylamine, acts via the release of presynaptic serotonin and, to a lesser extent norepinephrine and dopamine through interactions with the corresponding monoamine transporter, including trace amine-associated receptor 1 (TAAR1) and vesicular monoamine transporter 2 (VMAT2). These compounds have varied pharmacokinetics and pharmacodynamics [2]. Serotonergic hallucinogens produce “psychedelic” effects that are indistinguishable from each other, consistent with a shared primary mechanism of action [2]. The typical effects include enhanced sociality, feelings of closeness to others, openness to new experiences, emotional empathy, trust, feelings of bliss, audiovisual synesthesia, derealization, depersonalization, profound mystical experiences characterized by feelings of boundlessness, enhanced introspection and occasionally anxiety, fear/panic, dysphoria, paranoia, and auditory hallucinations [9-11]. MDMA, described as an “entactogen” and a psychostimulant (producing euphoria, anxiolysis, and a sense of inner peace), does not produce intense hallucinations as seen with classical psychedelics.

In this context, an investigation of the circumstances of this phenomenon becomes worthy since it has been promising in an area that lacks definitive treatments. To guide this discussion, the objective of the present study is to contextualize the rebirth of psychedelic therapy in the scenario of current clinical practice, in addition to explaining how psychedelic therapy resurfaced in the

clinical, psychiatric, and psychotherapeutic scenarios through the following research question: “What is the purpose of psychedelic therapy in the psychiatric and psychotherapeutic scope?” The justification for the choice of the theme is made by the relevance in the clinical scenario performed by this therapy and its benefits in patient management.

The selected studies were translated into Portuguese and subdivided into two frames. The first picture classified the selected articles according to the following information: Author/year, title, and general objective of the study. After analyzing the data, it was possible to observe that the years 2017 and 2019 were presented with 1 article each year, with a greater number of publications in 2018 with five articles. The year 2020 had eight eligible papers, and the year 2021 showed the number of 3 and 4 in other years were eligible publications in this field.

The second table shows the type of study and its main results. As for the type of study developed by the analyzed articles, 5 were a bibliographic review, 1 a cross-sectional study, and 1 a systematic review.

As shown in Table 3, all studies (N=22) highlight the benefits of psychedelic therapy in the management of patients who have psychiatric disorders, such as depression, mood disorders, anxiety, post-traumatic stress, and the improvement of chemical dependency on some substances such as alcohol, tobacco, cocaine, and opioids. Such findings are the most relevant of this study, pointing out the main benefits of psychedelic therapy treatment.

According to the data in Table 4, all selected studies (N=22) identified a strong correlation between the use of assisted psychedelic therapy and the improvement of symptoms in patients with a psychiatric disorder (major bipolar depression, mood, anxiety, and post-stress-traumatic) and chemical dependency on some substances, such as alcohol, tobacco, cocaine, opioids, and other substances.

## A REVIEW OF THE CANNABINOIDS

Cannabis is a plant that makes a thick substance full of chemical compounds called cannabinoids; Cannabidiol (CBD) and Tetrahydrocannabinol (THC) are the most common cannabinoids found in cannabis products. Cannabidiol, or CBD, is found in the cannabis Sativa plant; tetrahydrocannabinol, or THC, is the active ingredient in cannabis with psychoactive effects and alleviates anxiety symptoms[26]. According to a study published in 2015,

**Table 1: A Distribution of the most important studies analyzed for the authors/year, title, and general objective.**

N°	Author	Title	General aims
1	Carhart-Harris [11]	Trial of Psilocybin versus Escitalopram for Depression	direct comparisons between psilocybin and an antidepressant and establish treatments for depression
2	Mertens [12]	Therapeutic mechanisms of psilocybin: Changes in the amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression	Aiming to unravel the therapeutic mechanisms of psilocybin further, the present study extends this basic activation analysis. We hypothesized changed amygdala functional connectivity, more precisely decreased amygdala-ventromedial prefrontal cortex functional connectivity, during face processing after treatment with psilocybin.
3	Hutten [13]	Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo-controlled dose-effect finding study	The main objective of the present dose-finding study was to determine the minimal dose of LSD needed to affect mood and cognition.
4	Zeifman [14]	Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: results from an open-label trial	To examine the acute and post-acute effect of ayahuasca on suicidality among individuals with MDD.
5	Garcia-Romeu & Richards [15]	Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions	Provide a brief overview of how the serotonin 2A receptor (5-HT <sub>2A</sub> ) agonist hallucinogens (i.e., psychedelics) have been used for clinical or research purposes as part of therapeutic interventions
6	Hartogsohn [16]	The meaning-enhancing properties of psychedelics and their mediator role in psychedelic therapy, spirituality, and creativity	Defend the importance of another mediator of psychedelic action, which is fundamental to understanding the effects of psychedelics in therapy, creativity, and spirituality.
7	Johnson [17]	Psychiatry might need some psychedelic therapy	Determine the evolution and current state of psychiatry and how psychedelic therapy can be helpful.
8	Moreton, Szalla, Menzies & Arena [18]	Embedding existential psychology within psychedelic science: reduced death anxiety as a mediator of the therapeutic effects of psychedelics	Provide a complimentary review of the mechanisms by which psychedelics can reduce death anxiety
9	Noorani, Garcia-Romeu, Swift, Griffiths & Johnson [19]	Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts	Identify the perceived change mechanisms that lead to smoking cessation in the pilot study
10	Ross [20]	Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress	Identify the prevalence and adverse psychological, existential, and medical impact of a cancer diagnosis and how psychedelic therapy can be useful
11	Sessa [21]	Why MDMA therapy for alcohol use disorder? And why now?	Propose in an ongoing UK study that alcohol use disorder patients who have undergone medical detox may benefit from a course of MDMA-assisted psychotherapy
12	Sanches [22]	Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study	The objective of the present work was to assess the antidepressive potentials of ayahuasca in a bigger sample and investigate its effects on regional cerebral blood flow.
13	Sos [23]	Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression	Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects. Furthermore, high-affinity NMDA antagonists such as ketamine are associated with psychotomimetic effects. The link between the antidepressant and psychotomimetic effects of ketamine has not been explored. We examined the relationship between the antidepressant and psychotomimetic effects of a single ketamine infusion in subjects diagnosed with major depressive disorder.
14	Mathew [24]	Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial	replicates the acute efficacy of single-dose intravenous (i.v.) ketamine; tests the efficacy of the glutamate-modulating agent riluzole in preventing post-ketamine relapse; and examine whether pretreatment with lamotrigine would attenuate ketamine's psychotomimetic effects and enhance its antidepressant activity.
15	Krupitsky [25]	Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up	ketamine psychotherapy can increase the rate of success for abstinence from heroin addiction



Table 2: Distribution of analyzed studies regarding population and sample and main results.

N°	Author	Method	General Results
1	Carhart-Harris [11]	Clinical Trial	59 patients were enrolled; 30 were assigned to the psilocybin group and 29 to the escitalopram group. The mean scores on the QIDS-SR-16 at baseline were 14.5 in the psilocybin group and 16.4 in the escitalopram group. The mean ( $\pm$ SE) changes in the scores from baseline to week 6 were $-8.0 \pm 1.0$ points in the psilocybin group and $-6.0 \pm 1.0$ in the escitalopram group, for a between-group difference of 2.0 points (95% confidence interval [CI], -5.0 to 0.9) ( $P = 0.17$ ). A QIDS-SR-16 remission occurred in 70% of the patients in the psilocybin group and 48% of those in the escitalopram group, for a between-group difference of 22 percentage points (95% CI, -3 to 48); QIDS-SR-16 remission occurred in 57% and 28%, respectively, for a between-group difference of 28 percentage points (95% CI, 2 to 54). Other secondary outcomes favored psilocybin over escitalopram, but the analyses were not corrected for multiple comparisons. The incidence of adverse events was similar in the trial groups.
2	Mertens [12]	Clinical Trial	Results showed decreased ventromedial prefrontal cortex-right amygdala functional connectivity during face processing post- (versus pre-) treatment; this decrease was associated with levels of rumination at one week. This effect was driven by connectivity changes in response to fearful and neutral (but not happy) faces. Independent whole-brain analyses also revealed a post-treatment increase in functional connectivity between the amygdala and ventromedial prefrontal cortex to occipital-parietal cortices during face processing.
3	Hutten [13]	Controlled Clinical Trial	LSD showed positive effects in the majority of observations by increasing positive mood (20 mcg), friendliness (5, 20 mcg), arousal (5 mcg), and decreasing attentional lapses (5, 20 mcg). Negative effects manifested as increased confusion (20 mcg) and anxiety (5, 20 mcg). Psychedelic-induced changes in waking consciousness were also present (10, 20 mcg). Overall, the present study demonstrated the selective, beneficial effects of low doses of LSD on mood and cognition in most observations. The minimal LSD dose at which subjective and performance effects are notable is 5 mcg, and the most apparent effects were visible after 20 mcg.
4	Zeifman [14]	open-label trial	Among individuals with suicidality at baseline ( $n = 15$ ), there were significant acute (i.e., 40, 80, 140, and 180 min after administration) and post-acute (1, 7, 14, and 21 days after administration) decreases in suicidality following administration of ayahuasca. Post-acute effect sizes for decreases in suicidality were large (Hedges' $g = 1.31-1.75$ ), with the largest effect size 21 days after the intervention ( $g = 1.75$ ).
5	Garcia-Romeu & Richards [15]	Literature review	This study contributed seminal insights into how these substances can be used effectively and safely in targeted therapeutic interactions, including the importance of optimizing the whole (state of mind) and environment.
6	Hartogsohn [16]	Literature review	The enhancement of the significance of psychedelics is a hypothesis supported by several experience reports and clinical research, but it has not yet received the attention it deserves. This path of investigation can be opened up by using various psychometric tools to help assess the degree to which psychedelics increase their meaning and possible correlations with spiritual therapies.
7	Johnson [17]	Literature review	The psychiatric field is relatively stagnant, having not kept up with the evolution of the rest of medicine. Psychedelic therapy has shown promising results and may represent new perspectives in psychiatry.
8	Moreton, Szalla, Menzies & Arena [18]	Literature review	The study shows that psychopathology can arise from failed attempts to deal with the underlying death. Also evidenced was the ability of psychedelics to help with questions about mortality involving many of their therapeutic effects even in individuals without life-threatening illnesses.
9	Noorani, Garcia-Romeu, Swift, Griffiths & Johnson [19]	Retrospective Trial Study	Participants reported gaining vivid insights into self-identity and reasons for quitting in their psilocybin sessions. Preparatory counseling and a strong relationship with the study staff were vital in achieving abstinence. In addition, participants reported several positive changes beyond smoking cessation, including increased aesthetic appreciation, altruism, and prosocial behavior.
10	Ross [20]	Systematic literature review	This review identified ten published trials that studied serotonergic psychedelics to treat cancer-related psychiatric illnesses. Six published clinical trials included 341 participants (almost exclusively diagnosed with cancer and stress-related psychological and existential illnesses).
11	Sessa [21]	Literature review	MDMA has the potential to improve and enhance psychotherapeutic processes in the treatment of alcohol use disorder. It can also address symptoms of other conditions that are often comorbid with substance use disorders, particularly those symptoms associated with a history of psychological trauma.

**Table 2: Distribution of analyzed studies regarding population and sample and main results. (Continuation)**

12	Sanches [22]	Clinical Trial	Results suggest that ayahuasca may have fast-acting and sustained antidepressive properties. These results should be replicated in randomized, double-blind, placebo-controlled trials.
13	Sos [23]	Randomized Controlled Trial	Higher intensity of psychotomimetic symptoms, measured using BPRS, during ketamine administration correlated with alleviation in mood ratings during the following week, with a maximum on day seven. Ketamine was superior to placebo in all visits (day 1, 4, and 7) assessed by MADRS with effect sizes (Cohen's d) of 0.62, 0.57, and 0.44, respectively. There was no significant correlation between ketamine and nor-ketamine plasma levels and MADRS score change at any study time point.
14	Mathew [24]	Randomized Controlled Trial	The main outcome measure was time-to-relapse. An interim analysis found no significant differences in time-to-relapse between riluzole and placebo groups [log-rank $\chi^2(2) = 0.17$ , d.f. = 1, $p = 0.68$ ], with 80% of patients relapsing on riluzole vs. 50% on placebo. The trial was thus stopped for futility. This pilot study showed that a sub-anesthetic dose of i.v. Ketamine is well-tolerated in TRD and may have rapid and sustained antidepressant properties. Riluzole did not prevent relapse in the first month following ketamine. Further investigation of relapse prevention strategies post-ketamine is necessary.
15	Krupitsky [25]	Clinical Trial	This double-blind, randomized clinical trial of KPT for heroin addiction showed that a high dose (2.0 mg/kg) of KPT elicits a full psychedelic experience in heroin addicts as assessed quantitatively by the Hallucinogen Rating Scale. On the other hand, low-dose KPT (0.2 mg/kg) elicits "sub-psychedelic" experiences and functions as ketamine-facilitated guided imagery. High dose KPT produced a significantly greater rate of abstinence in heroin addicts within the first two years of follow-up, a greater and longer-lasting reduction in craving for heroin, and greater positive change in nonverbal unconscious emotional attitudes than low dose KPT.

**Table 3: Main benefits of psychedelic therapy.**

Reference	Key potential benefits of psychedelic therapy
Garcia-Romeu; Richards, [15]	Safety and therapeutic potential of psychedelics (LSD, psilocybin, mescaline, and DMT) as an adjuvant that can promote substantial changes for the treatment of chemical dependence such as alcoholism, smoking cessation, cocaine, and disorders such as anxiety, suicidal idealization, dependence on opioids, mood swings and even pain. In addition to alleviating the clinical symptoms of these conditions, psychedelic therapy can also stimulate creativity and spirituality and optimize individuals' physiological functions. When combined with motivational enhancement therapy, the results are more satisfying. The psychedelic pharmacological properties are its ability to evoke highly significant experiences that lend themselves to structured interventions designed to alter or modulate an individual's thinking, mood, or behavior patterns through skillful therapy.
Hartogsohn [16]	Spiritually significant experiences and ego-dissolving experiences, the occurrence of which is often correlated with the success of therapy. These substances have a remarkable tendency to increase the perception of meaning or, in other words, to make things appear to be dramatically more significant than they could otherwise be. Thus, psychedelic therapy improves patients' symptoms with a psychiatric disorder or chemical dependency on substances such as alcohol, tobacco, and cocaine.
Johnson [17]	Potential substantial antidepressant and anxiolytic effects for patients with psychological or organic comorbidities such as cancer. In addition, psychedelic therapy significantly contributes to treating patients with some chemical dependency, alcohol, tobacco, and cocaine, influencing the mind and behavior of patients.
Moreton, Szalla, Menzies & Arena [18]	Psychedelic therapy can reduce anxiety disorders associated with suicidal ideation, acting on the dissolution of the ego, admiration, and connection of patients with other people, and promoting improvement in other psychological disorders and the treatment of addiction to some substances chemical. In addition, psychedelic therapy can help clarify the psychological mechanisms underpinning the therapeutic effects of psychedelics and the role death anxiety plays in the etiology of mental illness.
Noorani, Garcia-Romeu, Swift, Griffiths & Johnson [19]	Assistance in treating alcohol withdrawal and substance abuse, smoking cessation, cocaine, and reducing psychological stress and suicidal ideation in psychiatric patients. Changes in behavior, mood, and attitudes in the personality of individuals.
Ross [20]	The use of psychedelic substances for treating patients with psychiatric disorders, such as depression and anxiety, an existential and spiritual disorder due to life-threatening comorbidities such as cancer, is beneficial in reducing depressive and anxiety symptoms, associated or not with cancer.
Sessa [21]	The use of psychedelic therapy can alleviate symptoms of post-traumatic stress disorder (PTSD) and dependence on substances such as alcohol, tobacco, cocaine, opioids, or other drugs that can cause chemical dependency. The association with motivational enhancement therapy can potentiate the effects.

**Table 4: Categorization of the main benefits of psychedelic therapy concerning psychiatric and chemical dependency.**

Main benefits of psychedelic therapy regarding the scope	Frequency of findings in the studies (%)
Psychiatric (depressive, mood, anxiety, post-traumatic stress disorders)	N=22 (100%)
Chemical dependency (alcohol, tobacco, cocaine, opioids, and other chemicals that can cause addiction)	N=22 (100%)

CBD can be useful for treating an array of anxiety conditions, including Post-Traumatic Stress Disorder (PTSD), social anxiety disorder, generalized anxiety disorder, panic disorder, and Obsessive-Compulsive Disorder (OCD). Also, 65% of patients with anxiety and insufficient sleep saw significant improvements in overall sleep quality scores after a month of continually taking 25mg of CBD per day [27, 28].

Therapeutic Effects of Cannabis and Cannabinoids are as follows: In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics [29]; In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms [30]; In adults with Multiple Sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms [31, 32]; and For these conditions, the effects of cannabinoids are modest [9]; for all other conditions evaluated there is inadequate information to assess their effects [33].

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS [34]. The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis [35].

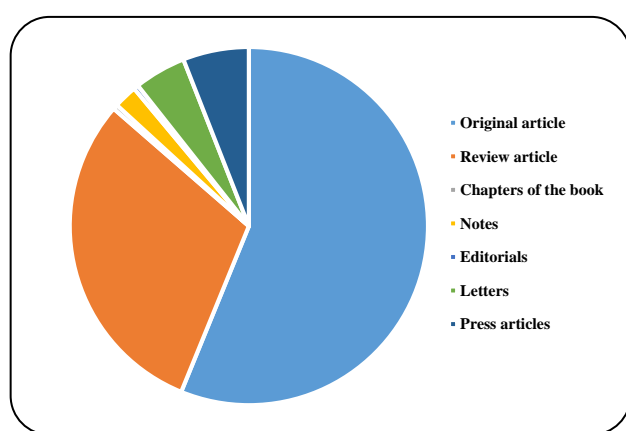
The latest World Drug Report from the United Nations Office on Drugs and Crime (unodc) confirmed that cannabis is the most widely used drug, with around 192 million users. This report also refers to the fact that the amount of cannabis seized worldwide decreased by 27% in 2016, mainly in North America, hypothetically influenced by the availability of medical cannabis in various jurisdictions in the United States. The medicinal

use of cannabis is understood as the modality of use of this plant (or its derivatives) to alleviate symptoms and treat a state or a medical condition [36]. Scientific interest has observed this phenomenon, showing differences regarding the implications, contribution, and impact that the medicinal use of cannabis would have on health, provoking a series of political, legislative, and judicial processes in different parts of the world to analyze the real value of the use of cannabis for medical and therapeutic purposes [37-39]. At present, the medicinal use of cannabis—despite its divergences on the subject—appears as an option in different societies, generating that some countries are regulating its use for this purpose and distinguishing it from purely recreational consumption [40], as well as the questioning about the role of disciplines and health professionals on this issue [41]. The objective of this study is to report the current evidence on the existing medicinal use of cannabis in Scopus between 2013 and 2021, including different types of publications. This comprehensive database is one of the most recognized and with the greatest coverage within the scientific world [42], covering more than 22,800 titles from 5000 international publishers of all subjects and disciplines, including the organization and indexing of journals and scientific books, which makes it a valid and reliable space for the search for evidence on this subject. Furthermore, the fact that a journal is housed in this database turns out to be an important choice criterion for those who publish the results of their studies. This is usually due to tradition and academic culture characteristics where citation metrics are used, incorrectly but commonly accepted, as a parameter to choose where to submit a research article [43].

From the search results, publications of different types and volumes about the medicinal use of cannabis emerge (see Table 5): research articles in greater quantity ( $n = 132$ ), secondly, review articles ( $n = 71$ ), and chapters were also identified in books, notes, editorials, letters, and articles in the press in less significant numbers. Table 5 shows the total number of publications on cum by country,

**Table 5. The number of publications according to type.**

Publication type	N
Original article	132
Review article	71
Chapters of the book	1
Notes	5
Editorials	1
Letters	11
Press	14
Total	235

**Fig. 4: Portfolio of the papers 2013-2021.**

showing a greater quantity in the United States with 127 publications, followed by Canada and Australia with 36 and 16 publications. On the other hand, Table 3 shows that the number of publications on the medicinal use of cannabis has been increasing in the period studied, with 2017 having the highest number of references. Interestingly, the number of publications on this topic is particularly low, evidencing a symptom of scientific research in these latitudes [44].

Cannabis is a plant that makes a thick substance full of chemical compounds called cannabinoids; Cannabidiol (CBD) and Tetrahydrocannabinol (THC) are the most common cannabinoids found in cannabis products. Cannabidiol, or CBD, is found in the cannabis Sativa plant; tetrahydrocannabinol, or THC, is the active ingredient in cannabis with psychoactive effects and alleviates anxiety symptoms[43]. According to a study published in 2015, CBD can be useful for treating an array of anxiety conditions, including Post-Traumatic Stress Disorder (PTSD), social anxiety disorder, generalized anxiety disorder, panic

disorder, and Obsessive-Compulsive Disorder (OCD). Also, 65% of patients with anxiety and insufficient sleep saw significant improvements in overall sleep quality scores after a month of continually taking 25mg of CBD per day[44] (see figures 3-6).

Therapeutic Effects of Cannabis and Cannabinoids are as follows: In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics[45]; In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms[6]; In adults with Multiple Sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms[7, 8]; and For these conditions, the effects of cannabinoids are modest[9]; for all other conditions evaluated there is inadequate information to assess their effects[46].

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS[47]. The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis[48].

The latest World Drug Report from the United Nations Office on Drugs and Crime (unodc) confirmed that cannabis is the most widely used drug, with around 192 million users. This report also refers to the fact that cannabis seized worldwide decreased by 27% in 2016, mainly in North America, hypothetically influenced by the availability of medical cannabis in various jurisdictions in the United States (106). The medicinal use of cannabis is understood as the modality of use of this plant (or its derivatives) to alleviate symptoms and treat a state or a medical condition [49]. Scientific interest has observed this phenomenon, showing differences regarding the implications, contribution, and impact that the medicinal use of cannabis would have on health, provoking a series of political, legislative, and judicial processes in different parts of the world to analyze the real value of the use of cannabis for medical and therapeutic purposes [50-55].

Table 6: The number of publications by country.

Country	Research Articles	Review Articles	Letters	Editorial	Press	Note	Chapter	Total
USA	78	40	-	2	1	4	2	127
Canada	15	6	1	1		5	8	36
Australia	10	5	-	1	-	-	-	16
Israel	11	2	-	-	-	-	2	15
Germany	2	3	-	-	-	2	-	7
UK	3	2	-	-	-	-	1	6
Italy	2	2	-	-	-	-	-	4
Mexico	2	1	-	-	-	-	-	3
Spain	-	2	-	-	-	-	-	2
Ireland	2	-	-	-	-	-	-	2
Norway	1	1	-	-	-	-	-	2
South Africa	1	-	-	1	-	-	-	2
Brazil	-	2	-	-	-	-	-	2
Argentina	-	1	-	-	-	-	-	1
Chile	-	1	-	-	-	-	-	1
France	1	-	-	-	-	-	-	1
Netherland	1	-	-	-	-	-	-	1
Poland	-	1	-	-	-	-	-	1
Switzerland	1	-	-	-	-	-	-	1
Malaysia	-	1	-	-	-	-	-	1
Undefined	2	1	-	-	-	-	1	4
Total								235

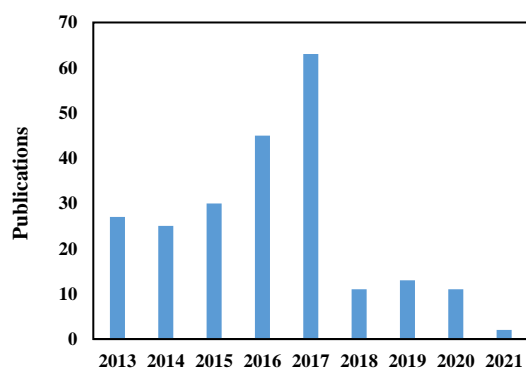


Fig. 5: Publications per year.

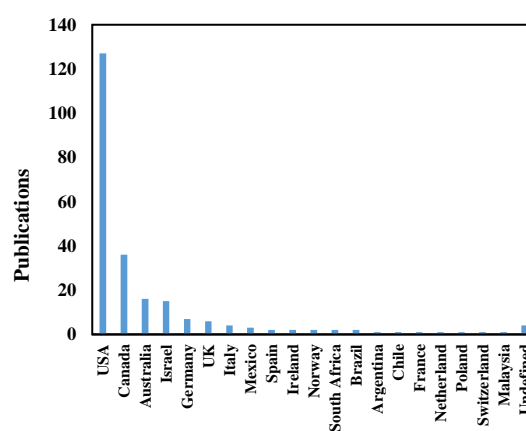


Fig. 6: The number of publications by country.

At present, the medicinal use of cannabis —despite its divergences on the subject— appear as an option in different societies, generating that some countries are regulating its use for this purpose and distinguishing it from purely recreational consumption [56], as well as the questioning about the role of disciplines and health professionals on this issue [57]. The objective of this study is to report the current evidence on the existing medicinal use of cannabis in Scopus between 2013 and 2021, including different types of publications. This comprehensive database is one of the most recognized and with the greatest coverage within the scientific world [58], covering more than 22,800 titles from 5000 international publishers of all subjects and disciplines, including the organization and indexing of journals and scientific books, which makes it a valid and reliable space for the search for evidence on this subject.

Furthermore, the fact that a journal is housed in this database turns out to be an important choice criterion for those who publish the results of their studies. This is usually due to tradition and academic culture characteristics where citation metrics are used, incorrectly but commonly accepted, as a parameter to choose where to submit a research article [59]. The systematic review of 235 publications involved an analysis of their essential contents. From its organization and synthesis, the main findings are given below.

#### ***Medicinal use of cannabis and prescription***

The evidence accounts for an intense debate and discussion about the prescription of cannabis for medicinal purposes [60]. A study of University of Washington residents and fellows reported that most deans reported that their graduates were unprepared to prescribe medical cannabis or answer questions about the medicinal use of cannabis. The vast majority of residents and fellows (89.5%) did not feel empowered to prescribe medical cannabis, while 35.3% did not feel ready to answer questions. 84.9% reported no medical school or residency education on medical cannabis [60-64].

The lack of preparation and the importance of the users' health makes it imperative that physicians exercise caution when recommending the medicinal use of cannabis [65-66]. In the case of Canada, users comment that it is difficult to find a doctor who supports their request to access the medicinal use of cannabis [68]. Minnesota

pharmacists report limited knowledge of medicinal use of cannabis policies and regulations. They feel they are inadequately trained in cannabis pharmacotherapy, thus requiring further instruction and education on the regulatory and clinical aspects of cannabis [69]. Some authors support the need to investigate and standardize the assignment of names, dosage, route of administration, and medicinal use of cannabis control [69-74].

#### ***Medicinal use of cannabis and users***

Regarding the characteristics and opinions of medical cannabis users, the evidence indicates that: a) medical cannabis is used equally in many groups of people and not exclusively in any specific group [75]; however, it is more frequent among adults hospitalized with a psychiatric emergency than in the general population [30]; b) the medicinal use of cannabis is perceived as an effective treatment for various conditions, with pain and mental health is the most highlighted by users [30-33]; c) three out of four patients reported symptomatic improvement [34]; d) sleep problems are very common in medical cannabis users and are closely related to pain [35]; and e) users are requesting improved standards for purity, yield, and further research on the medicinal use of cannabis [36].

#### ***Medicinal use of cannabis benefits***

Herbal cannabinoid preparations have been used medicinally since ancient times [37]. However, it has become a topic of growing interest [38-40].

Evidence indicates that the medicinal use of cannabis may have beneficial effects in addressing certain health conditions [40-46]. While there is a need for more information and randomized controlled trials [46-51], some preliminary studies have suggested that the medicinal use of cannabis may be beneficial in the treatment of certain conditions such as inflammation, spasticity, epilepsy, eating disorders, glaucoma, inflammatory bowel diseases, and neurological disorders [51-58].

Pain management is the most common reason for the medicinal use of cannabis [59]. Research reports positive therapeutic effects in refractory neuropathic pain together with traditional analgesics [60, 61], allowing the reduction of symptoms of Parkinson's disease in the initial stages of treatment [62] since it improves motor scores and pain symptoms in these patients [63]. In addition, it would act positively in the therapy for muscle spastic disorders [64].

Various research articles indicate the medicinal use of cannabis is safe and effective for many patients with chronic pain [65-73]. It is considered an alternative for those who receive prolonged analgesic therapies with multiple adverse effects, such as palliative pain in advanced cancer, and for the discomfort associated with chemotherapy due to its antiemetic effect, being safer than certain conventional drugs [73-77].

Other research finds it useful for the relief of anxiety and insomnia [77-81] and for reducing symptoms of stress disorder post-traumatic in some patients [82], as well as for decreasing the frequency of migraines [83]. A recent study indicates that cannabis oil would be safe and effective for the behavioral and psychological symptoms of dementia, so they suggest adding it to the pharmacotherapy of Alzheimer's patients as a treatment option [84]. Other research indicates that treatment with cannabidiol (CBD), one of the components of cannabis, for intractable epilepsy in a population of children and adolescents is promising, with evidence of a positive effect on the burden of seizures [84, 85].

#### ***Harmful effects of medicinal use of cannabis***

Among the harmful effects, the evidence suggests that the medicinal use of cannabis would be associated with a risk of problematic cannabis use and a greater probability of using prescription opioids for medical purposes [86]. Other studies propose that the medicinal use of cannabis in patients with chronic spinal cord injury may make them more vulnerable to complications and the appearance of risk factors for substance use disorders, such as social isolation [87]. Similarly, some research mentions that patients with chronic pain who use cannabis as a palliative may have a higher initial risk of substance use problems [88]. Likewise, cannabis would increase cognitive deterioration in patients with multiple sclerosis [89]. In line with those mentioned above, a study in the literature [90] concludes that the harmful effects of medicinal cannabis far outweigh any perceived benefit.

#### ***Medicinal use of cannabis and lack of evidence***

The information collected from the medicinal use of cannabis, beyond the perceived benefits and risks, is consistent in that there are important gaps concerning its evidence.

In particular, it is necessary to have controlled trials with humans to verify the efficacy of cannabis in treating and preventing medical conditions and alleviating the negative symptoms associated with these conditions [91, 92].

As an evidence-based science, medicine has been approaching the medicinal use of cannabis with great caution due to the lack of sufficient and supporting clinical data [93-96]. In this sense, they urge more research on the safety and efficacy of medicinal use of cannabis in different diseases and treatments, with clinical trials being especially necessary for patients with: a) risk of a cannabis use disorder, b) palliative treatment for cancer, and c) syndrome of the wasting of AIDS and other negative sequelae of HIV/AIDS [97, 98].

#### ***Medicinal use of cannabis, regulation, and legalization of cannabis***

The debate regarding the regulation or legalization of the medicinal use of cannabis is a controversial issue that inherently carries implications for health professionals, public policy makers, and society [99-102]. The belief that cannabis has medical benefits is particularly relevant for supporting the legalization of medical cannabis and for use intentions [99]. The recent increase in evidence supporting their contributions to health issues may increase the belief about the benefits of medicinal use of cannabis in the general population, increasing public support for its regulation or legalization [103]. Numerous publications study the existence of consequences of cannabis regulation and legislation, mainly in the US, reporting: a) that there is no general increase in the probability of cannabis use related to the policy change [99], however, in the United States, medical laws on cannabis appear to have contributed to increasing the prevalence of illicit cannabis use and use disorders [104]; b) that medical cannabis policies were significantly associated with the reduction of hospitalizations related to the use of opioid analgesics in the United States; c) that there was a reduction in deaths from traffic accidents, especially in the population between 25 and 44 years old [105], however, the negative relationship between legalization and deaths in traffic related to alcohol does not necessarily imply that driving under the influence of cannabis is safer than driving under the influence of alcohol [106]; d) that it is associated

with a lower overdose mortality rate [107]; e) that no statistically significant association is found between medical cannabis policies and suicide risk [108, 109]. However, a study carried out in the United States concludes that suicides among men aged 20 to 39 years decreased after the legalization of medical cannabis compared to those states that did not legalize it. The negative relationship between legalization and suicides among young men is consistent with the hypothesis that cannabis can be used to cope with stressful life events [110]; f) that medical cannabis laws also have no perceptible impact on alcohol consumption behavior among people aged 12 to 20 years, or on the use of other psychoactive substances in any of the age groups [111, 112]; g) that in the states that have passed the medicinal use of cannabis laws, the use of cannabis increased after enactment among people aged 26 years and over, not between the ages of 12 to 25 years [113]; and h) that a new appearance of unintentional ingestion of cannabis by young children was found after the modification of drug control laws for the possession of cannabis in Colorado [114].

Even with multiple ongoing regulation and legalization processes of the medicinal use of cannabis, numerous scientific, safety, and public health problems persist, in addition to limitations of the evidence in providing clear information on the probable effects of the legalization of cannabis and its medicinal use [115-117]. However, there is an agreement in the information collected that researchers need to be aware of the political context in which laws and regulations on the medicinal use of cannabis are enacted or not and consider how research results can achieve a higher profile in this context [118].

#### ***Medicinal use of cannabis and its association with criminal behavior***

There is no evidence of an association between the legal regulation of the medicinal use of cannabis with an increase in the prevalence of various crimes. Instead, significant drops in violent crime rates associated with UCM regulation are reported in various jurisdictions [119]. In California, United States, an investigation reports that the number of medical cannabis dispensaries is not related to violent crime in local areas but is positively related to crime in spatially adjacent areas; that is, the use of the law to Reduce medical cannabis dispensaries in California appears to have reduced crime in nearby

residential areas, but not in locations where dispensaries are established [120]. Papers in literature [121-127] reaffirm the above and suggest that the effects of the availability of cannabis outlets do not necessarily occur within specific crime areas but can occur in contiguous areas.

#### ***Medicinal use of cannabis and culture***

The production and consumption of cannabis for medical conditions are increasingly visible internationally. However, research on different aspects of the phenomenon is still scarce. An intercultural study reported that the cultivation of cannabis for medical purposes is widespread. The majority of growers for medicinal purposes reported that they grew cannabis for serious conditions, most of them having a formal diagnosis. Furthermore, although the number of medicinal growers is increasing, they do not necessarily have the proper advice and adequate medical guidance [128-132]. The cultivation is difficult to control and can generate unwanted consequences since it encourages minors to have access to cannabis products and, at the same time, exposes many individuals who are not users to the adverse consequences of the cultivation and use of cannabis in domestic environments [133].

#### ***Medicinal use of cannabis and dispensaries***

A study [134] states that medical cannabis dispensaries are widely accessible for therapeutic purposes. Although cannabis sales in stores are illegal in Canada, a federal program uses dispensaries. His experience reports that: a) patients who used dispensaries were older, more likely to have arthritis and HIV/AIDS, and less likely to have mental health problems than those who did not use dispensaries; b) those who accessed the dispensaries used greater amounts of cannabis, valued more access to specific strains and were more likely to have legal authorization for the medicinal use of cannabis; and c) the dispensaries were rated the same or more favorably than other sources of cum for their quality, safety, availability, efficiency, and sense of respect, and less favorably than their production and other producers for their cost. Some authors point out that the distribution of medicinal use of cannabis through dispensaries brings benefits and disadvantages, such as opportunities for increased criminal behaviors in the environments where they are located [135].



### **Medicinal use of cannabis in childhood and adolescence**

Currently, data on the medicinal use of cannabis's benefits and adverse effects in childhood are rather scarce, evidencing this population's lack of properly designed studies that support its efficacy and safety [136-137]. A growing body of data suggests a potential hazard in the medicinal use of cannabis in children, so a comprehensive and careful long-term assessment supported by developmental effects is recommended [133].

Regarding the youth population, recent research indicates that they are at higher risk of developing problem use after a cum, mainly because the amount of cannabis consumed and the rates of problem cannabis use were higher among young users compared to adults, middle-aged, and older adults [119-121].

Adolescents' perceptions of cannabis appear to be influenced by their advertising. Higher advertising exposure to medical cannabis was significantly associated with a higher probability of adolescent cannabis use and greater intentions to use it one year later [133-134]. Because of this, it seems reasonable to speculate that laws and regulations on the medicinal use of cannabis could amplify cannabis use by young people by dispelling the social stigma associated with recreational cannabis use (URC) and mitigating fears that cannabis use may lead to a negative health outcome [110-112]. However, other authors suggest that in places where legal regulations for the medicinal use of cannabis have been made, they have not seen an explosive increase in cannabis use in the first years after its enactment. After laws are implemented consistently and permanently, long-term results could be different [113].

It is mentioned that clinical trials supporting the efficacy of cannabis for pain in adolescents are essentially non-existent [115]. In addition, it is referred to in the evidence that the medicinal use of cannabis in adolescence can cause a series of physical symptoms, has a strong association with schizophrenia, can affect neurocognitive development in the brain of an adolescent who is not fully mature, and can lead to problems—school, relationship, and work, as well as car accidents. Furthermore, not all adolescent patients respond similarly to the medicinal use of cannabis [116-117].

### **Medicinal use of cannabis associated with other drugs**

The data found in this review on the medicinal use of cannabis and its association with other drugs suggest that:

a) the treatment comparison between cannabis and opioids reports that the levels of depression and anxiety are higher among patients with chronic pain who receive opioids prescribed in comparison with those who receive medicinal cannabis [118-119]. The clinically and statistically significant evidence suggests a reduction in the prescription of opioids and a better quality of life when considering the medicinal use of cannabis as a potential alternative for the treatment of chronic pain [120]; b) users of prescription pain medication (MRD) rated the efficacy of medicinal use of cannabis above MRD and indicated a strong desire to reduce consumption of the latter [121-122]; c) a recent study indicates that the enactment of any law on the medicinal use of cannabis, and especially the less restrictive ones, are associated with lower probabilities of alcohol consumption in adolescents during the last 30 days [123]; and d) other research proposes that medicinal use of cannabis can be a valid, safe and effective substitute for heroin, alcohol, and tobacco, as well as some opioid, benzodiazepine and antidepressant drugs [124-125]. This finding of cannabis use as a surrogate for other drugs (legal or illegal) suggests that the medicinal use of cannabis may play an important harm reduction role in problematic substance use and may have implications for drug-based treatment approaches. abstinence [126].

## **DISCUSSION**

### **Discussion of the Psychedelic Therapy**

The terms "psychedelic" and "psychedelia" were coined in 1957 by the British psychiatrist Humphry Osmond exchanging letters with the writer *Aldous Huxley* in 1956. Psychedelia translates to the idea of manifestation of the mind or revelation of the spirit, and psychedelic makes the soul, the self, or the psyche visible [26]. Although the term was new, psychedelics had been used for millennia in religious rituals and sacred contexts in Central America [1]. In the sense that it concerns the clinic, the sense of psychedelia refers to transformation experiences by reducing egoic control and expanding consciousness [26]. However, at the beginning of the clinical use of psychedelics, psychiatrists did not focus on the therapeutic capacity of the substance but mainly tried to induce psychosis [27]. As for the title and purpose of the articles, *Garcia-Romeu* and *Richards* [15] sought to talk about current perspectives on psychedelic therapy and the use of hallucinogens in interventions; *Hartogsohn* [16]

addressed the properties of psychedelics and their role in psychedelic therapy, spirituality, and creativity; *Johnson* [17] talked about how psychiatry might need psychedelic therapy; *Moreton* [18] studied the incorporation of existential psychology into psychedelic science and the reduction of death anxiety through psychedelic effects; *Noorani* [19] sought to study psychedelic therapy for the smoking cessation process; *Ross* [20] evaluated the therapeutic use of psychedelics for the treatment of cancer patients and, finally, *Sessa* [21] investigated MDMA therapy for alcohol abuse disorders [200].

From the diffusion of Lysergic Acid Diethylamide (LSD), Psychedelics' transformational potential became obvious, and their therapeutic use began [27]. Thus, in the 1950s and 1960s, several studies were carried out on the therapeutic potential of these substances, such as for the treatment of post-traumatic stress, depression, and incursion in psychoanalysis sessions [28]. However, with the 197 Controlled Substances Act, this field of research practically ceased [5]. However old it may be, *Garcia-Romeu* and *Richards* [15] found that psychedelic therapy has seen an encouraging renaissance with promising clinical trials in the early 21st century. Years and also due to the relative lethargy and low resolution in psychiatry since the 70s compared to the rest of medicine. Who sees in their hope for some of the most difficult problems in psychiatry. *Johnson* [17] believes that psychiatry needs help. He warns of epidemic suicide rates and the millions of deaths annually caused by tobacco addiction. He also remembers that the last great advance to treat depression was more than 30 years ago with the approval of the first SSRI (selective serotonin reuptake inhibitor) and that even these were simple, safer, and more selective evolutions of antidepressants already developed in the decade of 1950. Also, according to *Johnson* [17], it is important to emphasize that these drugs, even with relatively modest effects, are crucial for those whose depression puts them at risk of suicide, enabling a clear need and substantial room for improvement. The slow and modest advances in psychiatry are related to the lack of analytical mechanisms for various diseases. In this sense, psychedelics could be important in making "fundamental advances in a mechanical understanding (biological and psychological) of psychiatric disorders." *Noorani* [19] performed a qualitative retrospective analysis of interviews conducted with participants in pilot studies

for psilocybin-facilitated smoking cessation. Although these studies cannot demonstrate effectiveness, they converge with other results that indicate the significant therapeutic power of hallucinogens in treating smoking. The analysis concluded that the therapy provided other persistent positive effects, such as self-esteem, altruism, and smoking cessation. *Ross* [20] performed a systematic review of the literature on the clinical use of hallucinogens to treat cancer-related psychological distress. They point out that there was a promising early phase of clinical trials with hallucinogens between 1960 and 1970 and that it was halted before any definitive conclusions were reached. But in the last decade, clinical trials were resumed for the treatment of various psychiatric illnesses, which he cites: cancer-related suffering; depression; TOC; in addition to addiction disorders (alcohol, nicotine, and cocaine), is the use of classic hallucinogens for cancer-related suffering for which we have more robust data. The clinical trials reviewed for *Ross* [20] have significant positive results. They show they are related to acceptance, reflection on death, and spiritual enrichment, which would be key points of suffering due to anxiety about death itself.

*Moreton* [18] address existential psychology in psychedelic science. They argue that death anxiety plays a central role in psychopathology and that psychedelics a correlated with factors such as: confronting unconscious fears of death; reduced focus on self; changes in the perception of human consciousness; an increase in faith, and extensions of the meaning of life promote a reduction in death anxiety. For them, psychotherapists should turn their eyes to the conscious/unconscious as a solution to the stagnation noted in psychotherapy, and psychedelic science would be like a 'superroad' for this. *Hartogsohn* [16] investigated the apparent meaning-enhancing properties of psychedelics. The author found in studies carried out with questionnaires an increase in meaning for life and existential issues in patients who used psilocybin. For him, this happens due to a spontaneous human demand to assign meaning, and that psychedelics, through powerful access to what was previously subconscious, allow the creation of new concepts and definitions and can help in therapy, spirituality, and creativity. *Sessa* [21] proposes that an ongoing study with patients who have undergone medical detox for alcohol abuse disorder may have benefited from MDMA therapy[29]. To justify this point of view, the author argues that MDMA is safer than

the rest of the psychedelics. Its use has shown encouraging effects for alcohol abuse disorder and unresolved trauma on other occasions. Finally, he also argues that society and psychiatry are overwhelmed by results in the treatment of alcohol abuse disorder that “are a little better now than they were 100 years ago [30].” Among the limitations presented for this study, the low number of studies carried out on the subject stand out, requiring more randomized clinical trials and observational studies to help in a better understanding of psychedelic therapy and its benefits for the mental health of patients. Still, few studies explain the pharmacokinetic mechanisms of the action of psychedelics in the pathways that regulate and modulate neurotransmission related to mood disorders [31-42].

Authors believe we both share the unspoken assumption that psilocybin's use at this stage requires medical justification. It began as a psychotherapeutic aid in Western societies, but it comes from the mushroom family [201]. As Aldous Huxley put it, many believe and continue to believe that the justification for the use of such drugs lies in their ability to open the doors of perception. In this view, access to such drugs should be a recreational right, just like access to alcohol, cigarettes, and, increasingly, cannabis. As with cannabis, medical use is likely to encourage greater discretionary use for any reason. Some may still view the development of medical indications as a red flag [111-138].

The continued illegal status of psychedelics has an important result, however. It seems paradoxical, even unbelievable that such drugs should not be able to be used medically in conditions where euthanasia is already possible. Belgium's euthanasia laws first referred to neuropsychiatric disorders in 2004/5. From 2007 to 2011, 58 of the 100 first such patients considered for euthanasia were depressed. Within 12 months of the study's end, 48 participants were accepted for euthanasia (35 were completed), and six others had died by suicide. Most of the participants were females in their 40s and 50s. The Netherlands and Luxembourg allow euthanasia for psychological suffering [138-144]. Thus, I think we should use psilocybin in medicine, but we should not ignore human logic's failures, which means high-quality clinical trials are essential.

### ***Discussion on the Cannabinoid Therapy***

The review carried out in Scopus provided an information bank of 235 publications, of which 71 are

review articles, 14 book chapters, five notes, one editorial, 11 letters, 14 press articles, and 132 are research articles. The countries that report significant evidence on the medicinal use of cannabis are the United States with 127 publications, Canada with 36, and Australia with 16. Regarding research articles, the United States also shows a higher volume with 78 publications, in second place, Canada with 15, and Israel appears with 11. Among the articles for review, the United States again leads with 40 articles, Canada with 6, and Australia with 5. One relevant letter with the revision was reviewed and published in Canada within the publications. In the editorial category, the United States leads publications, being also the only country that presents two press articles in the period limited by this review. Within the notes, Canada has the highest indexes of publications with a total of 5, in second place in the United States with three, and finally Germany with a total of 2 [144-156]. In the book chapters, Canada leads with 8, followed by the United States and Israel with two posts each. We can corroborate, from this review, that the publications regarding the medicinal use of cannabis suggest a growing, progressive and constant increase in the last five years. In 2013 there were 28 publications; in 2015, it increased to several 30; in 2016, it rose to 46, and in 2017, another 63 were published. However, in 2018-2021 we can see a decline in this field, which reached two confirmed papers in 2021 [157-169].

The image of cannabis is among the drugs of abuse and the most consumed worldwide. This social perception tends to make the beneficial effects that different studies attribute to the medicinal use of cannabis invisible. However, advertising also causes a reduced effect in the perception of the risks associated with URC, mainly in the adolescent population. The controversy in the scientific world generates divisions when weighing the risks it poses to people's overall health and the benefits it can provide. In this sense, it is important to generate an explicit division for analyzing the medicinal use of cannabis and URC [170-195].

According to the evidence reviewed, the findings of an endocannabinoid system accelerated the biological interest in understanding the medicinal role of cannabis in human functioning. However, there is also an important need to carry out methodologically sound studies that fill in the research gaps concerning the medicinal use of cannabis. Prescription, dosage regulation, and effective administration

need concrete standardizations. In addition, more data is required regarding the efficacy and safety of the medicinal use of cannabis in different diseases and treatments and its application at different stages of the life cycle [189].

Like any medication, the advantages of its consumption must be weighed concerning the adverse effects. The evidence indicates that the final decision to apply a treatment based on cannabis or its derivatives in a patient must have the same medical criteria governing the administration of any other drug. To consider whether its use and distribution are adequate, health professionals must update on the medicinal use of cannabis's concerns in different medical conditions.

In general terms, the evidence analyzed reports important and recognized benefits of the medicinal use of cannabis, mainly for the general relief of chronic pain. In addition, its effects would be positive as a palliative of pain in cancer cases and discomforts derived from chemotherapy (nausea and vomiting), in spastic muscle disorders, refractory neuropathic pain, anxiety, insomnia, and epilepsy. On the other hand, it is reported that the medicinal use of cannabis reduces the symptoms of post-traumatic stress disorder in some patients, the pain caused by multiple sclerosis, to address attention deficit hyperactivity disorder and rheumatic pain. Another finding lies in the substitution of multiple substances for the medicinal use of cannabis, such as prescription drugs, opioids, antidepressants, benzodiazepines, alcohol, tobacco, and illicit drugs, which could be useful in addressing problematic drug use under a harm reduction approach [133].

On the harmful effects recorded in the evidence, the potential risks that medicinal use of cannabis later becomes a problematic use of cannabis or other substances are emphasized. However, the information collected on the medicinal use of cannabis and its legal regulation indicates that they have not measurably affected the use of cannabis for non-medical purposes. There is no conclusive evidence that associates the medicinal use of cannabis with an increase in URC levels in the population. Nor is the evidence conclusive on an association between the medicinal use of cannabis and its regulation with increased criminal behavior [134-137].

Concerning the medicinal use of cannabis in the infant and adolescent population, the available evidence is insufficient and aimed at assessing the risks of its application at this stage of the evolutionary cycle, given

the dangers to neurodevelopment that the medicinal use of cannabis can generate in the medium and long term in children and adolescents. This is an area in which research on the medicinal use of cannabis requires an imperative development and expansion that allows a controlled evaluation of safety and the positive and adverse effects that its application may entail [112].

Like its study and analysis, the medicinal use of cannabis should be a priority objective in discussing health professionals needing to differentiate the debate concerning the URC that pursues other purposes. This is why the discussion about the regulation or legalization of the medicinal use of cannabis must be based on reliable scientific evidence, including medical, economic, and macrosocial aspects [99, 102].

## CONCLUSIONS

According to several authors, psychotherapy itself appears as a reason for psychedelic therapy's resurgence. Psychopathology is not highly resolvable, and the evolution of psychotherapy in medicine is generally unsatisfactory. It is seen as an exciting new horizon in this field that is taking advantage of society's paradigm shift to advance in research related to the treatment of serious health problems such as depression and death anxiety, as well as alcoholism and smoking addictions, where the results have been encouraging and where researchers expect and need significant advancements in the future. An overview of the history of psychedelic therapy is provided here, and the latest research marks its rebirth. That demonstrates its applicability and potential and the demand for it. We are not interested in determining the effectiveness of mechanisms of action of treatments in this study. Accordingly, any conclusion derived from this study is not precise. Future research should aim to clarify the relationship between hallucinogens and biological therapeutic effects for individuals, the psychological benefits of psychedelic therapy, and highlighting any possible adverse effects. A better understanding of how psychedelics affect neurotransmission is also necessary to better understand their benefits. Based on a review of Scopus, an information bank of 235 publications was compiled. Of these, 71 are review articles, 14 are book chapters, five are notes, and one is an editorial, 11 are letters, and 14 are press articles. Of these, 132 are research articles. Furthermore, there is an urgent need for further research and evidence regarding the safety

and efficacy of medicinal cannabis use in different diseases, treatments, and age ranges, and the design of clinical trials that allow for data analysis and comparison. The limitations of this review are that the authors searched for evidence on cum only in Scopus, which poses the challenge of expanding and comparing these results from other databases. In addition, it is suggested to conduct new studies and reviews that will enable Latin America to participate in research on this topic, which is expanding both in scientific controversy and political, health, and social discourses.

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