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Biological properties and therapeutic applications of cannabidiol

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***Cannabis* sp. has important pharmacological activities, so it has been the focus of attention of the scientific community. Through the search for new drugs, it was found that cannabinoids present in the plant can modulate transient potential receptors (TPR). Cannabidiol (CBD), also known as "medical marijuana", represents the second most abundant phytocannabinoid of the Cannabis plant and it is widely used in the management of pain, nausea and migraine in cancer patients. In fact, CBD exhibits various therapeutic effects and constitutes up to 40% of Cannabis extracts and it is devoid of the typical psychological effects of Cannabis used in social use as a psychoactive drug, and has low affinity for endocannabinoid receptors CB1 and CB2. Thus, this article aims to conduct an integrative review of CBD and its potential benefits for human health. The results of this research confirmed CBD therapeutic actions in diseases such as schizophrenia, anxiety, epilepsy and motor disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathic pain, childhood convulsive disorders, Lennox-Gastaut and Dravet syndromes. Thus, cannabidiol has an important relevance for medical applications and also has anti-inflammatory, antioxidant, anticonvulsant, anxiolytic, neuroprotective, antipsychotic, antiemetic, analgesic and antibiotic activities.**

Key words: Medical marijuana, cannabinoids, Cannabidiol (CBD), medicinal use.

INTRODUCTION

The *Cannabis sativa* L. plant contains over 100 chemical compounds that share a similar chemical structure (Crippa et al., 2018). Of these, at least 70 are cannabinoids, including seven cannabidiol acids (CBDA) and 11 tetrahydrocannabinolic acids (THC) (Perucca, 2017). With high pharmacological values, their potentialities and applications are not only limited to the biological activities of cannabinoids, but also defined by non-cannabinoid compounds. Combining other cannabinoids with non-cannabinoid components could increase the beneficial effects of THC and reduce undesirable side effects (Pollastro et al., 2018).

The chemistry of *Cannabis* sp. is known to be very complex, capable of producing chemical structures that represent almost all different biogenetic classes (Pollastro et al., 2018). Chemical characterization

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highlights the presence of various constituents, including flavonoids, spiroindanes, dihydro-stilbenes, dihydrophenanthrenes, lignanamides, steroids and alkaloids as well as carbohydrates, fatty acids and their esters, amines, phytosterols and cannabinoids (Andre et al., 2016; Pollastro et al., 2018). Some biological activities of cannabinoids are potentiated by the presence of terpenes and flavonoids due to a synergistic action (Pellati et al., 2018).

The effects of cannabinoid compounds are largely mediated by cannabinoid receptors CB1 and CB2, referred to as the endocannabinoid system (ECS). CB1, cloned in 1990 (Matsuda et al., 1990), is widely expressed in the central nervous system (CNS), where it probably mediates most of the psychotropic and behavioral effects of cannabinoids. CB2 is mainly expressed in peripheral tissues (Munro et al., 1993). Cannabinoid receptors belong to the class A protein G-coupled receptor (GPCR) family, which signal through heterotrimeric Gα and/or inhibitory G proteins, proteins involved in cell signal transduction, which is an important mediator of metabolic pathways (Begg et al., 2005; Balapal, 2017; Kumar et al., 2019; Lorenzen and Sakmar, 2019).

Probably additional receptors may contribute to the behavioral, vascular and immunological actions of Δ9 tetrahydrocannabinol (THC) and endogenous cannabinoids (Begg et al., 2005). In the search for new therapeutic treatments, it was found that cannabinoids can modulate transient potential receptors (TPR). These receptors modulate ion entry, especially Ca^{2+}, mediating a variety of neural signaling processes. mplicated in temperature sensation, pressure, and pH, as well as in smell, taste, sight, and pain perception (Muller et al., 2019). Thus, it influences neuroplasticity, apoptosis, excitotoxicity, neuroinflammation and cerebrovascular degradation associated with stroke and trauma.

Phytocannabinoids and endogenous cannabinoids function as retrograde messengers that provide feedback on inhibition of excitatory and inhibitory transmission in the brain through activation of presynaptic CB1 receptors (Maroon and Bost, 2018). CBD, also known as “medical marijuana” represents the second most abundant phytocannabinoid in the *Cannabis* sp. Plant after the psychoactive tetrahydrocannabinol (Δ9-THC). Unlike THC, CBD is non-hedonic, that is there is no known abuse potential, no detectable psychoactive properties, and has low affinity for endocannabinoid receptors CB1 and CB2 (Pertwee, 2008).

In fact, CBD exhibits various therapeutic effects ranging from anti-inflammatory, antioxidant and neuroprotective to anticonvulsant, antiemetic and analgesic (Jiang et al., 2013; Zendulka et al., 2016; Hahn et al., 2017; Pollastro et al., 2018; Ostrovky et al., 2018). Thus, it acts on the endogenous cannabinoid system by influencing mood, motor coordination, cognition, pain and neuroinflammation (Devinsky, 2018; Chen, 2019).

Chronic cannabis use is associated with neuro-anatomical changes in the hippocampus. Studies suggest that CBD acts as a neuroprotective, as it may improve brain damage, including protection against hippocampal volume loss (Beale et al., 2018). Several anti-epileptic, anxiolytic drugs with better safety profiles have been approved in the last two decades. However, the vast majority of patients remain drug resistant, causing an increased risk of injury, premature death, psychosocial dysfunction and reduced quality of life.

CBD can constitute up to 40% of cannabis extracts and is devoid of the typical psychological effects of cannabis when used as a recreational drug. Cannabidiol has a growing scientific relevance for medical applications and has been shown to be effective in diseases such as schizophrenia, anxiety, epilepsy and motor disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathic pain and seizure disorders in childhood, Lennox syndromes. Gastaut (LGS) and Dravet (Andre et al., 2016; Cheliah et al., 2018; Crippa et al., 2018; Thiele et al., 2018; Lorenzen and Sakmar, 2019). Thus, this article aims to conduct an integrative review on cannabidiol (CBD) and its potential benefits for human health.

MATERIALS AND METHODS

This is an integrative literature review, performed by following the steps (Whittermore et al., 2005):

Research strategy

First, it set guiding questions: Does CBD have biological properties about any disease? What are the benefits of CBD for human health? From this, the categorization of the studies was selected for extraction and data collection.

The database search was conducted from June to July 2019. The search was initiated by potential studies in large electronic databases such as MEDLINE, EMBASE, LILACS, SCOPUS, PubMed, Web of Science, Cumulative Index to Nursing and Akllied Health Literature (CHIN), Australasian Medical Index, Chines Biomedical Lietarture Database. We also searched unpublished sources in progress and gray literature. Descriptors in Health Sciences (DECS) and Medical Subject Headings (Mesh) were used to classify information and facilitate bibliographic searches as well as locate and retrieve articles in databases. At the same time, a bibliographic mapping of the main references on the theme was performed, contributing to the object of study investigated.

Research terms included

Inclusion criteria defined for study selection were: full, original, peer-reviewed articles depicting the following descriptors: cannabidiol, *cannabis*, CBD, medical marijuana, pharmacology, pharmacokinetic properties, chemical composition, health benefits, therapeutic use, chemical analysis, phytocannabinoid and medicines. Boolean operators “and” and “or” were employed.

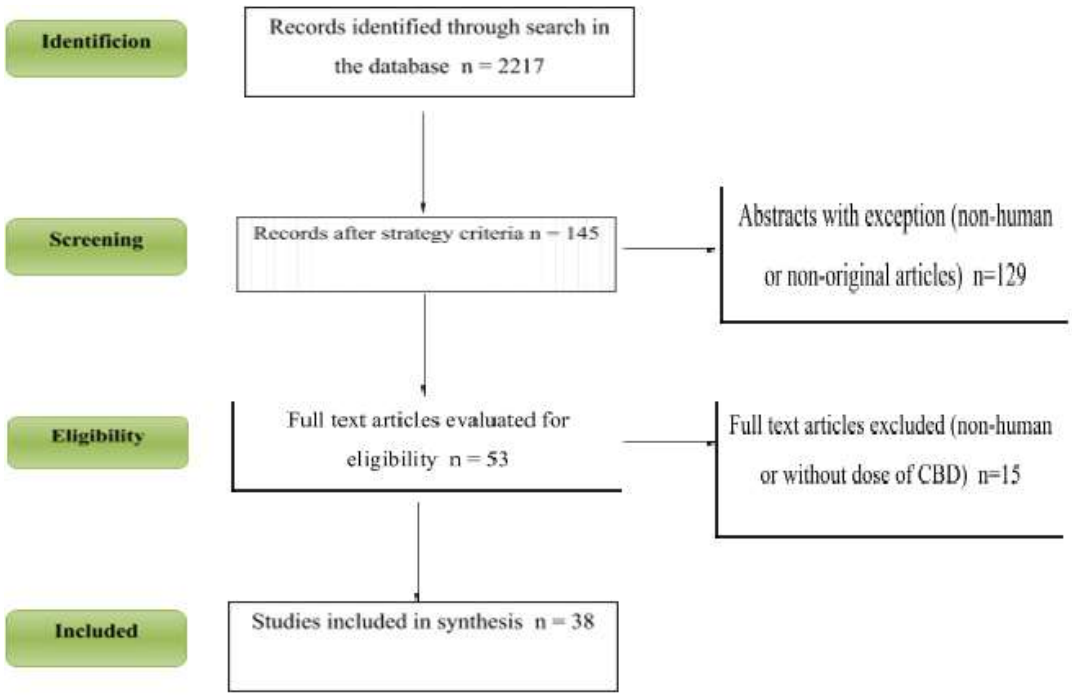

Figure 1. Flowchart for study retrieval and selection.

Restrictions on publication date (last two years) and languages (English, Spanish, and Portuguese) apply. We used as criteria search strategy publication that involved administration of CBD in humans at least one pharmacokinetic measurement without criteria for age and gender.

Eligibility criteria

The studies were selected after the evaluation of titles and abstracts, strictly obeying the inclusion and exclusion criteria defined in the research. After identifying the most relevant studies, the complete publication was purchased and reviewed by the authors to determine eligibility for final inclusion. Inappropriate articles were rejected.

Data acquisition

Included articles were analyzed and the following data extracted: sample size, gender, route of administration, source and dose of CBD, and any pharmacokinetic details, where available.

Analysis

The analysis and data extracted from the selected studies were descriptive, allowing observing, counting, describing and classifying the data, in order to gather the knowledge produced about the theme explored in the review.

RESULTS AND DISCUSSION

In this study a final sample with 2,217 scientific articles was used for the descriptor: cannabidiol. Thirsteen articles were found on the LILACS database, but four articles were selected; on the IBECS database, three articles were obtained (two selected); and from the MEDLINE 1,237 articles (53 selected) according to the inclusion and eligibility criteria (Figure 1). All studies included in the research were considered of good scientific quality and are described in Table 1, with their respective authors, methodologies, population, age group, administration, treatment (disease) and their respective results, and the conclusion of the study.

CBD is a non-psychotomimetic cannabinoid compound found in *Cannabis* plants; this effect is believed to be due to the action of CBD on the end ocannabinoid system. Elms et al. (2018) demonstrated that 91% of patients had decreased severity of posttraumatic stress disorder (PTSD) symptoms after CBD dosing.

Beale et al. (2018) conducted a long-term CBD treatment study on users of *Cannabis* sp. They compared heavy and light users to explore the influence of prior cannabis exposure on CBD treatment outcomes. They found that the volume of the left subicular complex (parasubiculum, presubiculum and subiculum) increased significantly from baseline to posttreatment by 1.58% (Cohen d = 0.63; 2.83% in parasubiculum), noting that the increase in the volume of the left subicular complex was driven by heavy users, particularly the marked growth that occurred on the left presubiculum, which normalized posttreatment volumes

Table 1. CBD (cannabidiol) use in humans (last two years)

References	Methodology	Population/ test subject	Age group	Administration	Treatment (disease)	Result	Study conclusion
Varadkar et al. (2018)	Randomized, double-blind, placebo-controlled study.	Human	-	20 mg/kg/day and once.	Lennox-Gastaut (LGS)	Decrease in seizure	CBD has benefit in reducing seizure frequency.
Thiele et al. (2018)	Randomized, double-blind study	Human	18-55 years-old	20 mg/kg/day and once. 4 weeks	Lennox-Gastaut (LGS)	Decrease in seizure	Seizure Reduction
Devinsky et al. (2018)	Double-blind, placebo-controlled study.	Human	2-55 years-old	20 mg/kg/ two daily doses. 14 weeks 10 mg / kg two daily doses.	Lennox-Gastaut (LGS)	Redoxes seizure frequency	Elevation of liver aminotransferases
Cunetti et al. (2018)	They evaluated 07 patients who used CBD for pain management. With an average age of 64.5 years-old	Human	58-75 years-old	Doses increasing 50 to 150 mg twice a day. 3 weeks	Chronic pain	Mild adverse effects	CBD was well tolerated and there were no adverse effects.
Elms et al. (2018)	Retrospective case series with CBD use on PTSD symptoms.	Human	-	11 patients. Eight weeks	Posttraumatic Stress Disorder (PTSD)	It presented reduction in the severity of PTSD symptoms. CBD was well tolerated	Oral CBD administration reduced symptoms in adults with PTSD. It also offers relief to patients with PTSD symptoms.
Chelliah et al. (2018)	Case study	Human	Case 1- 38 weeks. Case 2 -3 years. Case 3- 10 years	Case 1- Nebulized CBD oil over area 2-3 times daily. Case 2 - CBD oil applied topically twice a day. Case 3 - Topical CBD Cream	Epidermolysis Bullosa	Case 1- Blister reduction, morphine elimination. Case 2- Blister reduction and healing time Case 3- Blister reduction and keratoderma.	Reduction in pain and blisters, rapid wound healing. Additional studies are needed to prove the effectiveness of CBD.
Beale et al. (2018)	Open pragmatic study with CBD administration using structural magnetic resonance.	Human	18-55 years-old	Daily oral capsule with 200 mg of CBD for 10 weeks.	Hippocampal Pathology (Schizophrenia, Alzheimer's and depressive disorder)	Increased left subicular volume.	Beneficial effect of CBD treatment on brain structural damage. Potential for treatment in restoring hippocampal pathology.

Table 1. Contd.

Bravo et al. (2018)	Case Study of an Adult Woman with DS	Human	19 years-old	Patient treated with stipipenol, clobazam, valproic acid and administration of CBD as adjuvant therapy	Síndrome de Dravet (SD)	STXBP1 mutation may be the basis of Dravet syndrome in patients who do not have a SCN1A mutation, and the STXBP1 mutation is related to the motor phenotype with parkinsonian characteristics.	Patient responded well to CBD treatment, however, further studies are needed to validate the efficacy of cannabidiol.
Chen et al. (2019)	Searches using the terms cannabidiol, CBD, epiolex. 3 trials were selected. Multinational, double blind, placebo controlled for 4 weeks and treatment for 14 weeks	Human	≥ 2 years-old	This article provides a summary of clinical data, including EAP evidence and the top 3 phase III trials.	(DS) and (LGS)	CBD use by DS and LGS patients offers a new treatment option.	100% reduction in primary seizure and total seizures
Kenyon et al. (2018)	Systematic review and randomized controlled trials to analyze the efficacy and safety of cannabis-based drugs in patients with mental disorders.	Human	50-72 years-old	10 mg duas vez ao dia. Estudo randomizado em 119 pacientes com câncer durante quatro anos	Mental disorder	Effectiveness in treating any mental disorder	Synthetic cannabidiol is a candidate for the treatment of cancer and glioma patients.
Orrin et al. (2018)	Phase III, double-blind, multinational, randomized study	Human	2-55 years-old	Starting at 2.5 mg / kg, the dose was increased over 2 weeks to 20 mg / kg. for 14 weeks	(LGS)	Seizure Reduction (50%)	A phase III trial demonstrated benefits for a new drug application.
Palmieri et al. (2019)	Spontaneous retrospective study, patients with psoriasis and atopic dermatitis	Human		CBD-enriched topical ointment on damaged skin twice daily for 3 months	Skin disorders	It significantly improved symptoms. No irritating or allergic reactions.	CBD-enriched ointment is a safe and effective non-invasive alternative to improve patients' quality of life.
Poleg et al. (2019)	Review of preclinical and clinical data on safety and efficacy of medicinal cannabis, including CBD.	Human	Younger people	Cannabinoid use in general and CBD in particular in the treatment of numerous mental conditions are growing	(DEA)	Studies on possible applications of cannabinoids are needed	

Table 1. Contd.

Sekar et al. (2019)	Review of several recent large-scale studies using Epidiolex focusing on its adverse effects.	Human	NE		Refractory Epilepsy	Reduction of seizure frequency in animal	
Shannon et al. (2019)	Case study in psychiatric clinic involving CBD application	Human	Adults/ Younger people	25 mg / kg / 50 mg / kg and 75 mg / kg single daily dose	Anxiety and Sleep Problems	CBD was well tolerated	CBD may be beneficial for anxiety disorders
Solowij et al. (2019)	CBD administration on psychological and cognitive symptoms	Human	25 years-old	Open 200 mg oral test, for 10 weeks.	Psychological symptoms and cognition.	CBD was well tolerated with no side effects.	Prolonged CBD treatment may have promising therapeutic effects

compared to those seen in mild users. Similarly, only heavy users showed a significant increase in entitlement. These results suggest that CBD may be a useful treatment and therapeutic complement to a number of clinical disorders characterized by hippocampal pathology (e.g., schizophrenia, Alzheimer's disease, and depressive disorder). Thus, the authors suggest a protective role of CBD against brain structural damage conferred by chronic use of *Cannabis* sp.

Chelliah et al. (2018) observed that topical use of CBD for Bullous Epidermolysis (EB) was effective in treating three subjects who benefited from topical CBD use, specifically observing a reduction in pain and blistering and rapid healing of wounds. However, the mechanism of action for the observed benefits still needs to be elucidated.

Generally, the most abundant cannabinoid present in *Cannabis ruderalis* Janisch (hemp) are cannabinoic acids such as cannabidiolic acid (CBDA) and cannabigerolic acid (CBGA), followed by their decarboxylated forms, cannabidiol (CBD) and cannabigerol (CBG) (Andre et al., 2016). Hahn et al. (2017) suggest that the use of CBD may be useful in the treatment of psychotic disorders, regardless of the concomitant use of *Cannabis* sp. CBD is highly lipophilic and has low oral bioavailability. The absorption rate of CBD is variable and undergoes extensive first-pass hepatic metabolism by CYP2C19 and CYP3A4 isozymes (Jiang et al., 2013; Zendulka et al., 2016).

Ostrovsky et al. (2018) obtained interesting results on the efficacy of CBD as a therapeutic complement in reducing seizures in patients with Lennox-Gastaut Syndrome (LGS), uncontrolled with other drugs. Among the results presented there was a significant improvement in the control of epileptic seizures with CBD, assuming remarkable recognition as the first randomized controlled trial to study a cannabinoid specifically for LGS.

Chen et al. (2019), for reviewing the efficacy, safety, pharmacology and pharmacokinetics of pure plant-derived CBD (CBD, Epiolex) in the treatment of Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS), observed that ingestion of CBD formulation significantly reduced seizures as a complement to standard antiepileptic therapies in patients ≥ 2 years-old.

In their double-blind, placebo-controlled study, Devinsky et al. (2018) treated patients with LGS. In this study, a mean percentage reduction in the frequency of seizures during the treatment period was observed: 41.9% in the group using20 mg of cannabidiol, 37.2% in the group with 10 mg, and 17.2% in the group. placebo group (Table 1).

Chelliah et al. (2018) observed that topical use of CBD in patients with epidermolysis bullosa produced faster healing, fewer blisters and reduced pain. According to Crippa et al. (2018), cannabinoid receptors (CB1 and CB2) are highly prevalent in the human nervous system. THC has a well-documented mechanism of action via cannabinoid receptors; however CBD has a relatively low affinity for binding to CB1 and CB2 receptors, which may inhibit THC binding to CB1 cardiac receptors.

Recent findings indicate that some cannabinoid

effects are not mediated by CB1 and CB2 receptors, and in some cases there is compelling evidence to implicate additional receptors in these actions (Muller et al., 2019). Thus, for Begg et al. (2005), transient potential receptor (TRP) may imply endothelium-dependent vasodilatory effect and presynaptic inhibition of glutamatergic neurotransmission in the hippocampus. TRP are a group of membrane proteins involved in transducing chemical and physical stimuli in neurons. These receptors modulate the input of ions, mainly Ca^{2+}, mediating a variety of neural signaling processes implicated in sensation of temperature, pressure and pH, as well as in smell, taste, vision and pain perception. Many diseases involve TRP channel dysfunction, including neuropathic pain, inflammation, and respiratory disorders. In the search for new treatments for these disorders, it has been found that cannabinoids can modulate a subset of TRP channels (Muller et al., 2019).

CBD is used as an antiepileptic drug and several mechanisms have been established to reduce excitability and neuronal transmission such as: inhibition by g-aminobutyric acid; modulation of intracellular calcium by transient potential receptors (TPS) such as TRPM8, TRPA1, TRPV1 and TRPV2, G protein-coupled GPR55 receptor (Muller et al., 2019). The chemistry of *Cannabis* sp. is known to be very complex, its potentialities and applications are not only limited to the biological activities of cannabinoids, but also defined by non-cannabinoid compounds (Pollastro et al., 2018). According to Andre et al. (2016), several biological effects have been attributed to *Cannabis sp*., including anti-inflammatory, antimicrobial, neuroprotective and antiproliferative activities. In particular, studies show that flavonoids, canflavins A and B have an anti-inflammatory action and their molecular targets have been identified as prostaglandin E2 synthesis found in the microsomal fraction (mPGES-1) and 5-lipoxygenase (5- LO) (Wertz et al., 2014) and finally, flavonoids can also modulate pharmacokinetics of some cannabinoids by inhibiting liver enzymes P450 (Andre et al., 2016). Dihydrostilbenoids represent another class of polyphenolic substances isolated from *Cannabis* sp., of which canniprene is the main representative and exerts anti-inflammatory activity by inhibiting the production of eicosanoid proinflammatory drugs (Alledrone et al., 2017; Pollastro et al., 2018).

Cunetti et al. (2018) evaluated the use of CBD in patients with chronic pain and as a result, cannabidiol showed good tolerance and no adverse effects were observed. Bravo et al. (2018) were successful with their patients, who responded well to CBD treatment by treating Dravet's Syndrome (DS), genetic epilepsy.

Hoch et al. (2019) performed a systematic review and randomized controlled trials (RCTs) to analyze the efficacy and safety of Cannabis sp. in patients with mental disorders. According to the authors, THC and CBD-based medications, administered as adjuncts to pharmacotherapy and psychotherapy, were associated with improvements in various symptoms of mental disorders, but did not produce remission.

Kenyon et al. (2018) evaluated the effects of CBD pharmaceutical grade synthetics on a variety of cancer patients. Results showed a reduction in circulating tumor cells in 92% of the 119 cases studied. Poleg et al. (2019) have noted growing interest from researchers about cannabinoids, especially CBD, either as monotherapy or as an additional treatment for the main symptoms and comorbidities of Autism Spectrum Disorder (AED).

The National Academy of Sciences, Engineering and Medicine claims that there is substantial evidence for the effectiveness of *Cannabis* sp*.* in the treatment of chronic pain in adults, there is moderate evidence of improvement in short-term sleep disorders in patients with chronic pain (Romero-Sandoval et al., 2018). *Cannabis* sp. has been used for centuries in many cultures to treat a wide range of medical conditions. More recently, therapeutic considerations have gone beyond plant extract to explore and produce more pharmacologically refined compounds (Hua et al., 2016).

Cannabis sp. induces its analgesic and mood-enhancing effects through cannabinoid receptor 1 (CB1), a G protein-coupled receptor (GPCR) that signals mainly through adenylyl cyclase Gi inhibitory heterotrimeric G protein. Activation of CB1-Gi signaling pathways has the potential to treat various neurological disorders and, therefore, is crucial to understand the mechanism of CB1 deactivation of Gi (Basavarajappa, 2017).

Cannabinoids are currently used to reduce pain and nausea that often accompany cancer. Several cannabinoids have been shown to exert anti-proliferative and pro-apoptotic effects on various types of cancer, both in vitro and in vivo (Massi et al., 2013). Thiele (2018) suggests that the mechanism of action of CBD is related to modulation of TNF-α (Tumor Necrosis Factor alpha) release by inhibiting adenosine reuptake.

Some biological activities of cannabinoids are reinforced by the presence of secondary metabolites in *Cannabis* sp. extracts, as in cases of sleep and anxiety disorders (Russo et al., 2011). This effect has been attributed to a close interaction between cannabinoids and terpenes, resulting in a synergistic action (Russo et al., 2011). Terpenes are able to increase blood-brain barrier permeability and can also interact with neurotransmitter receptors, contributing to cannabinoid-mediated analgesic and psychotic effects (Andre et al., 2016).

Conclusion

Some biological activities of cannabinoids are reinforced

by the presence of secondary metabolites in *Cannabis* sp. extracts, as in cases of sleep and anxiety disorders. This effect has been attributed to a close interaction between cannabinoids and terpenes, resulting in a synergistic action. Terpenes are able to increase blood-brain barrier permeability and can also interact with neurotransmitter receptors, contributing to cannabinoid-mediated analgesic and psychotic effects.

All studies included in the research were considered of good scientific quality and are described in Table 1. CBD is a non-psychotomimetic cannabinoid compound found in *Cannabis* plants. This effect is believed to be due to the action of CBD on the endocannabinoid system. There is a growing interest of researchers in cannabinoids, especially CBD, either as monotherapy or as an additional treatment for the main symptoms and comorbidities of Autism Spectrum Disorder (AED). The National Academy of Sciences, Engineering and Medicine claims that there is substantial evidence for the effectiveness of *Cannabis* sp. in the treatment of chronic pain in adults. There is moderate evidence of improvement in short-term sleep disorders in patients with chronic pain.

Cannabis sp. has been used for centuries in many cultures to treat a wide range of medical conditions. More recently, therapeutic considerations have gone beyond plant extract to explore and produce more pharmacologically refined compounds. *Cannabis* sp. is a complex plant capable of producing over 480 chemical entities that represent almost all different biogenetic classes. Cannabidiol (CBD) is considered the non-psychoactive component of the plant and has a multitude of pharmacological activities. There is scientific evidence that CBD can be used as a useful treatment for different therapeutic conditions such as schizophrenia, anxiety, epilepsy and motor disorders such as Parkinson's disease, among others CBD and phytocannabinoids have potential health benefits for human health.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Alledrone G, Pollastro F, Magagini G, Taglialatela-scafati O, Seegers J, Koeberle A, Werz O, Appendino G (2017). The bibenzyl canniprene inhibits the production of pro-inflammatory eicosanoids and selectively accumulates in some Cannabis sativa strains. Journal of Natural Products 80(3):731-734.

Andre CM, Hausman JF, Guerriero G (2016). *Cannabis sativa:* The plant of the Thousand and one molecules. Frontiers in Plant Science 7(19):1-17.

Basavarajappa BS (2017). Chapter 2 - Cannabinoid Receptors and their Signaling Mechanisms. In: Rodríguez EM, The Endocannabinoid System. Genetics, Biochemistry, Brain Disorders, and Therapy. pp. 25-62. Available at https://www.sciencedirect.com/science/article/pii/B9780128096666000022?via%3Dihu b

Beale C, Broyd SJ, Chye Y, Suo C, Schira M, Galettis P, Martin JH, Yuce M, Solowiji N (2018). Prolonged Cannabidiol Treatment Effects on Hippocampal Subfield Volumes in Current Cannabis Users. Cannabis and Cannabinoid Research 3(1):94-107.

Begg M, Pacher P, Batkai S, Osei-hyiaman D, Offertáler L, Mo FM, Liu J, Kunos (2005). Evidence of new cannabinoid receptors. Pharmacology and Therapeutics 106(2):133-145.

Crippa JA, Guimarães FS, Campos AC, Zuardi AW (2018). Translational investigation of the therapeutic potential of Cannabidiol (CBD): Toward a New Age. Frontiers of Immunology, 9:2009.

Hua T**,** Vemuri K, Pu M, Qu L, Han GW, Wu Y, Zhao S, Shui W, Li S, Korde A, Laprairie RB, Stahl E, Ho JH, Zvonok N, Zhou H, Kufareva I, Wu B, Zhao Q, Hanson MA, Bohn LM, Makriyannis A, Stevens RC, Liu ZJ (2016). Crystal structure of the Human Cannabinoid Receptor CB1. Cell 167(3):750-762.

Jiang R, Yamaori S, Okamoto Y, Yamamoto I, Watanabe K (2013). Cannabidiol is a potent inhibitor of the Catalytic Activity of Cytochrome P4502C19. Drug Metabolism and Pharmacokinetics 28(4):332-338. Available at https://www.sciencedirect.com/science/article/abs/pii/S1347436715304225?via%3Dihu b

Kumar KK, Shalev-benami M, Robertson M, Hu H, Banister SD, Hollingsworth SA, Latorraca NR, Kato HE, Hilger D, Maeda S, Weis WI, Farrens DL, Dror RO, Malhotra SV, Kobilka BK, Skiniotis G (2019). Structure of a Signaling Cannabinoid Receptor 1-G Protein Complex. Cell 176(3):448-458.

Lorenzen E, Sakmar TP (2019). Receptor Structures for a Caldron of Cannabinoids. Cell 176(3):409-411.

Maroon J, Bost J (2018). Review of the neurological benefits of phytocannabinoids. Surgical Neurology International 9:91.

Massi P, Solinas M, Cinquina V, Parolaro D (2013.) Cannabidiol as potential anticancer drug. British Journal of Clinical Pharmacology 75(2):303-312.

Matsuda LA, Lolait SJ, Brownsten M, Young AC, Bonner TI (1990). Structure of a cannabinoid receptor and functional expression of cloned cDNA. Nature 346:561-564.

Muller C, Morales P, Reggio PH (2019). Cannabinoid Ligands Targeting TRP Channels. Frontiers in Molecular Neuroscience 11:487.

Munro S, Thomas KL, Abu-shaar M (1993). Molecular characterization of a peripheral cannabinoid receptor. Nature 365(6441):61-65.

Pertwee RG (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ^9-tetrahydrocannabinol, cannabidiol and Δ^9 –tetrahydrocannabivarin. British Journal of Pharmacology 153(2):199-215.

Perucca E (2017). Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? Journal of Epilepsy Research 7(2):60-76.

Pellati F, Brighenti V, Sperlea JI, Marchetti L, Bertelli D, Benvenutri S (2018). New Methods for the Comprehensive Analysis of Bioactive Compounds in *Cannabis sativa* L. (hemp). Molecules 23(10):2639.

Pollastro F, Minassi A, Fresu LG 2018. Cannabis phenolics and their bioactivities. Current Medicinal Chemistry 25(10):1160-1185.

Romero-Sandoval EA, Fincham JE, Kolano AL, Sharpe BN, Alvarado-Vázquez PA (2018). Cannabis for Chronic Pain: Challenges and Considerations. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 38(6):651-662.

Wertz O, Seegers J, Schaible AM, Barz D, Koeberle A, Allegroned G, Pollastro F, Zampieri L, Grassi G, Appendino G

(2014). Cannflavins from hemp sprouts, a novel cannabinoid-free hemp food product, target microsomal prostaglandin E2 synthase-1 and 5-lipoxygenase. Pharma Nutrition 2(3):53-60.
Whittermore R, Knafl K (2005). The integrative review: updated methodology. Journal of Clinical Nursing 52(5):546-553.
Zendulka O, Dovrtelová G, Nosková K, Turjap M, Sulcová A, Hanus L, Jurica J. (2016). Cannabinoids and Cytochrome P450 Interactions. Current Drug Metabolism 17(3):206-226.