

Cannabidiol (CBD) for relief from pain, anxiety, and epilepsy: A review

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ABSTRACT

Cannabis or marijuana (*Cannabis sativa*) contains more than one hundred chemical compounds. Of these, tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most common chemicals. THC is the chemical that gives a “high” and has various psychoactive characteristics. Cannabidiol, on the other hand, has no intoxicating qualities yet provides all the medical benefits, such as relief from anxiety, depression, insomnia, cancer, neuropathic pain, epilepsy, acute respiratory distress syndrome, Parkinson’s disease, Alzheimer’s disease, etc. In the present article, CBD oil extraction techniques, the mechanism of action of cannabinoids, and the role of CBD in relief from pain, anxiety, depression, and epilepsy have been reviewed.

Keywords: Anxiety, Cannabidiol (CBD), Depression, Epilepsy, Tetrahydrocannabinol (THC), Pain.

1. INTRODUCTION

CBD is one of the more than 100 cannabinoids (chemical compounds) found in the cannabis or marijuana (*Cannabis sativa*) plant. THC is the most common and psychoactive of these hundreds of chemicals. CBD, on the other hand, is not psychotropic like THC. In 1964, Prof. R. Mechoulam in Israel isolated and described the chemical structure of CBD (Gaoni and Mechoulam, 1964). After that, he identified the structure of THC. He was the first to discover that THC is a psychoactive compound (Mechoulam, 1986). Due to its non-psychoactive property, CBD is becoming increasingly popular among people who want relief from pain and other symptoms without the mind-altering effects of marijuana or other pharmaceutical medicines. CBD oil is manufactured by extracting cannabidiol from the cannabis plant and diluting it with a carrier oil such as coconut or hemp seed oil.


Some scientific research indicates that CBD oil can help in various medical applications, including anxiety and depression treatment, stress reduction, diabetes prevention, pain relief, cancer symptom relief, and inflammation relief (Grand View Research, 2021). Hence, it is gaining popularity in the health and wellness industry. Many teams of experts worldwide are investigating the medical benefits of cannabinoids. In the mid-1970s, the British Pharmacopoeia approved a cannabis tincture for therapeutic use that was “full-spectrum” CBD oil. In the USA, New Mexico was the first state to recognize cannabis as a medicine in 1978. During the same period, Mechoulam (from Israel) and a group of researchers studied CBD use in patients with severe epilepsy. Considerable improvements in patients’ conditions with few or no adverse effects have been reported (Cunha et al., 1980). This trial is regarded as a watershed moment in clinical marijuana research.

Growing consumer desire for plant-based supplements, awareness of CBD’s medical benefits, particularly its restorative effects, and legalization of hemp-derived CBD

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products in various countries are all driving the expansion of the CBD consumer market. The recent research trends and commercial prospects of cannabis-based products have been recently reviewed (Chaturvedi and Agrawal, 2021). In the present article, we have reviewed research-based evidence on the beneficial effects of CBD on pain, anxiety, and epilepsy. We further mentioned CBD oil extraction and the mechanisms of action of cannabinoids and highlighted the prospect of CBD in managing pain, anxiety, epilepsy, and depression. Thus, we propose to pay attention to the importance of CBD as a prospective drug alternative.

2. MATERIALS AND METHODS

We performed an extensive literature search by screening PubMed, Scopus, and Web of Science to compile the data about the mechanism of action of cannabinoids with a special focus on CBD-associated pain, anxiety, and epilepsy relief. We further mentioned CBD oil extraction techniques. Thus, we aimed to emphasize the eminence role of CBD as a prospective agent in managing pain, anxiety, and epilepsy (Fig. 1).

3. CBD OIL EXTRACTION

Cannabis sativa leaves, stems, and flowers contain high quantities of CBD. After harvest, the leaves and plant materials are subjected to various methods to extract the cannabidiol component. The most common techniques to extract CBD oil use (i) carbon dioxide, (ii) steam distillation, or (iii) natural solvents. Brief procedures of these techniques

and their advantages and disadvantages in CBD oil extraction are given in Table 1 (Anonymous, 2022).

After extraction, the obtained CBD oil is classified as “full-spectrum.” The “full-spectrum” CBD oil may contain cannabinoids such as cannabidiolic acid (CBDA), cannabidivarin (CBDV), THC, terpenes, and amino acids (Ohtsuki et al., 2022). These constituents in CBD oil are helpful in the “entourage effect”; however, there are products only with CBD isolates and no THC in them. The extract is cooled and refined into crystalline isolate to make CBD. Compared to full-spectrum CBD, isolated CBD has no smell or odor and is less expensive per milligram. Finally, CBD oil (full-spectrum or an isolate) is added to other substances to create CBD products such as CBD gummies, CBD capsules, CBD vape oils, CBD creams, etc. (Ohtsuki et al., 2022; Healthline, 2022).

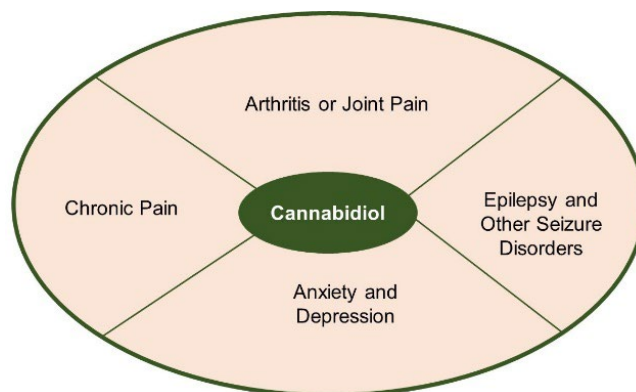


Fig. 1. The possible role of CBD as an alternative drug candidate in the management of pain, anxiety, and epilepsy

Table 1. CBD oil extraction procedures: advantages vs. disadvantages

CBD oil extraction techniques	Brief procedure	Advantages	Disadvantages
Carbon dioxide (CO ₂)	CO ₂ is used in liquid (-69°F) and gaseous forms. Liquid CO ₂ acts as a solvent to separate oil from the plant material.	<ol style="list-style-type: none"> 1. CO₂ is inexpensive, not combustible, and germicidal. 2. Highly safe for the producer and consumer. 3. Environmentally friendly. 4. Physiologically harmless 5. CO₂ is recycled 6. Products are solvent-free 7. Yields high-quality CBD products. 	<ol style="list-style-type: none"> 1. High setup cost 2. Needs monitoring by experts.
Steam distillation	The technique uses water steam-like solvent distillation to separate oil in plant matter.	<ol style="list-style-type: none"> 1. Simplicity 2. Low-cost 	<ol style="list-style-type: none"> 1. Low efficiency 2. Steam overheating may spoil plant material and oil. 3. It may result in a degraded product with fewer therapeutic benefits.
Solvent distillation	Solvents such as ethanol, butane, propane, naphtha, etc., are used to extract CBD from the plant material.	<ol style="list-style-type: none"> 1. Most commonly used method 2. Low-cost 3. Very effective 	<ol style="list-style-type: none"> 1. Solvents used are highly flammable 2. If not appropriately eliminated, solvents may leave toxic residue in the final product 3. May result in an unpleasant smell and taste in the final products

4. MECHANISM OF ACTION OF CANNABINOIDS

Cannabinoids are identified as endogenous cannabinoids, phytocannabinoids, and synthetic cannabinoids. Endogenous cannabinoids exist in animals and humans, phytocannabinoids are produced in the cannabis plant, and synthetic cannabinoids are generated in a laboratory (Sarfaraz et al., 2008). Phytocannabinoids possess a lipid structure presenting alkylresorcinol and monoterpene moieties in their molecules. They are categorized into two groups, neutral cannabinoids (without carboxyl group) and cannabinoid acids (with carboxyl group) (Hanus et al., 2016), and occur in numerous plant species, such as *Cannabis sativa*, *Acmella oleracea*, *Helichrysum umbraculigerum*, *Echinacea angustifolia*, *Echinacea pallida*, *Echinacea purpurea* and *Radula marginata* (Messina et al., 2015). Phytocannabinoids are mainly subdivided into ten classes, among which THC and CBD are well-known and comprehensively studied (Bonini et al., 2018; O'Brien and Blair, 2021). THC and CBD have slightly different chemical structures (Fig. 2a, b). They are both functional isomers with identical molecular formulas (C₂₁H₃₀O₂). An alcoholic group is present in CBD near the double bond (> C = CH₂) in an open moiety. THC also contains an etheric group, forming an extra six-membered heterocyclic ring.

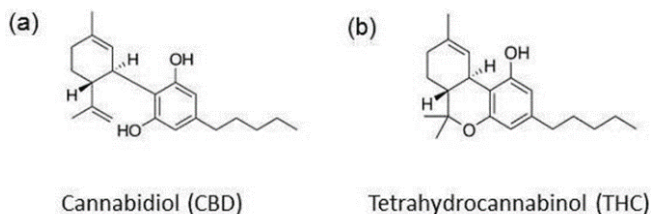


Fig. 2. Chemical structures of CBD and THC

Cannabinoids, alone or in combination, play a role in the peripheral and central nervous systems by affecting various targets, thus blocking chronic pain (Wong and Cairns, 2019). Cannabinoids usually act on cannabinoid receptors (CB1 and CB2) (Fig. 3). In addition, they may regulate pain by interacting with the putative non-CB1/non-CB2 cannabinoid G protein-coupled receptor 55 (GPR55) and GPR18 (NAGly) receptors (Guerrero-Alba et al., 2019), as well as other well-known G protein-coupled receptors (GPCRs), such as serotonin (5-HT) and opioid receptors (Zhao and Abood, 2013). Furthermore, cannabinoids can bind to numerous transient receptor potential (TRP) channels and modulate their therapeutic potential, such as the TRP vanilloid (TRPV), TRP ankyrin (TRPA), and TRP melastatin (TRPM) subfamilies, the dysfunction of which may imply neuropathic pain, respiratory disorders, and inflammation (Muller et al., 2018). The anti-inflammatory effect of cannabinoids may be associated with their

analgesic action (Klein, 2005).

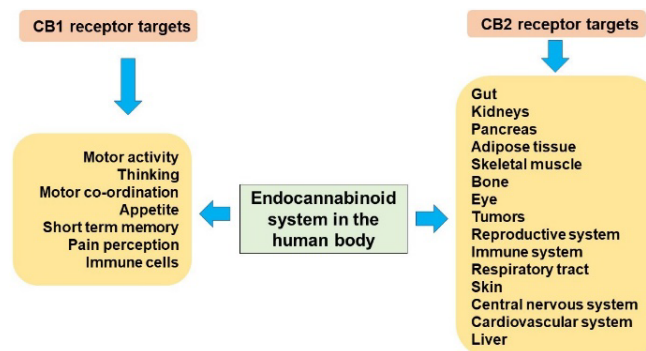


Fig. 3. CB1 and CB2 receptors and their major roles in human activities/functions in the human body

5. CBD IN CHRONIC PAIN

Considering the ongoing challenges in managing chronic pain due to opioid usage, people are still looking for efficient, safer alternatives to control pain. Despite ethnobotanical aspects and scientific evidence about Cannabis-based therapies to control pain, insufficient data exist regarding their potential health and safety profile benefits. In this regard, relatively safer and non-psychoactive ingredients of the cannabis plant (e.g., CBD) may draw attention. However, many surveys have focused on the psychoactive constituent of the cannabis plant Δ⁹-THC.

Current findings have suggested CBD in the management of chronic pain. No approved pharmaceutical medicine is available containing CBD alone (Cuñetti et al., 2018; Argueta et al., 2020; Verrico et al., 2020; FDA, 2022). However, a combined product of THC/CBD in a ratio of 1:1, nabiximols, may make us think about its likelihood of action in pain control. In addition, many CBD products exist as supplements, although they are non pharmaceuticals and lack clinical experimental data. The outcomes of in vivo experimental models pointed out the analgesic activity of CBD by affecting numerous targets in association with inflammatory, endocannabinoid, and nociceptive systems (Kumar et al., 2001).

Wade et al. (2003) applied double-blind, randomized, placebo-controlled single-patient crossover trials. The pain relief effect of THC and CBD with improved side effects compared to placebo was found, demonstrating their capacity to ameliorate neurogenic symptoms (Wade et al., 2003). Cuñetti et al. (2018) assessed CBD's safety, effect, and probable drug interactions for chronic pain in patients with a kidney transplant. CBD was well tolerated, with no acute side effects. Several researchers have evaluated the effect of CBD on chronic pain. The emerging concept is that CBD does not remarkably alleviate the degree of chronic pain but improves the side effect profile and quality of life (Argueta et al., 2020). Identification of CBD-associated pain relief and possible underlying mechanisms in

numerous diseases with chronic pain (e.g., cancer, diabetic neuropathy, rheumatic diseases) in long-term use are urgently needed.

Due to the lack of approved pharmaceutical products that currently comprise only CBD for pain control, investigations specifically centered on nabiximols (Sativex®). Sativex®, a standardized pharmaceutical product developed from Tetranabinex® (composed mainly of THC extract) and Nabidiolex® (composes CBD extract substantially) in a ratio of 1:1, has been prescribed in the handling of neuropathic pain in multiple sclerosis since 2005 in Canada and of cancer pain in 2007 resistant to opioid intervention (Russo, 2008). Unfortunately, the assertion of CBD administration alone for pain management is not a rational assumption due to its joint application with THC. Further studies of higher quality are warranted to assess CBD's pharmacodynamic and pharmacokinetic profile associated with pain manipulation.

6. CBD IN ARTHRITIS OR JOINT PAIN

CBD represents a potential therapeutic agent for handling arthritis and joint pain-associated symptoms. Preclinical and clinical data in the literature pay attention to the possible use of CBD as an alternative therapy approach against arthritis and arthritis-relevant pain. Various examples are indicated below.

Assessing the therapeutic potential of CBD in joint-related diseases, the anti-arthritic action of CBD was demonstrated. When Malfait et al. (2000) administered CBD to bovine or murine with type II collagen (CII)-induced arthritis (CIA) intraperitoneally or orally, it significantly hindered arthritis development *in vivo*. *Ex vivo*, extracted lymph node cells from CBD-administered mice revealed a decline in CII-specific proliferation and IFN- γ generation and a lessened release of tumor necrosis factor by knee synovial cells. Furthermore, the *in vitro* effects of CBD suppressed mitogen-stimulated and antigen-specific lymphocyte proliferation dose-dependently and diminished the zymosan-triggered reactive oxygen burst *in vitro*, suggesting potent anti-arthritic effects of CBD in CIA (Malfait et al., 2000).

In another study, CBD obstructed sodium monoiodoacetate-induced joint pain occurrence, preventing osteoarthritis pain. It was also neuroprotective, avoiding the later development of pain and nerve injury in a rat model of osteoarthritis (OA). All proposed CBD as a safe, beneficial cure in the convention of OA joint neuropathic pain (Philpott et al., 2017).

Analyzing the efficacy of transdermal CBD in a rat complete Freund's adjuvant-induced monoarthritis knee joint model, CBD gels remarkably alleviated joint swelling, spontaneous pain, hardening of the synovial membrane, and immune cell infiltration. Immunohistochemical investigation of spinal cord dorsal root ganglia uncovered lessened proinflammatory biomarkers without any side

effects on brain function, indicating pharmacological aspects against arthritis and arthritis-pain-associated clinical symptoms (Hammell et al., 2016).

The possible benefits and mechanism of action of CBD on rheumatoid arthritis were further demonstrated by Lowin et al. (2020). CBD enhanced intracellular calcium levels while alleviating cell viability, proliferation, and the generation of IL-6/IL-8 in rheumatoid arthritis synovial fibroblasts through transient receptor potential ankyrin activation and stimulation of mitochondrial targets. This demonstrates the anti-arthritic activity of CBD via synovial fibroblasts (Lowin et al., 2020).

Recent clinical studies have demonstrated the beneficial impacts of CBD in arthritis and arthritis-relevant pain, while extensive research has demonstrated no statistically significant effect (Gusho and Court, 2020). In a randomized, double-blind, placebo-controlled trial, liposomal-encapsulated or high-dose naked CBD significantly ameliorated the quality of life of patients with a spontaneous canine model of osteoarthritis (Verrico et al., 2020), whereas no acute effects in patients with hand osteoarthritis and psoriatic arthritis compared to placebo were detected in a survey conducted by Vela et al. (2021). Likewise, in evaluating the efficacy of Sativex® in a randomized, double-blind, parallel-group study, potent analgesic and beneficial effects of CBD were observed, while mild or moderate adverse effects were demonstrated in many patients with rheumatoid arthritis (Blake et al., 2006). CBD use in arthritis and joint pain management remains speculative despite preclinical and clinical outcomes. Prospective controlled studies assessing CBD's efficacy and toxicity profile are required to prove the administration of CBD as a therapeutic agent.

7. CBD IN ANXIETY AND DEPRESSION

Mental health is a substantial public health problem globally, and approximately one in five people suffer various mental health issues throughout their lives (WHO, 2022). CBD has drawn significant interest due to the absence of current therapy regimens in managing neuropsychiatric disorders without the capacity to become an abused drug. Ongoing evidence suggests that CBD may become worthy of providing potential for various anxiety disorders and thus requires further investigation in relevant communities. The examples below summarize the anxiolytic and antidepressant influences of CBD.

Studies in various animal models have revealed that CBD is effective and has an anxiolytic-like impact at intermediate doses but not at low or high doses (García-Gutiérrez et al., 2020). CBD-associated anti-anxiety and antidepressant effects were proven by several tests, such as the elevated plus-maze (EPM), forced swimming test (FST), and Vogel conflict test (VCT) (de Mello Schier et al., 2014). The interaction of CBD with the 5-HT_{1A} neuroreceptor was shown to be an underlying mechanism involved in the

anxiolytic activity (de Mello Schier et al., 2014). Further experimental outcomes in animal models pointed out the decline in anxiety- and compulsive-like behaviors by CBD (Moreira et al., 2006; Nardo et al., 2014). Moreover, CBD modulated THC's influences in the case of their coadministration at a 1:1 (CBD: THC) dose ratio. It reinforced THC-induced locomotor repression in contrast to its reductive impact arising from THC-induced hypothermia and anxiety through the downregulation of c-Fos expression in many regions of the brain (Todd and Arnold, 2016). On the other hand, the long-term coadministration of CBD and THC was more composite, holding potential as a supra-additive property. It did not diminish the behavioral effects or anxiogenic effects of THC at a 5:1 (CBD: THC) dose ratio, emphasizing that the probable action of CBD is linked to the CBD: THC dose ratio (Todd et al., 2017).

CBD exhibited antidepressant activity in assorted animal models of depression, either administered alone or coadministered with sub-effective doses of the antidepressant fluoxetine, acting synergistically, mainly through the activation of 5HT_{1A} serotonergic receptors (Abame et al., 2021). Antidepressant-like activities of CBD were also found to be linked to other factors in animal models of depression, such as NF- κ B pathway activation, plasma, brain IL-6 levels, indoleamine 2,3-dioxygenase activity (Florensa-Zanuy et al., 2021), stimulation of the brain-derived neurotrophic factor (BDNF)-tropomyosin-related kinase B (TrkB) signaling pathway (Sales et al., 2019), and enhanced mRNA expression levels of BDNF and synaptophysin in the brain (Xu et al., 2019).

The outcomes of numerous clinical studies further proved CBD's antidepressant and anxiolytic action. Masataka (2019) investigated the efficacy of CBD treatment on Japanese teenagers with a social anxiety disorder (SAD) in a double-blind study. The anxiety problems of those receiving cannabis oil containing 300 mg CBD were markedly attenuated, suggesting that CBD is a beneficial alternative for ameliorating social anxiety (Masataka, 2019). In another double-blind, randomized design study, patients with SAD were pretreated with CBD, and their anxiety, cognitive impairment, and discomfort were remarkably alleviated compared to patients receiving a placebo. Furthermore, no difference was noted regarding cognitive impairment and discomfort between the CBD-treated group and healthy volunteers (Bergamaschi et al., 2011). On the other hand, some clinical studies aiming to prove CBD-associated anxiolytic effects have failed (Hundal et al., 2018). Therefore, the therapeutic activity of CBD in terms of the convention of anxiety is still a dilemma and requires further clinical trials.

Regarding the clinical assessment of the antidepressant profile of CBD, a similar situation exists in the clinical confirmation of CBD-linked anxiolytic effects. Thus, additional clinical trials are warranted. Nevertheless, current evidence is prone to demonstrate the antidepressant action of CBD (Solowij et al., 2018). Thus, these studies render preliminary ground confirming the efficacy and

safety of CBD on depression and anxiety, although more extensive clinical trials are needed to achieve precise decisions.

8. CBD IN EPILEPSY AND OTHER SEIZURE DISORDERS

Current scientific documentation has pointed out the role of cannabidiol in epilepsy and other neuropsychiatric disorders. In this context, CBD-relevant aspects of physiology, pharmacology, and mechanisms have been stated in this section.

In vitro and in vivo experimental models revealed the anticonvulsant impact and relevant modes of action of CBD. CBD exhibited anticonvulsant action in many acute animal models of seizures, while limited evidence exists in animal models of chronic epilepsy or animal models of epileptogenesis (Leo et al., 2016). Many investigations have revealed the antiepileptic effects of CBD in animal models (Izquierdo et al., 1973; Jones et al., 2012). Moreover, CBD enhanced the antiseizure effect of numerous antiepileptic drugs, such as phenytoin. It alleviated the anticonvulsant potencies of chlordiazepoxide, clonazepam, trimethadione, and ethosuximide, suggesting drug-drug interactions of CBD.

Clinical studies have further confirmed the anticonvulsant action of CBD in epilepsy, although there is a lack of data gained from well-organized double-blind, randomized, controlled studies (Devinsky et al., 2016; McGrath et al., 2019). Nevertheless, we can assume that the outcomes of recent scientific data represent hope for patients with epilepsy who are refractory to standard antiepileptic drugs.

Several placebo-controlled trials of a pharmaceutical-grade CBD formulation also resulted in regulatory approval for managing seizures relevant to Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex (Bioscience, 2018; Franco et al., 2021). Despite positive outcomes in these severe epilepsy syndromes, seizure control still seems limited, and further improvements are warranted.

CBD exhibited anticonvulsant activity in managing epileptic seizures by affecting assorted targets. The antiseizure action of CBD was substantially mediated by (1) the attenuation of the synaptic release of glutamate arising from its antagonism on the G protein-coupled receptor (GPR) (Leo et al., 2016; Gray and Whalley, 2020) and (2) the stimulation of transient receptor potential of ankyrin type 1 (TRPA1) channel (Kowalski et al., 2020), (3) the blockage of the synaptic uptake of various mediators such as adenosine, GABA, noradrenaline, dopamine (Ibeas et al., 2015), (4) the activation of 5-HY_{1A} receptors (Martínez-Aguirre et al., 2020), (5) promoting the activity of α 3 and α 1 glycine receptors (Ahrens et al., 2009), (6) promoting transient receptor potential of vanilloid type 1 (TRPV1) and 2 (TRPV2) channels (Pumroy et al., 2019).

9. CBD AND COMMERCIAL PROSPECTS

In 2019, nutraceuticals had the highest revenue share of 62.4 percent. The growth's primary factors are growing consumer awareness of CBD's health advantages. The USA dominated the CBD consumer market with a revenue share of 59.8% in 2019. The CBD global market was approximately US \$2.8 billion in 2020. However, due to various health benefits and strong demand by the health and wellness industry, the demand is predicted to increase in the coming decade, with a compound annual growth rate of 21.2%. More CBD-infused products are likely to be seen in the market in the coming years. In 2018, the US government approved the Farm bill, which legalizes cannabis plants with the cultivation and manufacturing of cannabis-derived products containing less than 0.3% THC (a mind-altering compound) in the United States. Due to this relaxation in the law, the use of CBD-infused products is expected to grow at a compound annual growth rate of 26.9% in the coming years. Nutraceutical products containing CBD are used in weight loss, sports, and overall health and well-being. Due to high business potential, more companies, especially in Europe, are joining the CBD nutraceuticals industry. Additionally, the consumer base is expanding, and the demand for these products is expected to accelerate rapidly in the coming years (Grand View Research, 2021).

10. CONCLUSION

Nonpsychotropic CBD exerts several effects, many of which may hold therapeutic value or fulfill pharmaceutical drug development models. Despite insufficient data about the modes of action of CBD, recent studies on CBD's action on pain, anxiety, and epilepsy relief may lead to clarification of this longstanding mystery. The growing demand for unregulated CBD products demands sufficient education and adjustment about the advantages and disadvantages of CBD use on individuals' health. This becomes more of an issue in the case of pregnancy because, in such cases, the use of CBD and its derivatives hold a risk for the growing fetus and future offspring. Unfortunately, comprehensive discussions about the hazards of CBD use are still lacking and need urgent attention to prevent erratic damage to individuals' health.

Nature is a unique source of new chemical entities that enable selective and effective drug leads with fewer side effects. Furthermore, it makes a way to discover new drug leads and prospective design (semi) synthetic derivatives, suggesting drug candidates with improved pharmacological features. Considering recent developments in CBD-associated pain, anxiety, and epilepsy easement, more effective (semi) synthetic CBD derivatives with fewer side effects may become possible for pain, anxiety, and epilepsy relief.

In the last two decades, evidence-based research has shown a significant increase in the medicinal use of CBD-

infused products to treat various ailments/indications, such as anxiety, depression, sleep disorders, epilepsy, cancer, and neuropathic pain. While the USA remains the lead market for CBD-based products, more Europeans are embracing CBD edibles and topicals. Countries such as Switzerland, Germany, and the United Kingdom are increasing the use of cannabidiol oil, which is projected to fuel the European market.

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