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The Possibilities of Medical Cannabis Application in Dentistry in the Era of Cannabis Legislation in Morocco, One of the World's Largest Producers of Cannabis

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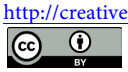

Abstract

Objective: The aim of this review is to discuss the potential applications of *Cannabis sativa* L. and its secondary metabolites in dentistry, and the legal aspect of medical cannabis in Morocco, one of the world's largest producers of cannabis. **Methods:** The data was searched through PubMed database, Scopus and Science Direct-Elsevier by several keywords in various combinations with a time period 2005-2022. Unavailable in full text, non-English, non-French data were excluded, as well as studies conducted on animals. **Results:** The articles were of various natures and were filtered after eliminating duplicates and reading the title, summary and full text. Of the 382 articles selected, 35 were deemed relevant. **Conclusions:** Although *Cannabis sativa* L. and its compounds have officially been approved for medical use in Morocco, more clinical investigations are needed to overcome the remaining challenges to the full adoption of medical cannabis in dentistry.

Subject Areas

Dentistry

Keywords

Cannabis, Cannabinoids, Cannabidiol, Dentistry, Periodontitis, Dental Caries, Oral Mucositis

1. Introduction

Recently, the progress of scientific research regarding the therapeutic utility and

medical properties of *Cannabis sativa* L. has been in conjunction with the review of former strict laws worldwide forbidding its use, as many countries have recently initiated the regulation and legislation of medical cannabis including Morocco, the world's largest producer of cannabis resin.

In fact, its use for medical and therapeutic purposes goes back to the origins of civilizations and has been described in almost all ancient cultures where it has been used in traditional medicine for the relief of dental pain, prevention of dental caries and reduction of gum inflammation [1].

Oral and dental conditions are a major global concern, with the most common being tooth decay (dental caries), toothache, periodontitis, gingivitis, Burning Mouth Syndrome (BMS), oral mucositis and oral cancers. With recent studies detecting cannabinoid receptors in the oral cavity, they may represent potentially a valuable target for the treatment of oral and dental diseases [2] [3].

The medical and pharmaceutical attributes of *Cannabis sativa* L. are reported to be its complex mixture of secondary metabolites, including cannabinoids and non-cannabinoid-type constituents. More than 500 compounds have been reported from *C. sativa*, of which 125 cannabinoids have been isolated and/or identified as cannabinoids notably Cannabidiol (CBD) and Tetrahydrocannabinol (THC). The non-cannabinoid constituents include: flavonoids, terpenes, and others [4].

In light of the ongoing worldwide race to exploit and regulate medical cannabis, Morocco, one of the world's leading suppliers of cannabis, has recently made significant strides toward the legislation of medical cannabis and the regulation of this industry, one of the main ones in the country. The objectives of this literature review are: 1) To outline the history of the use of *Cannabis sativa* L. in the treatment of oral and dental diseases; 2) To expand on the potential applications of cannabis in dentistry and its adverse effects; 3) To clarify the legal status and regulation of medical cannabis in Morocco.

2. Materials and Methods

To meet the objectives of our work, a literature review regarding the possibilities of medical cannabis application in dentistry in the era of cannabis legislation in Morocco was conducted. The data was searched through PubMed database, Scopus and Science Direct-Elsevier by several keywords in various combinations with a time period 2005-2022. Unavailable in full text, non-English, non-French data were excluded, as well as studies conducted on animals.

2.1. Materials: Databases and Keywords

We adopted an electronic search strategy based on a systemic query of 3 databases: PubMed, Scopus and Science Direct. Searches were conducted using relevant predefined keywords and MeSH terms such as "cannabis", "cannabinoids", "cannabidiol", "dentistry", "periodontal", "periodontitis", "gingivitis", "oral mucositis" and "dental caries".

2.2. Methods: Search Strategy

These keywords were used in multiple combinations and equations using Boolean operators "AND", "OR", to create the search string for studies' titles and abstracts.

2.3. Methods: Inclusion Criteria

The articles included in the search were articles: meeting the objectives of the study, published between 2005 and 2022 and involving clinical studies conducted on humans and *in vitro* studies. We excluded publications written in languages other than French or English, articles unavailable in full text, and studies conducted on animals.

3. Results

3.1. Study Selection Process and Flow Chart

Using the 3 search engines: PubMed, Science Direct and Scopus, our strategy identified 382 articles.

Of these 382 articles, 121 were eliminated as they were duplicates.

Among the remaining 261 articles, a first reading based on titles and abstracts was performed for pre-selection purposes.

This screening allowed the elimination of 187 articles that were not directly related to the subject.

Of the 74 articles retained, a third level of screening, consisting of a critical reading of the full-text articles, allowed us to retain 35 articles that met the research objectives.

In the end, 35 articles were included as relevant to our research (**Figure 1**).

3.2. Analysis of Selected Articles

The bibliographic search was conducted in English and French on 3 different search engines. A total of 35 studies were included in our review: 14 *in vitro* studies, 1 *in vivo* study, 1 ex vivo study, 1 systematic review, 13 literature reviews, 2 randomized clinical trials, 2 comparative studies and 1 prospective cohort study.

Out of the 35 articles that were selected as relevant to our research: 28 focused on the potential applications of medical cannabis in dentistry, 2 on the chemical composition of Cannabis sativa, 2 articles addressed the regulation and legislation of medical cannabis, 1 article covered the background of medical cannabis use in dentistry, 1 article treated the endocannabinoid system and 1 article concerned the side effects associated with *Cannabis sativa* L.

4. Discussion

4.1. History of *Cannabis sativa* L. in the Treatment of Oral and Dental Diseases

Studies retrace the medical use of *Cannabis sativa* L. in the treatment of oral and dental diseases back to 2700 BC in China where it was used for toothache

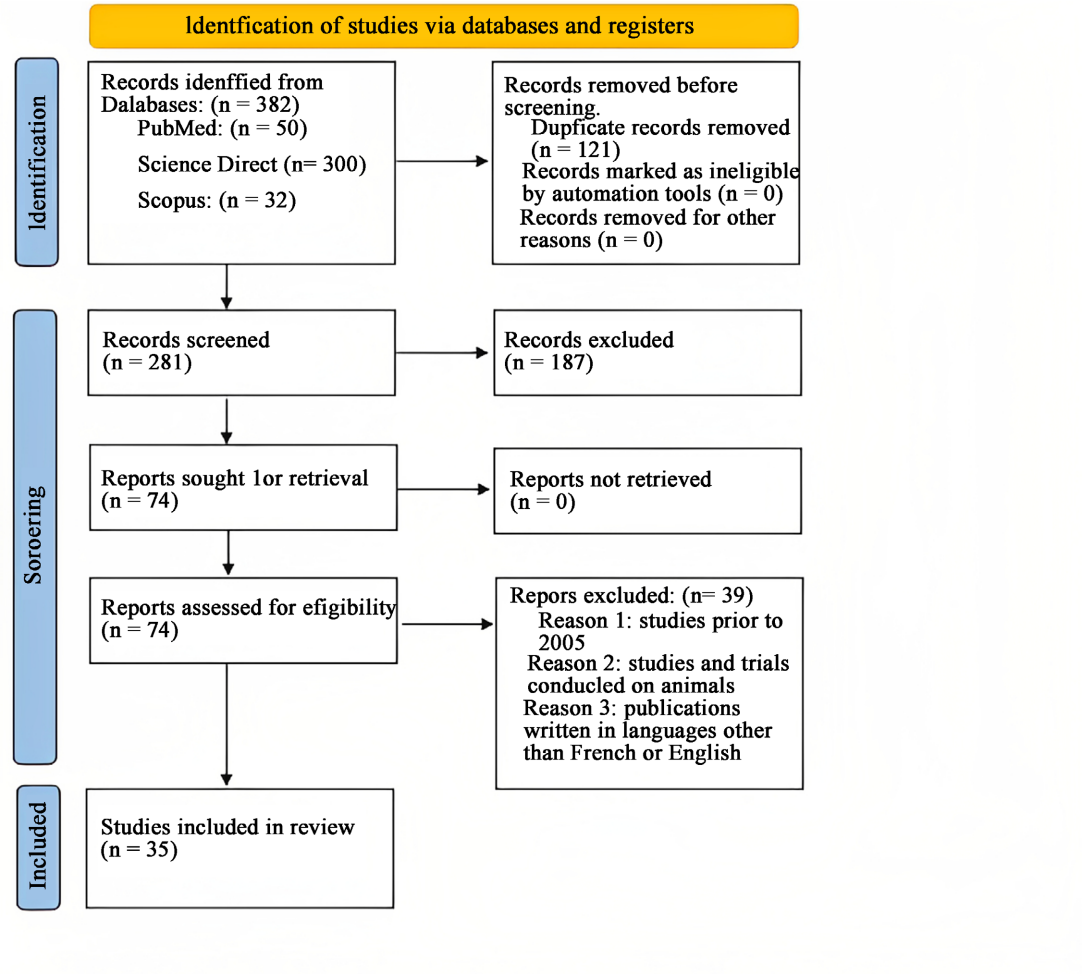

Figure 1. Flow chart as per PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

management, the treatment and prevention of dental caries and reduction of gum inflammation [1].

The topical application of cannabis to treat inflammation is also mentioned in the Ebers papyrus, written in Egypt around 1500 BC. Moreover, the Naturalis Historia of Pliny the Elder (c. 23-79), the oldest existing encyclopedia of the Greco-Roman world discusses the medical uses of cannabis and indicates analgesic and anti-inflammatory properties of the plant [5].

Cannabis finally reached Western medicine at the end of the 19th century and the beginning of the 20th century thanks to the first modern reports of the therapeutic properties of cannabis in the 19th century by the Irish physician William Brooke O'shaughnessy (1839). A major obstacle to the use of cannabis was the

fact that the active ingredient had not yet been isolated, and THC was not identified until 1964 [6].

A new era began with the discoveries of scientists Yehiel Gaoni and Raphael Mechoulam, who in 1964 in Israel identified for the first time the chemical structure of the cannabinoid, named Δ-9-Tetrahydrocannabinol (Δ-9-THC).

Studies continued until the 1990s with the discovery of cannabinoid receptors and the cannabinoids and the characterization of endocannabinoids and the endocannabinoid system, the actual biological target of phytocannabinoids, which rekindled scientific interest in interest in Cannabis, leading to the publication of thousands of articles that have clearly highlighted the therapeutic potential of this plant [6].

4.2. Potential Applications of Medical Cannabis in Dentistry

4.2.1. Understanding the Endocannabinoid System

In 1987, it was demonstrated for the first time that most of the effects attributed to cannabinoids are due to their binding to specific receptors. The main cannabinoid receptors identified to date, type I (CB1) and type II (CB2) cannabinoid (CB2), TRPV (Transient Receptor Potential Vanilloid), and GPR55 receptors [7].

According to Schwertschlag, the endocannabinoid system is a complex intercellular communication system, similar to a neurotransmitter system, but which extends not only in the brain, but also in other organs and tissues of the body. Its function is to balance metabolic processes and to optimize the functioning of our organism.

The endocannabinoid signaling system includes:

1) At least two G protein-coupled receptors, called cannabinoid receptors CB1 and CB2 cannabinoid receptors.

2) Endogenous agonists of these receptors, known as endocannabinoids, including anandamide and 2-arachidonoylglycerol are the best known.

3) The proteins and enzymes that regulate the levels of endocannabinoids and their action on the receptors [8].

In the oral cavity, several studies have identified CB1, CB2 and TRPV receptors in epithelial cells of the tongue and major salivary glands. CB1 and CB2 receptors have also been located in the dentin-pulp junction and nerve endings of dental pulp, in addition to periodontal ligament and oral mucosa cells [9].

4.2.2. Potential Applications of Cannabis and Its Secondary Metabolites in Dentistry

The field of potential applications of medical marijuana in dentistry is immense, ranging from dental anxiety where CBD administered sublingually significantly reduces psychic and somatic dental anxiety, to orofacial pain where Nabilone has a significant analgesic effect in patients with Neuropathic or Facial Pain (NOP), including trigeminal neuralgia, fibromyalgia and burning mouth syndrome [10] [11].

In Temporo-Mandibular Disorders (TMDs), a randomized, double-blind trial

by Nitecka-Buchta *et al.* suggests that CBD applied via a dermal patch on patients with Temporo-Mandibular Joint (TMJ) disorders shows significant muscle relaxant and antinociceptive effects [12].

Regarding periodontal disease, numerous studies have located cannabinoid receptors CB1R and CB2R in the gingival connective tissue which suggests that these receptors could be valuable targets for the development of novel therapeutic strategies. In addition, phytocannabinoids and synthetic cannabinoids promote periodontal healing and are effective anti-inflammatory and antioxidant agents in the regulation of periodontal inflammation. Moreover, the activation of CB2R by an agonist such as synthetic cannabinoid HU-308 is able to enhance osteogenic differentiation of Periodontal Ligament (hPDL) cells and create a favorable osteogenic microenvironment. This implies that CB2R could play an important role in the remodeling and regeneration of alveolar bone [13] [14] [15].

Regarding oral hygiene and dental plaque, an *in vitro* study conducted by Vasudevan and Stahl in 2020, aimed at comparing the efficacy of cannabinoids to commercially available oral hygiene products in reducing the bacterial content of dental plaque. It was reported that cannabinoids are significantly more potent in reducing the number of colonies of the bacterial strains of dental plaque than well-established synthetic oral hygiene products (**Figure 2**) [16].

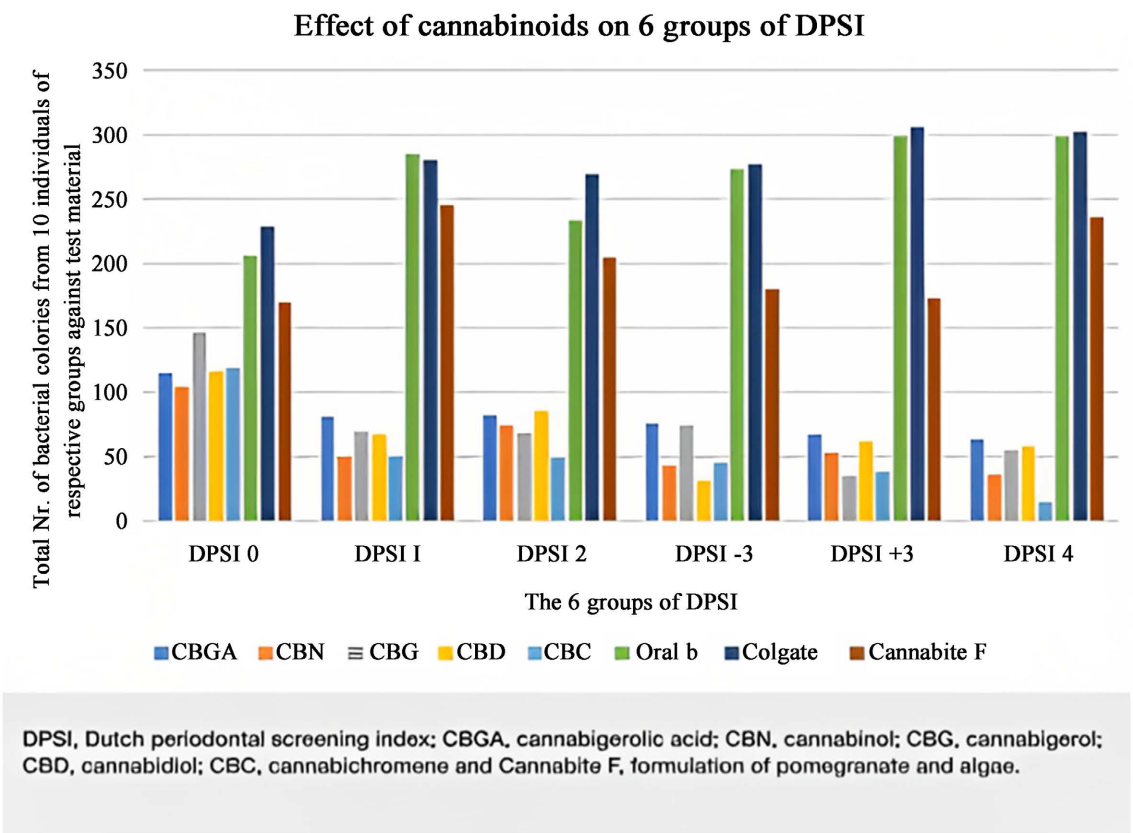

Figure 2. Comparison of the 6 DPSI (Dutch Periodontal Screening Index) research groups according to the total number of bacterial colonies [16].

The number of bacterial colonies reported was significantly higher in the Colgate, Oral B and Cannabite F (pomegranate and algae) treatments, while the number of colonies was significantly lower in all cannabinoid treatments.

Likewise, on average, CBC and CBN are effective against plaque bacteria in more than one research group [16].

In the matter of toothache, a common health problem, particularly among people with poor oral hygiene, the anagesic properties of major cannabinoids such as THC, CBD and other secondary metabolites including terpenes and flavonoids make these active cannabis constituents potential valuable assets in the treatment and management of toothache [1].

A 2010 study by Beneng *et al.* suggests that cannabinoid CB1 receptor is expressed by nerve fibers in healthy and painful human dental pulp, and hypothesizes that the CB1 agonists currently in development could provide further progress in the treatment of dental dental pain [17].

Similarly, a 2017 study by Que *et al.* demonstrates that CB1 and TRPV receptors involved in pain and analgesia are expressed by human odontoblasts [2].

On the topic of dental caries, a widespread condition that affects approximately 2.3 billion people worldwide, including 530 million children. It is the result of several factors, including biofilm forming bacteria such as Streptococcus mutans (*S. mutans*), the most common pathogen associated with dental caries. Cannabigerol (CBG) shows promising antibacterial effects against these cariogenic bacteria. According to Aqawi *et al.*, CBG acts at multiple levels: it exerts a bacteriostatic effect that is affected by the initial density of the bacterial cells; it causes immediate hyperpolarization of the membrane and reduces membrane fluidity while increasing its permability; it prevents the pH drop caused by *S. mutans*, thus preventing its cariogenic property: CBG is able to maintain neutral pH at 7 for at least 8 hours at all concentrations tested, the maintenance of neutral pH is strongly related to the reduction of bacterial proliferation (**Figure 3**).

The interference of CBG with the caries causative *S. mutans* may provide a novel innovative way to combat dental caries [18].

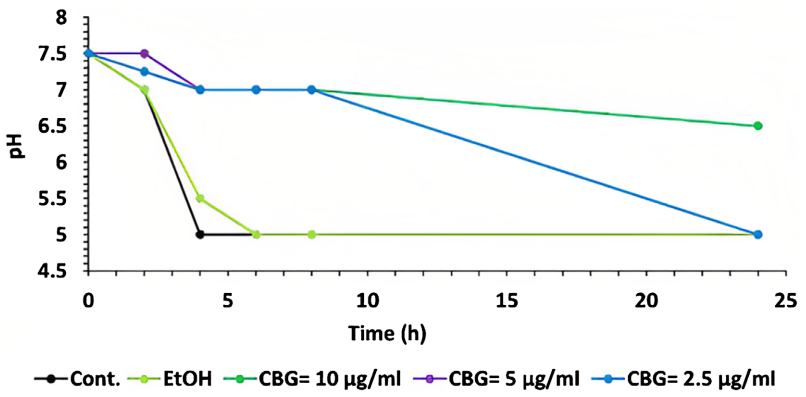

Figure 3. CBG prevents the decrease in pH caused by *S. mutans*. A kinetic change in the pH values of the medium of untreated and CBG (0 - 10 µg/ml)-treated *S. mutans* [18].

CBG is able to maintain the pH at 7 for at least 8 h at all concentrations tested. After 24 h, the pH of CBG samples at 2.5 and 5 µg/ml had reached 5, similar to the control samples, while 10 µg/ml CBG was still able to prevent acidification favorable to bacterial growth (pH = 6.5) [18].

On the subject of Oral Mucositis (OM), the most common complication of cancer-related Chemotherapy (CT) and Radiation Therapy (RT), the lack of effective strategies for the management of OM has prompted researchers to explore new therapeutic agents. The antioxidant, anti-inflammatory, and analgesic activity of cannabinoids, particularly CBD, as well as its tolerability, are decisive factors in generating interest for its use in this field. A recent *in vitro* study conducted by Li *et al.* in 2022 concludes that CBD attenuates chemotherapy-induced oral mucositis by improving defense against oxidative stress, decreasing mucosal inflammation, promoting cell proliferation and inhibiting apoptosis on healthy human cells of the oral mucosa [19].

In a similar way, the terpene β-Caryophyllene (BCP), known for its potent anti-inflammatory, anti-oxidant and anti-cancer properties, is the main subject of the *in vitro* study conducted by Picciolo *et al.*, who point out that BCP which targets the receptors located in the immune system, reduces relevant inflammatory cytokines such as TNF-α and IL-1β and increases the expression of the anti-inflammatory IL13, and thus exerts a pronounced curative effect in a preclinical model of oral mucositis that deserves to be confirmed in a clinical setting [20].

As for oral cancer, the sixth most common form of cancer, squamous cell carcinoma account for 90% of cancers of the oral cavity and pharynx. The results of the 2016 study by Theocharis *et al.* reveal for the first time the presence of cannabinoid receptors CB1 and CB2 in human squamous cell carcinoma cells (**Figure 4**) [21].

In addition, an *in vitro* study performed by Whyte *et al.* in 2010 on human oral cancer malignant cells highly resistant to anti-cancer drugs, demonstrates that exposure to Δ-9-Tetrahydrocannabinol (THC) significantly inhibits mitochondrial oxygen consumption and thus their cellular respiration and presents a strong toxicity to these highly malignant cells [22].

In a similar fashion, the terpene Linalol shows promising anti-tumor capabilities. The study conducted by Weijuan and Guohua concludes that oral cancer cells treated with 10 µM of Linalool exhibit reduced viability due to apoptosis and cell cycle arrest, as well as loss of mitochondrial membrane potential [23].

With most of the studies conducted to date having been performed on *in vitro* cell lines or on animals, more clinical studies are needed to determine the potential benefits of medical cannabis in the treatment of cancer.

4.3. Side Effects Related to Medical Cannabis

The therapeutic effects of cannabis are not specific but could affect the whole body. This means that the desired effect in one case can be considered as undesirable in another case. According to Sachs, the already complex interactions of

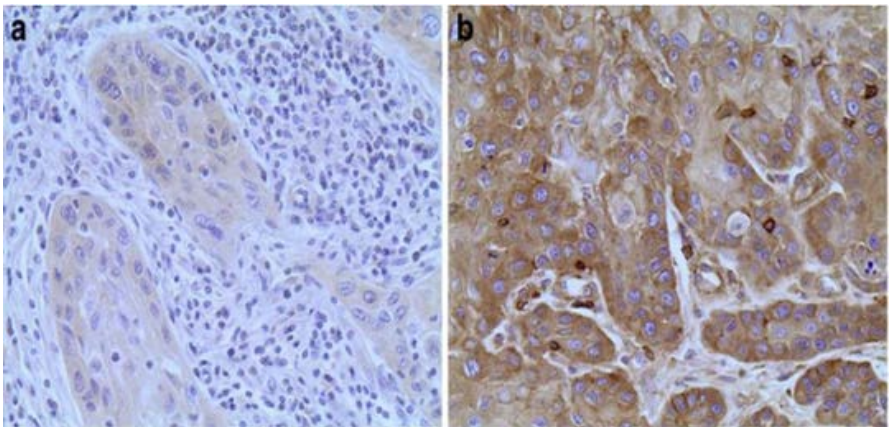

Figure 4. Expression of: a: Cannabinoid receptors CB1; b: Cannabinoid receptors CB2 in squamous cells of squamous cell carcinoma of the mobile tongue [21].

exogenous and endogenous cannabinoids within the endocannabinoid system are further obscured by the different methods of administration, inconsistent dosing measurements, and the highly variable cannabinoid content of cannabis plants. Cannabinoid content and resulting potency show extreme variance depending on various factors related to the diversification of the cannabis plant [24].

"Cannabis is not an entirely benign substance. It is a potent drug with a broad spectrum of effects. However, with the exception of negative effects associated with the products of combustion, the undesirable side effects of cannabis are comparable to the tolerated effects of other drugs.", statement in 1999 by the U.S. Institute of Medicine on the potential side effects of cannabis. This opinion is now widely shared and explains that cannabis is indeed neither very dangerous nor completely harmless [7].

4.4. Current State of Cannabis Policies around the World

The process of lifting prohibitions against cannabis use is known as legalization, while sparing criminal sanctions (such as fines, prison, or mandated treatment) against people possessing or using it is known as decriminalization. Cannabis is a controversial plant. The narcotic aspect of the plant calls for its continued criminalization, but at the same time its beneficial aspects are hard to ignore. The history of criminalization of cannabis goes back to the first decades of the 20th century. Fear of the psychoactive effects of the plant and intentions to ban its international trade prompted the international community to begin discussing the possible regulation of cannabis. As these efforts grew, cannabis was included in the 1925 League of Nations Opium Convention in Geneva. Although this event did not impose absolute restrictions on trade and use, it did establish a benchmark for the regulation of cannabis in various countries [6].

Cannabis use for medical purposes is permitted in many countries, particularly in Europe and North America (**Figure 5**). Recreational Cannabis is permitted in Canada, The Netherlands, Malta and Uruguay while it is decriminalized in

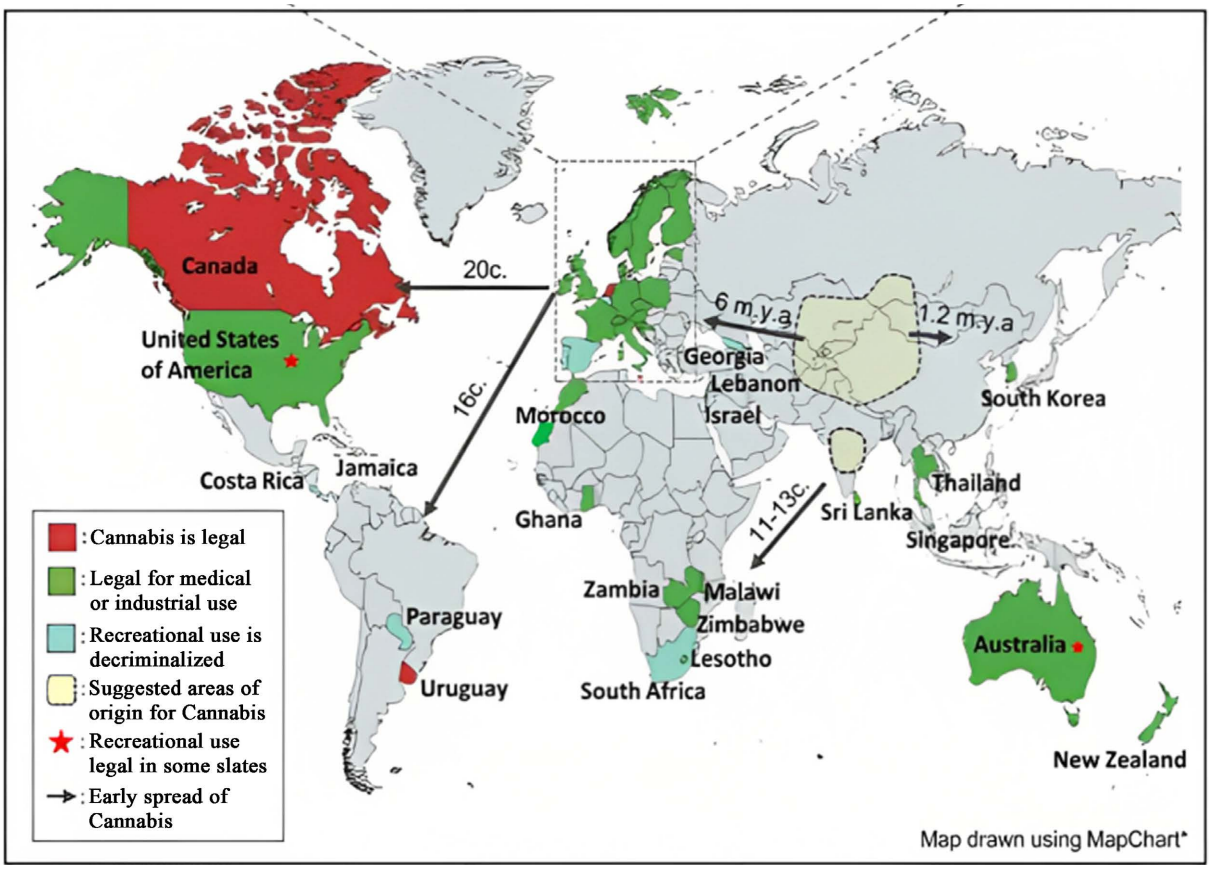

Figure 5. Legal status and early spread of Cannabis. From its proposed centers of origin (Central and Southern Asia), Cannabis spread to the other continents of the world. Today, Cannabis use for medical purposes is permitted in many countries, particularly in Morocco and North America [25].

Portugal, Spain, Luxembourg, Belgium, Georgia, Costa Rica, Paraguay, Jamaica and South Africa [25].

For instance, in Italy, cannabis is decriminalized and permitted for scientific research and medical use for conditions such as chronic pain, multiple sclerosis, spinal cord injury, nausea and vomiting caused by chemotherapy, radiotherapy. Possession for personal use is also permitted (with a maximum threshold of the narcotic principle (THC) set between 0.2% - 0.5%) [26].

Contrastingly, in France, cannabis is not decriminalized and all acts are prohibited: possession, production, trafficking, and distribution. Only usage for certain medical indications is allowed since 2020 [26].

4.5. Cannabis Legislation in Morocco

The opportunities of development of medical, cosmetic and industrial cannabis in Morocco are promising, given the considerable natural and economic assets of the Kingdom.

Morocco is ranked among the top five producers of cannabis in the world and the presence of the substance in the country dates back to the third century. Additionally, Morocco is the world's largest producer of cannabis resin (Hashish),

according to annual report 2020 published by the UN [27].

Moroccan policy on cannabis dates back to the years of the French occupation between 1912 and 1956. The Dahir of 3 November 1919 regulating the cultivation of hemp implemented measures allowing people interested in growing hemp to do so under certain conditions including obtaining a prior authorization for cultivation.

Later on, the Dahir of April 24, 1954, regarding the prohibition of cannabis, revoked all laws and regulations governing the cultivation of hemp by imposing and explicitly forbidding any person to proceed to any activity related to cannabis, namely the cultivation, possession, trade, consumption...

This legislation remained unchanged for about 20 years after independence. It was not until when Morocco approved the single convention on narcotics of New York in 1961 that cannabis was classified as a narcotic according to the provisions of the Dahir of May 21, 1974.

In addition, the Dahir of April 3, 2002 confirmed the prohibition of cannabis cultivation except for small quantities needed for scientific research purposes [27].

At last, Dahir No. 1-21-59 of 3 hija 1442 (July 14, 2021) promulgating Law No. 13 - 21, regulating the legal use of cannabis for medical, cosmetic or industrial purposes is adopted by the House of Representatives and the House of Councilors. Entry into force at the end of July 2021, this law provides the depenalization of medical cosmetic and industrial uses of cannabis, and gives an idea of the contours of this future legal market with the creation of a national agency to regulate cannabis-related activities. Recreational cannabis use remains prohibited and liable to prosecution [28].

4.6. Local Perceptions of Cannabis Law in Morocco

Medical cannabis remains a controversial subject among the Moroccan public opinion, given the psychotropic properties of cannabis plant, as well as the religious aspect linked to Islam, official religion of the country, which prohibits the use of any substance with psychotropic properties.

The results of an online survey conducted by Tingman in 2019 regarding Moroccan opinion on medical cannabis and its potential legislation conclude that the majority of Moroccans believe that cannabis should be legal for medical purposes. Indeed, the response of the citizens who participated in the survey was unanimous. The majority thinks that *Cannabis sativa* L. should be allowed for medical use.

These participants believe that recent studies confirm the medical and pharmaceutical properties of cannabis, and that it could provide new therapeutic solutions that conventional medicine cannot provide, however, further studies need to be conducted in order to clarify the potential side effects of this substance [29].

5. Conclusions

With Morocco being one of the world's largest producers of cannabis, and in

light of the recent legislation of medical cannabis in the kingdom, special considerations can be summarized as follows:

- Many innovative opportunities are emerging for dentists for the management and treatment of oral and dental diseases through the pharmacological and medical properties of cannabis secondary metabolites.
- The confirmed beneficial properties of cannabinoids, flavonoids and terpenes make cannabis a potential major asset in the therapeutic arsenal of health professionals.
- Cannabinoid-based medications have already been approved and are being used worldwide in the treatment and management of several oral and systemic conditions.
- The clinical hindsight regarding the application of medical cannabis in dentistry is lacking, the studies carried out in this field are very recent and their number is largely insufficient.
- Another obstacle to the adoption of medical cannabis in dentistry is the plant's reputation plant as a narcotic, the strict legal framework as well as the divided opinion of the population.
- Therefore, further clinical studies are needed in the future to overcome the challenges relevant to the full-scale introduction of medical cannabis in dentistry.

Conflicts of Interest

The authors declare no conflicts of interest.

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