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Evolution of Marijuana Research at the Biopsychosocial Level: a General View

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Abstract

In recent years, there have been important changes related to marijuana use at the therapeutic, legislative, and social levels. Our goal is to know how they have influenced scientific research through the articles published in the Health Sciences journals in the last two decades (2001–2020). Marijuana articles included in the Web of Science Core Collection were retrieved, including their PubMed identifier (PMID) which was used to check whether these articles were also indexed in PubMed, obtaining a total of 36,982 documents. After, their descriptive terms (MeSH) on the specific branches of Chemicals and Drugs, Psychiatry and Psychology, and Anthropology, Education, Sociology, and Social Phenomena were extracted to (1) conduct a correspondence analysis between terms and years to know the temporary evolution and (2) study the frequency per years of the terms "marijuana abuse," "marijuana use," and "medical marijuana." The temporary analysis of the three branches showed a change in the use of terms from those more punitive to others more generic, more related to therapeutic issues, or more normalizing. The analysis of frequency showed that the most recent terms "marijuana use" and "medical marijuana" have gained weight on "marijuana abuse." Starting with research on the negative consequences and ending with elements related to legislation and the therapeutic possibilities of marijuana shows a trend that has not been observed for any other drug. It would be advisable for scientific research and policy actions to take this into account in the development of prevention programs.

 $\textbf{Keywords} \ \ Cannabis \cdot Marijuana \cdot MeSH \cdot Descriptors \cdot Social \ networks \cdot Temporal \ analysis$

The area of knowledge of addictions has been consolidating over the last 50 years with an increase in scientific production that includes basic research studies, social sciences, and health sciences (Aleixandre-Benavent et al., 2021). This increase and strengthening of research in the area of addictions has been reflected in both substance addictions and addictive disorders (Khalili et al., 2018) as well as in non-substances (Sixto-Costoya et al., 2021). This consolidation has contributed to the creation of various organizations and entities focused on controlling supply (mainly legislative, police, and judicial actions), dressing

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demand (through prevention, treatment, and social reinsertion programs), developing public policies, and promoting research in the area.

These organizations and public opinion have shown an interest in both the negative consequences of marijuana use and its impact on the health of the population (Volkow et al., 2014), as well as regulatory changes for its legalization. According to the latest available data published by the United Nations Office on Drugs and Crime published in 2021, it is estimated that there would be around 200 million marijuana users worldwide in the last year, which corresponds to approximately 4% of the population between 15 and 64 years old (United Nations, 2021b). If the decade from 2010 to 2019 is considered, the number of marijuana users in the last year increased globally by 18%. Currently, marijuana is, after alcohol and tobacco (legal in virtually all countries), the most widely consumed drug worldwide (Bahji et al., 2020). In addition, in this last decade, an increased number of marijuana products with high levels of $\Delta 9$ -THC (the main active ingredient in marijuana and responsible for the psychoactive effect) have been detected (Jeffers et al., 2021; Manthey et al., 2021). From the point of view of demand, there is equally worrying data, since a mismatch has been detected among young people between the perception and the risk involved in marijuana use, which may be aggravated by the higher amount of THC detected (United Nations, 2021a). If we take into account the consequences of consumption on health, the data obtained in the systematic meta-review of meta-analyses conducted by Dellazizzo, Potvin, Giguère, and Dumais (2021) on the acute effects of marijuana use on neurocognitive function. The results of this study showed that marijuana intoxication causes small to moderate deficits in numerous cognitive domains, particularly in executive functions, verbal learning, and memory and processing speed. Furthermore, these acute deficits are associated with residual effects suggesting that the detrimental effects of marijuana persist beyond the period of acute intake.

Given this reality, research must address marijuana-related issues from different fronts. Among these fronts are the studies of the plant and the different types of cultivation (Decorte, 2010), consumption patterns (Cooke et al., 2020), social aspects (Bilgrei et al., 2021), the irruption of synthetic cannabinoids (Castaneto et al., 2014), the effects related to its consumption (Hall & Degenhardt, 2009), the benefits and harms of the medical use of marijuana (Pratt et al., 2018), research on endocannabinoid receptors (Howlett, 2002) and the legalization of the substance (Laqueur et al., 2020), as well as the harms and benefits of its legalization (Lake & Kerr, 2016; Rotermann, 2019).

However, to obtain a global vision of marijuana research and to be able to make appropriate decisions related to the management of material and human resources, it is necessary to know what is being published, when, how much, where, and how. In this regard, several works have been detected in the scientific literature that seeks to know the status of research regarding addictions using bibliometric techniques, some focused on specific substances, such as alcohol (González-Alcaide et al., 2014) or tobacco (de Granda-Orive et al., 2009), and others on addictions in general (Bramness et al., 2013; Khalili et al., 2018; Sixto-Costoya et al., 2021). Concerning marijuana, several papers have also been detected in the literature that addresses this topic using bibliometrics, with different objectives. Among them, some have a more generic approach to marijuana, where long periods are studied and results are presented by countries, institutions, authors, and evolutionary trends through journal categories (Jingting et al., 2021; Matielo et al., 2018; Vogelzang et al., 2010); others are more focused on addressing specific topics, such as trends in publications on marijuana for therapeutic purposes (Martín-Banderas et al., 2013; Treister-Goltzman et al., 2019); some, in finding out which have been the most relevant papers based on the number of citations (Wai et al., 2019); while others have focused on inquiring



about the best strategies within bibliometrics to address the subject matter of the papers (Valderrama-Zurián et al., 2021).

However, to date, no work has been detected in the literature on the evolution of marijuana research in Health Sciences. Therefore, given the importance of the subject of marijuana use, its highly changing legislative situation, and the number of people it affects, this paper aims to address the following aspects:

- To analyze the chronological evolution at the chemical and pharmacological, psychiatric
 and psychological, and anthropological and sociological levels in the Health Sciences
 journals that focuses on marijuana issues.
- 2. To analyze the frequency of use of the MeSH terms that include the term "marijuana" which are "marijuana use," "marijuana abuse," and "medical marijuana."

Methods

At the methodological level, the data processing guidelines used by Valderrama-Zurián et al. (2021) were followed. Firstly, a total of 51,170 articles were obtained from the Web of Science (WoS) Core Collection for the 2001–2020 period. The reason for choosing WoS was to ensure the quality standard of the mainstream journals. In second place, we used the Pubmed (PM) Identifier (PMID) to check whether these 51,170 articles were also indexed in the PM database. After this combination, a total of 36,982 articles were obtained, being the total of the final sample for this study. PM also includes the most widely accepted controlled vocabulary for the document indexation, the Medical Subject Headings (MeSH), created and maintained by the National Library of Medicine which are not necessarily the same that the author keywords.

In this sense, the MeSH terms that identify the content of the documents in the PM database were extracted from these documents and combined with the MeSH thesaurus to obtain not only the terms themselves but also the other information associated with them, such as the root or roots in which they appear, their location in the thesaurus branch, and the hierarchical relationships in which each of the terms is involved.

Data processing has been carried out by combining a relational database management system (SQLite) with tools for statistical processing and data visualization, specifically the statistical package R (2020), using its different libraries. Figure 1 shows the workflow followed.

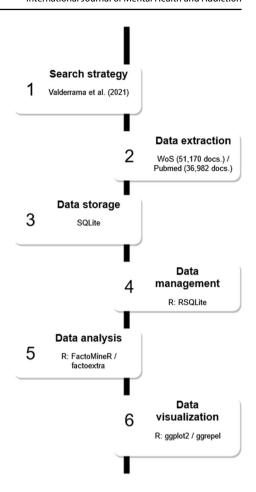
Given the perspective of this study, it was decided to work only with three of the MeSH branches: branches D (Chemicals and Drugs), F (Psychiatry and Psychology), and I (Anthropology, Education, Sociology, and Social Phenomena). In total, 5054 different terms were considered for the three branches for the 36,982 records analyzed.

To find patterns of evolution in the use of MeSH terms over time, it was decided to use multivariate analysis techniques. Specifically, MeSH terms were compared with the date of publication of the documents, so that changes in the focus of scientific research in the area of study could be observed. For this purpose, the technique of correspondence analysis was applied (Nenadić & Greenacre, 2007).

¹ The word "marijuana" refers to parts of or products from the plant *Cannabis sativa* that contain substantial amounts of tetrahydrocannabinol (THC) according to the MeSH. In this study, the term marijuana refers to the plant "cannabis sativa," their active principles, or cannabis as psychoactive substance.



Fig. 1 Workflow followed



The analysis of MeSH descriptors including the word marijuana, such as "marijuana use," "marijuana abuse," and "medical marijuana," was performed in terms of frequency and annual evolution. For this analysis, the term "marijuana smoking" was not considered because it refers to a way of consumption and not to the conduct per se, as is the case for the other three terms.

Results

Analysis of the Chronological Evolution of the Terms in the Three Selected Branches

The study of the correspondence analysis made it possible to produce three figures in which the evolution of MeSH terms in each of the branches analyzed can be observed throughout the study period. The figures show how the terms belonging to each branch have been awarded to the articles along the two decades analyzed. In this regard, the first thing that can be observed is the clear chronological arrangement of the terms along the horizontal axis, because in the three cases, the variability is high (58.9% in the case of



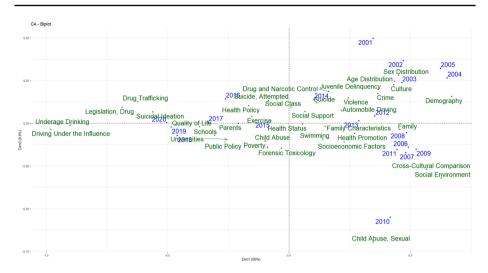


Fig. 2 Correspondence analysis of MeSH I branch

Anthropology, Education, Sociology, and Social Phenomena (Fig. 2), 78.4% in Chemicals and Drugs (Fig. 3), and 81.7% in Psychiatry and Psychology (Fig. 4)).

The specific characteristics of the terms evolution in each branch is explained separately in the following paragraphs.

Terms related to the branch "Anthropology, Education, Sociology and Social Phenomena"

In the first years (located to the right of the axis), it can be observed that the publications are mainly focused on topics related to sociodemographic aspects of cannabis use ("age distribution," "sex distribution," "demography"), to later move on to judicial or legal aspects ("crime," "violence," "juvenile delinquency," "child sexual abuse"), and finally health-related aspects ("exercise," "health promotion," "health policy"). Likewise, it is observed that the difference is found from 2015 toward the left, being more evident from 2018 to 2020. In recent years, aspects related to legislation, concomitant alcohol consumption, and driving under the influence of substances have predominated, where alcohol consumption has been included with other substances such as cannabis or drugs. In this regard, the change in terms related to legal control is noteworthy, evolving from the term "drug and narcotic control" (MeSH definition: "control of drug and narcotic use by international agreement, or by institutional systems for handling prescribed drugs. This includes regulations concerned with the manufacturing, dispensing, approval (drug approval), and marketing of drugs") to the term "drug trafficking" (MeSH definition: the illegal acquisition, sale, production, transport, movement, and distribution of controlled substances such as narcotics), and finally, the more recent "legislation drug" ("laws concerned with manufacturing, dispensing, and marketing of drugs"). On the other hand, it can also be observed that suicide has undergone variations throughout the period studied, going from the term "suicide" to "suicide, attempted" and "suicidal ideation."

Terms related to the branch "Chemical and Drugs"



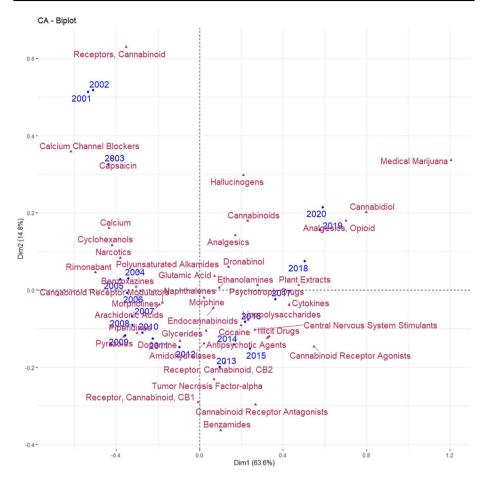


Fig. 3 Correspondence analysis of the MeSH D branch

Firstly, an association with terms such as "receptors, cannabinoid" in general and modulators of the same that affect calcium channels is distinguished at the beginning of the period (this time located on the left of the axis); terms such as "capsaicin" that is related to the production of anandamide, an endocannabinoid that has been studied in experimental research for the treatment of the cannabinoid hyperemesis syndrome, are also observed; cannabinoids from other plants ("polyunsaturated alkamides"), cannabinoid agonists ("piperydines"); antagonists ("pyrazoles"); the relationship of cannabis to the neurotransmitter dopamine ("dopamine"); and descriptors related to the endocannabinoid system ("endocannabinoids," "arachidonic acids," "glycerids"). It can also be seen that, over the years, the study of receptors has become more specific, with terms such as "receptor, cannabinoid, CB1" and "receptor, cannabinoid, CB2" appearing. If we continue to observe the evolution over the years, we can also distinguish a relationship between cannabis and other substances and concepts related to addictive potentials, such as "cocaine," "hallucinogens," "psychotropic drugs," "illicit drugs," and "central nervous system stimulants." Focusing attention in recent years, there has been a progressive evolution to terms related to therapeutic or medicinal use, observed in terms linked to antipsychotic effects "Antipsychotic



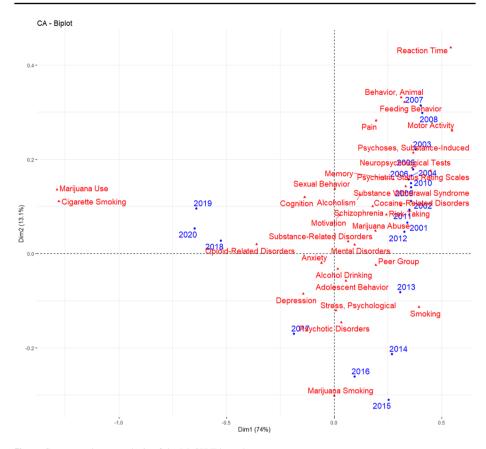


Fig. 4 Correspondence analysis of the MeSH F branch

Agents," analgesics "Analgesics," "Analgesics, Opioid," and appearing terms such as "cannabidiol," a component extracted from *Cannabis sativa* to control pain, reduce anxiety and improve sleep, and as "medical marijuana" (MeSH definition: product of the Cannabis plant, Cannabinoids, or synthetic derivatives thereof, used in the treatment of a wide range of clinical symptoms).

• Terms related to the branch "Psychiatry and Psychology"

At the beginning of the studied period, there is a special presence of reference to experimental studies in terms such as "reaction time," "feeding behavior," "motor activity," and "behavior animal," and with studies related to psychological and memory evaluation, which can be seen in descriptors such as "neuropsychological tests," "psychiatric status rating scales," and "memory." Subsequently, aspects related to the consequences of consumption ("substance withdrawal syndrome," "psychoses, substance-induced"), the relationship with the consumption of other substances ("cocaine-related disorders," "alcoholism," "opioid-related disorders"), the relationship with other psychological or psychiatric disorders ("anxiety," "depression," "stress," "schizophrenia," "psychotic disorders"), and behavioral aspects ("alcohol drinking," "peer group," "motivation," "sexual behavior," "cognition,"



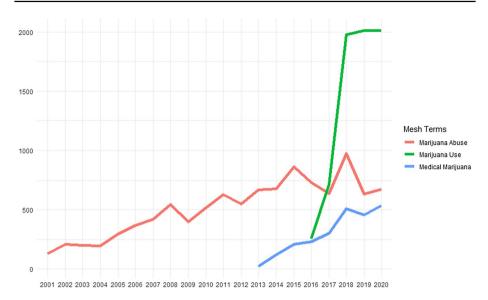


Fig. 5 Evolution of the use of the MeSH terms "marijuana abuse," "marijuana use," and "medical marijuana" over the two decades studied

"adolescent behavior"). The most remarkable aspect of this figure is the temporal evolution perceived in the use of descriptors that are directly related to negative aspects of cannabis use, to the use of more neutral ones. From older to more recent, this is seen in the terms "marijuana abuse" (MeSH definition: use of marijuana associated with abnormal psychological, social, and/or occupational functioning), "smoking" (MeSH definition: willful or deliberate act of inhaling and exhaling smoke from burning substances or agents held by hand), "marijuana smoking" (MeSH definition: inhaling and exhaling smoke from cannabis), "cigarette smoking" (MeSH definition: the smoking of cigarettes), and "marijuana use" (MeSH definition: medicinal or recreational utilization of marijuana).

Analysis of Terms That Include the Word "Marijuana"

A graph has been produced for each MeSH term containing the word marijuana ("marijuana use," "marijuana abuse," and "medical marijuana").

Of these three terms, one of them ("marijuana abuse") arises before the last two decades, whereas in the case of "medical marijuana" and "marijuana use," their indexing was much later (2013 and 2016, respectively), signifying a change in the National Library of Medicine's treatment of the content of marijuana papers.

In terms of the frequency of occurrence of each term over the two decades studied, the most frequently used term was "marijuana abuse" (n=10,314) followed by "marijuana use" (n=6966) and "medical marijuana" (n=2394). However, of the three, an annual increase in use from the first year studied (2001) to the last (2020) is only observed for "marijuana use" and "medical marijuana," being much more notable in the case of marijuana use, which goes from appearing 256 times in 2016 to 2010 times in 2020, which implies an increase of 685.2% (Fig. 5).



Discussion

This study has provided insight into changes in marijuana research in the decade from 2001 to 2020. It was made possible thanks to the individual indexing of each article provided by MeSH. This indexing ensures that all papers are relevant and eliminates the possibility of including papers that are not. To date, we are not aware of any other study of these characteristics in the field of marijuana research in the literature.

Thus, the chronological evolution through the terms related to the areas of "Chemicals and Drugs," "Psychiatry and Psychology," and "Anthropology, Education, Sociology, and Social Phenomena" allows us to draw a general conclusion. That is, research on marijuana-related topics has evolved toward aspects related to therapeutic use, legislative development, and the various uses of marijuana-derived compounds. In the three temporal evolutions analyzed, a trend toward the normalization of the use of marijuana and its derivatives can therefore be intuited (Coley et al., 2021; Laqueur et al., 2020; Room, 2014; Webster, 2018).

Without being exempt from both political and medical controversy, what is certain is that scientific publications indicate that marijuana has gone from being considered almost exclusively as a substance with addictive potential, to opening up other possibilities that change its conception in some way (Brusa et al., 2022). This has been observed in the three branches of MeSH when viewed separately. In the case of "Anthropology, Education, Sociology and Social Phenomena" (branch I), the evolution is observed in several groupings of terms, among which we would highlight the shift from concepts related to crime and delinquency in the early years to a more focused concern on health promotion and policies about health and quality of life, as well as its association with associated harms such as driving under the influence of substances and their concomitant consumption with alcohol. Another relevant aspect observed in this network is the concepts related to legislation, where it is observed that there is a shift from a direct allusion to the control of drug trafficking to a generic "legislation," which is evidence of the influence of legislative changes in the research (Badurally Adam et al., 2015; Dioun, 2021). In this sense, legislation is a reflection of a society that has changed its relationship with this substance in a relatively short period, especially about legislation on recreational use, whose first manifestations in some US states and Uruguay date back a little more than a decade (Lachance et al., 2022; Room, 2014). The topic of suicide, its related concepts, and its presence, especially in the last 5 years studied, deserve special mention. Suicide attempted suicide and suicidal ideation are currently topics of great concern in society, given the figures handled and the COVID-19 pandemic has brought to light (Brennan et al., 2020; Organización Mundial de la Salud, 2022). The relationship between suicide and marijuana use has been reflected in several studies that have addressed this issue from different perspectives, such as the study of suicidal ideation in this study on young Mexicans (Borges et al., 2017) or deaths by suicide among adolescents in the US states where recreational consumption has been legalized (Doucette et al., 2021).

About the topic of "Chemical and Drugs" (branch D), it is perhaps where a temporary evolution toward different possibilities of marijuana-derived compounds has been observed. In this sense, what has been seen is a clear trend toward concepts related to the therapeutic possibilities of marijuana and its derivatives. This indicates that there is a clear interest in research on these topics, which is also in line with what was observed in the branch I concerning concepts related to the legislation and the use of marijuana (Jugl et al., 2021; Pazos Rodríguez & Grandes Moreno, 2017). In addition, a significant level of concreteness in terms of understanding the neurophysiological aspects of marijuana is also



observed in its evolution, which could be related to the enormous development that the study of this substance has had in the last two decades (Matielo et al., 2018).

About the study of psychological and psychiatric aspects (branch F), the annual evolution from the first years studied to recent times also shows that the last years are more related to concepts that deal with the subject generically. Of note in this branch is the presence in the second decade of very specific disorders that are currently the focus of great concern, such as depression, stress, and anxiety, which could indicate where attention in psychology and psychiatry has been directed about the use or abuse of marijuana. In this regard, studies have been found in the literature that relates the use of marijuana as a way to alleviate symptoms of disorders such as depression, stress, and anxiety, such as that of Glodosky and Cuttler (2020) y el de Boumparis et al. (2019), which, according to these authors, can also become counterproductive and generate tolerance. Another study, a systematic review and meta-analysis on the association between marijuana use in adolescents and the risk of depression, anxiety, and suicide in young adults, has concluded that there does appear to be a relationship about depression and suicide, which is related to what has been discussed in previous paragraphs (Gobbi et al., 2019).

The study of frequencies that has been carried out with the three MeSH terms on marijuana confirms what has already been commented on concerning temporal evolution. Although it is true that the term marijuana abuse has a long history and has been widely used, the term marijuana use, much more generic and applicable not only to the negative aspects, has emerged strongly, as has the term medical marijuana. These two terms are, moreover, the only ones that have grown in use over the years.

Conclusions

What this work confirms in the study of scientific publications is that research on marijuana in the last two decades is an example of the complexity of the subject. The temporal evolution, which begins with research into the negative consequences and the understanding of the effects of the substance on the organism and ends up including other elements in the equation related to legislation and therapeutic possibilities, is proof of this complexity. As has been observed, the mixture of negative and positive elements is sometimes so diffuse that it is difficult to differentiate them with certainty. Both scientifically and socially, it is difficult to find another substance in similar circumstances, in that "middle ground" between "good and bad," "positive and negative." In this sense, "positive" refers to the possibilities of the substance at the pharmacological level that have become evident in the last few years studied, as well as to the legislative changes aimed at decriminalizing or even legalizing recreational use that have taken place in some countries, while the terms with more negative connotations would be those that appear most frequently in the first years of this study, such as crime, violence, and suicide. Therefore, in order not to run the risk of diluting the negative consequences without detriment to the therapeutic possibilities, it would be advisable for science to make this distinction clearly to offer society clear lines that can inspire policies and actions. Among these policy actions, the three levels of addiction approach (prevention, treatment, and reinsertion) should be taken into account to make clear this distinction between the risk that the consumption of marijuana involves, especially for the young population, and the therapeutic possibilities of some of the active principles of the plant.



Limitations

This study has limitations that should be commented on. Firstly, we are aware that the coverage of WoS and PubMed, whose records were related to Health Sciences areas, could result in an underrepresentation of Social Sciences works (i.e., Sociology or Anthropology), what otherwise suggest a new line of future study.

On the other hand, three branches of the MeSH (I, D, and F) have been chosen because of their relevance to the topic addressed, but there are other branches that could be interesting to address, such as the Anatomy MeSH-related terms.

As discussed in the "Methods" section, the term "smoking marijuana" was not considered for our analysis in this study. Although we had considered it relevant in the early stages of our work, we later realized that, following the MeSH definitions, this term refers to a form of consumption and not to the behavior *per se*. This led to a logical overlap with the other three terms studied, as the action of smoking marijuana could occur in cases of both medical and recreational use without consideration of its positive or negative consequences.

Moreover, in this first study, we do not distinguish between minor and major terms assigned to the selected articles. Also, it could be possible that there were articles that due to the high novelty of their studied topic, there is not yet a MeSH-specific term for them.

Proposals for the Future

With a view to the future, we propose to continue this line of research by addressing other approaches that could enrich the results. First, it would be very interesting to find out a methodological way that allows us to delve into the Social Sciences journals approach on the marijuana topic, which could complete the results shown in our work. Furthermore, it would be interesting to explore, within the MeSH branches, a methodology that considers the distinction between minor and major terms to find out if there are differences depending on this specification. Finally, another relevant line would be to investigate the differences that exist between countries or geographic regions in terms of cannabis research at the article level, using MeSH as a way to ensure the relevance of publications. This study at the country/region level would allow us to understand, among other issues, if the different legislations, for example, between American and European countries, affect the marijuana research focus.

Data, Materials, and/or Code Availability Not applicable

Author Contributions Juan Carlos Valderrama-Zurián, Elías Sanz-Casado, Andrea Sixto-Costoya, Carlos García-Zorita, Antonio Serrano-López: conception and design of the study. Acquisition of data, analysis and/or interpretation of data, writing—original draft: Carlos García-Zorita, Antonio Serrano-López, Andrea Sixto-Costoya. Juan Carlos Valderrama-Zurián, Elías Sanz-Casado: writing—review and editing.

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Declarations

Ethics Approval Not applicable

Consent to Participate Not applicable

Competing Interests The authors declare no competing interests.

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