The endocannabinoid system and orofacial pains: updates and perspectives

O sistema endocanabinoide e as dores orofaciais: atualidades e perspectivas

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ABSTRACT

BACKGROUND AND OBJECTIVES: Since the relatively recent discovery of the endocannabinoid system (ECS) and its fundamental role in regulating other systems, the subject has aroused interest in all areas of health, including Dentistry. Among the possible uses and benefits of cannabinoids are their performance in pain and its predisposing or perpetuating factors, such as bruxism and sleep disorders. Although the literature is still scarce, the mechanisms of action and satisfactory results of cannabinoids and other cannabis derivatives in these situations already allow their safe prescription. The objective of this study was to verify the current evidence on the use of cannabis derivatives in orofacial pain (OFP), reviewing what is known, to date, about the ECS and the prospects for its use with support and criteria.
CONTENTS: This research carried out a brief review of the cannabis plant history, addressing issues such as prejudice, prohibitions and interests, as well as its therapeutic use. Then, a review on ECS and its mechanisms of interest in OFP was presented. Next, the products derived from the plant and their effects, indications, contraindications, adverse effects, drug interactions, peculiarities and perspectives were discussed.
CONCLUSION: The more knowledge is gained about the ECS and the therapeutic benefits of cannabis components and derivatives, the greater the conviction that a new therapeutic frontier has indeed emerged. The growing number of good outcomes, including cases of OFP, obtained through well-conducted studies, brings a mixture of satisfaction and excitement. No therapy will achieve good results if it does not start from an accurate diagnosis. Thus, it is of the utmost importance to know the ECS, the products and derivatives of the plant, the synthetic cannabinoids, their indications and effects. New studies are necessary and, at this moment, it can be said that the perspectives are very good and a new and challenging horizon is emerging.
Keywords: Cannabidiol, Cannabis, Orofacial pain, Endocannabinoids, Dentistry.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Desde a descoberta relativamente recente do sistema endocanabinoide (SEC) e seu papel fundamental da regulação de outros sistemas, o assunto tem despertado interesse de todas as áreas da saúde, incluindo-se a Odontologia. Dentre as possíveis utilizações e benefícios dos canabinoides, está sua atuação na dor e seus fatores predisponentes ou perpetuadores, como o bruxismo e os distúrbios do sono. Embora a literatura seja ainda escassa, os mecanismos de ação e resultados satisfatórios dos canabinoides e demais derivados da cannabis nessas situações já permitem sua prescrição com segurança. O objetivo deste estudo foi verificar as atuais evidências sobre a utilização de derivados da cannabis nas dores orofaciais (DOFs), revisando o que se sabe, até o momento, sobre o SEC e as perspectivas de sua utilização com respaldo e critério.
CONTEÚDO: Esta pesquisa realizou uma breve revisão da história da planta cannabis, abordando temas como preconceito, proibições e interesses, além de sua utilização terapêutica. Em seguida, foi apresentada uma revisão sobre o SEC e seus mecanismos de interesse na DOF. Na sequência, foram discutidos os produtos derivados da planta e seus efeitos, indicações, contraindicações, efeitos adversos, interações farmacológicas, peculiaridades e perspectivas.
CONCLUSÃO: Quanto mais são adquiridos conhecimentos sobre o SEC e os benefícios terapêuticos dos componentes e derivados da cannabis, mais há um convencimento de que surgiu, de fato, uma nova fronteira terapêutica. O número crescente de bons desfechos, incluindo casos de DOF, obtidos através de estudos bem conduzidos, traz um misto de satisfação e empolgação. Nenhuma terapia obterá bons resultados se não partir de um diagnóstico preciso. Assim, é de suma importância que se conheça o SEC, os produtos e derivados da planta, os canabinoides sintéticos, suas indicações e efeitos. Novos estudos são necessá-

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HIGHLIGHTS
- The effects of cannabis and its synthetically derived products on orofacial pain.
- Phytocannabinoids, such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), can be employed as a therapy for orofacial pain.
- Scientific evidence, albeit not very robust, suggests that cannabinoids can reduce temporomandibular pain and different neuropathic orofacial pain.

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rios e, nesse momento, pode-se afirmar que as perspectivas são muito boas e um novo e desafiador horizonte está despontando.
Descritores: Canabidiol, Cannabis, Dor orofacial, Endocanabinoides, Odontologia.

INTRODUCTION

Cannabis sativa L. is a phenomenal plant with approximately 500 chemical compounds and 120 identified phytocannabinoids (PHYTs), many not yet fully clarified by science. One of the most eye-catching elements is the recreational use of Δ9-tetrahydrocannabinol (THC), which has both relaxing and hallucinogenic effects. Cannabidiol (CBD), as well as cannabigerol (CBG) have therapeutic properties indicating their use.

Living beings present in their organic systems the need and the ability to keep themselves in balance by means of an internal regulation process called homeostasis. In order for homeostasis to be maintained, in the face of external and internal changes to the individual, cellular metabolism, which corresponds to the set of cellular chemical reactions that constitute the basis of life, needs to respond to stimuli by means of compensation. If this compensation is successful, health will be maintained, otherwise there will be the development of a dysfunction or disease.

In this context, it is important to understand the fundamental role that the nervous system (NS), as a central command, has on cellular metabolism. All transmission of information by means of nerve impulses is controlled by the NS, which also comprises the regulation of all neurotransmitter and hormone production. During the process of communication by nerve impulses, neurotransmitters are released into the synaptic cleft (SC), leading to interactions between pre- and postsynaptic neurons. When this communication ceases, it is necessary to modulate the release of neurotransmitters and to contain cellular energy expenditure, thus a retrograde signaling starts to act in the SC. The retrograde process is carried out by the ECS[1].

The ECS is a neuromodulatory network that was discovered in 1988[2], and has three main components: the cannabinoid receptors CB1 and CB2 coupled to the G protein, the endogenous ligands of these receptors, the endocannabinoids, the best known being anandamide and 2-araquidonoilglycerol (2-AG), and the enzymes that act in their biosynthesis and degradation or deactivation. These components are widely spread throughout the human body[3].

Regarding the breadth of its distribution, ECS performs its functions in all areas of the body, such as: its role in the regulation of neuronal energy metabolism through the presence of CB1 receptor on neuronal mitochondria membrane[4], its action in the gastrointestinal system with specific actions, involved with regulation of food intake, gastric secretion and gastroprotection, cell proliferation in the intestine[5], and immune response regulation with the expression of CB2 receptors in hematopoietic system cells[6], in addition to its action in tissue homeostasis of the entire skin, since it is also present in keratinocytes and dermal nerve cells[7].

Thus, imbalances that occur on the ECS disturb the body homeostasis and can lead to numerous pathologies. Therefore, the study of the system itself and the effects that PHYTs can have is primordial to health, and especially to the quality of life of individuals affected by diseases that are difficult to control, with chronic pain, and poor prognosis, as in the case of neurodegenerative diseases[5].

The PHYTs extracted from *Cannabis sativa* L. interact with ECS through CB1 and CB2 receptors[8], and their applications can be the most diverse, depending on the pathological condition in question, which reflects on the type of PHYT to be administered, its dosage and frequency of use.

CBD is one of the main phytocannabinoids used for therapeutic purposes, presenting analgesic, anti-inflammatory, anticonvulsant, immunomodulatory, antidepressant, anxiolytic, antibacterial, antipsychotic, and neuroprotective effects. It can be toxic to some cancer cell lines. THC is the main psychoactive agent, and despite its benefits (providing anti-inflammatory, analgesic, antiemetic, antispastic, and antineoplastic effects, besides being a bronchodilator and a potent antioxidant), its use can lead to side effects, such as immunosuppression, anxiety, tachycardia, sedation, and memory loss[9-11].

In dentistry, PHYTs' indication is broad, such as in toothpastes, for antimicrobial action, for the induction of bone formation in cases of grafting, in the treatment of degenerative diseases, for temporomandibular joint dysfunctions (muscular and articular), besides bruxism, insomnia, and apnea, among others[12].

It is worth mentioning that sleep has the function of restoring and conserving energy. It is a fundamental aspect for the human being, directly related to a good quality of life. On the other hand, its deprivation can lead to great losses in patients' daily activities, not only in the physical but also in the cognitive state[13]. In this scenario, the Brazilian Sleep Association (*Associação Brasileira do Sono*)[14] shows that the prevalence of disorders related to insomnia is a common problem among Brazilians, which leads to a high demand for professionals in order to treat the dysfunction.

The most indicated treatments are changes in daily habits, such as physical exercise and good diet, psychological monitoring, and sometimes the use of controlled benzodiazepines (BZD) and non-benzodiazepines (non-BZD). But due to the great problems brought about by these drugs, new proposals and treatments for their replacement are increasingly appearing. The main substances, THC and CBD, present several therapeutic properties in synergy with other components of the plant that compose oils known as "full spectrum". In the last decades numerous researches have been conducted aiming at use of cannabinoids in the treatment of several neuropsychiatric conditions, among them neuropathic pain, autism, epilepsy, and insomnia[15].

In temporomandibular joint dysfunctions (TMD) and OFP, prescriptions already show important results for awake bruxism, anxiety, stress and sleep deficit, reduction of chronic, and persistent orofacial pain, without allopathic drugs and interocclusal plates[12,16,17].

As cannabinoids become more widely accepted and legally available, more research is being conducted on their medical use, particularly in pain relief and pain control. This can be evidenced by a number of recently published articles, including a systema-

tic review of randomized clinical trials led by the International Association for the Study of Pain (IASP) Task Force on cannabis and cannabinoid analgesia[18,19].

It is not enough to know how to prescribe, it is necessary to understand the mode of action of the drug and accompany the patient throughout the treatment, understanding that each individual reacts differently.

HISTORIC

Paleobotanical studies point to the presence of cannabis approximately 11700 years BC in the Central Asian region, possibly being used as food, but also for making hammocks and clothing[20].

According to archaeological records, cannabis was one of the first plants to be cultivated by mankind. The hemp fibers were used by the peoples of Mesopotamia for making clothes and ropes, besides its possible medicinal and spiritual use[21].

Inside a grave from Yanghai desert dated 2700 BC, archaeologists found a harp, horse reins and cannabis branches that, according to the beliefs of that time, were to be used in the afterlife[21].

Described in Egyptian papyri from around 1550 BC, cannabis was used as an anti-inflammatory, with a mention of the goddess Seshat, protector of knowledge, whose image is depicted with a branch of cannabis on her head[21].

Reflecting the association between cannabis and humanity, some Indian myths point to divine properties of the plant. The god Shiva allegedly used cannabis as a form of mystical inspiration. In Ayurvedic medicine, the plant has been used for thousands of years to treat nausea, anxiety, to improve quality of sleep and appetite[21].

In 50 AD, the Greco-Roman physician Pedanius Dioscorides, considered the father of pharmacology, in his work "*De Materia Medica*", described more than 1000 plants with medicinal properties, pointing to cannabis as efficient for treating epilepsy, pain, and inflammatory processes[21].

Cannabis arrived in Brazil around 1550, brought by African slaves and was known as "*fumo d'Angola*" (Angola smoke). There are records that Queen Carlota Joaquina used it to treat her chronic pain[21].

During the 18th and 19th centuries cannabis became quite popular in Europe and was included in the United States of America's pharmacopoeia for alcoholism, cholera, gout and neuralgia treatments. Until the 1930s large laboratories such as Lilly, Squibb and Park Daves marketed cannabis products for therapeutic purposes[21].

The first so-called "Golden Age" of medical cannabis took place in the late 19th and early 20th centuries, when Queen Victoria of England used cannabis for pain, while Empress Elisabeth ("Sissi") of Austria used it for cough treatment and as an appetite stimulant[20].

In the beginning of the 20th century the plant began to be used in America for recreational purposes, starting a process of questioning and persecution of its users, which culminated in the prohibition of its planting and consumption. Political and religious issues, prejudice, xenophobia, and competition with other industries and crops, such as tobacco and cotton, led to these bans[21]. Commissioned studies, using what is now called pseudoscience, have served as argument against the use of cannabis for any purpose, including medical[21].

However, Professor Raphael Mechoulan, an Israeli researcher, in 1963 isolated cannabidiol (CBD) and the following year the tetrahydrocannabinol (THC)[21]. Following this, the study[22] identified the first cannabinoid receptor (CB1) in mice and in the human brain. Four years later, the first endocannabinoids were isolated, baptized as anandamide, in reference to the Sanskrit term "ananda", which means "well-being"[23]. In the 1970s, in Brazil, Professor Elisaldo Carlini proved the efficacy of cannabinoids in reducing and controlling seizures[21].

Today, the ECS is understood as the set formed by some endogenous cannabinoids, the main ones being anandamide and 2-AG (2-Arachidonoylglycerol), and by CB1 and CB2 receptors, besides the enzymes that synthesize and degrade these endocannabinoids[1].

In 2013, there was Charlotte Figi's case, presented on national television in the United States, who had convulsions caused by Davet syndrome controlled by cannabinoids. This reopened the discussion about research and use of cannabinoids for medicinal purposes, being soon after regulated and released for use in 35 American states, as well as in several countries[21].

In Brazil, in the year 2015, the family of Anny Fisher, a girl with a rare form of epilepsy, obtained the first judicial release for cannabis use. This episode generated a documentary entitled "Illegal: life does not wait" (*Ilegal: a vida não espera*), which won international awards for presenting the families' struggle for the release of medical cannabis[21]. Also in 2015, the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*) removed cannabidiol from the prohibition list, approving in 2017 the first cannabis-based drug for multiple sclerosis treatment[21].

In 2019, the specific Resolution of the Collegiate Directorate (*Resolução de Diretoria Colegiada* - RDC) for importation and prescription of cannabinoids was published, updated on 03/30/2022, consolidating two previous resolutions, RDC 335/20 and RDC 570/21, which were revoked, making RDC 660/22 the current one in force. In its text, the resolution defines criteria and procedures for the importation of cannabis-derived products by individuals, for their own use, upon prescription by a health professional legally qualified in their class council[21].

ENDOCANNABINOID SYSTEM MECHANISM

Endocannabinoids and their receptors are found throughout the body (brain, connective tissues, glands, and immune system), performing different functions in order to modulate homeostasis. This system is responsible for the regulation of pain, inflammation, muscle control, metabolism, sleep, mood, thermoregulation, and memory, among others[21].

Researchers have recently identified two cannabinoid receptors: CB1 and CB2. The first is highly expressed in presynaptic neurons, spinal cord and dorsal root ganglia. The second in immune system and its structures (myeloid cells, macrophages, microglia,

lymphoid cells, and mast cells)[23,24]. CB receptors belong to G protein-coupled receptors family, physiologically activated by endocannabinoids, derived from the arachidonic acid, such as anandamide (AEA or N-arachidonoylethanolamine) and 2-Arachidonoylglycerol (2-AG). While AEA acts as a partial agonist of CB1 and CB2 cannabinoid receptors, 2-AG is a full agonist, primarily of CB1[25].

Production of endocannabinoids occurs in response to increased intracellular calcium concentration. While N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL) enzymes are involved in AEA and 2-AG production, respectively, the degradation of these endocannabinoids is mediated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) enzymes.

AEA also acts as a full agonist of transient receptor potential vanilloid subtype 1 (TRPV1) which are involved in synaptic regulation associated with the modulation of nociception and inflammation. Studies show that endocannabinoids can also regulate peroxisome proliferator-activated receptor gamma (PPARγ) and peroxisome proliferator-activated receptor alpha (PPARα), as well as G protein-coupled receptors, exerting neuroprotective and anti-inflammatory functions[26].

Although the human body produces its own cannabinoids, the system can be supplemented by exogenous FITs derived from plants such as cannabis, mainly sativa and indica species. Other plant species (*echinacea*, black pepper, black truffle, *helichrysum* species sunflower, cocoa, etc.) have also been used because they have cannabinoid-like compounds, called cannabimetics, which also act on the ECS[25-28].

Both CB receptor subtypes lead to inhibition of adenylate cyclase and, consequently, reduced formation of the intracellular messenger substance cyclic adenosine monophosphate (cAMP). CB1 receptors are activated by THC and CBD and are responsible for the local analgesic effect. The chemical structure and mechanism of action of THC and CBD are different. THC acts as an agonist for cannabinoid receptors and CBD acts as an antagonist[25].

However, some of the cannabinoid-mediated effects attributed to CBD may be due to its ability to inhibit endocannabinoid degradation via the fatty acid amide hydrolase (FAAH) enzyme. This in turn increases endocannabinoid levels, causing receptor activation, mainly by anandamide. Full agonism at serotonin 5-HT1A receptors and TRPV1 channels is responsible for anxiolytic and analgesic effects. Partial agonism at dopamine D2 receptors may explain the effect of CBD on memory processing by the ventral portion of the hippocampus. Another function described is the general inhibitory effect that CBD has on sodium and calcium channels, exerting a modulatory effect on the membrane electrical potential[26].

A third G55 protein-coupled cannabinoid receptor (GPR55) has been proposed, accounting for some effects attributed to cannabinoids that do not appear to be mediated by CB1 or CB2 receptors. A research[28] has shown that cannabinoid receptor agonists, such as CP55940, HU210 and Δ9-THC, can bind and signal in heterologous cells expressing FLAG-tagged human GPR55. As with its activity at CB1 or CB2 receptors, CBD appears to function as a GPR55 receptor antagonist. The physiological function of GPR55 is unclear, but it has been proposed that it plays a role in energy regulation, bone resorption, cancer and pain[29].

It is important to note that drugs acting on cannabinoid receptors and endocannabinoid regulatory enzymes are determined not only by their class, affinity, efficacy and potency, but also by the drug target's cellular compartmentalization[24].

INDICATIONS

In dentistry, there are several possible indications, such as orofacial pain, mucositis, awake bruxism, periodontitis, caries prevention, oral surgery, pulpitis and dental anxiety. Among them, chronic orofacial pain is the indication for which there is the most robust scientific evidence. The greatest advantage of using cannabinoids is the improvement in quality of life and a better benefit and safety profile compared to other drugs commonly used to control chronic pain, such as neuropathic pain[30].

Neuropathic pain (NP) is caused by an injury or disease of the somatosensory nervous system and is difficult to control. Although many studies have been conducted to evaluate the efficacy and mechanisms of action of cannabinoids and endocannabinoids in animal models of NP in body parts outside the orofacial region, there are few studies using orofacial pain models[31]. However, it is worth noting that the pharmacological therapy used to control NP is basically the same, regardless of the body site where it occurs, and cannabinoids have been considered a good option for orofacial NP control[32,33].

In trigeminal neuralgia secondary to multiple sclerosis there is a clinical case report in which the use of nabiximol, a cannabis extract in the form of oral spray, which contains CBD 2.5 mg + THC 2.7 mg/spray, 5 sprays/day for one year, practically eliminated trigeminal neuralgia[34]. In burning mouth syndrome (BMS), which is another type of NP, cannabinoids have the potential to contribute to treatment, considering their neuroprotective, anti-inflammatory, antioxidant and antiapoptotic properties[35].

BMS is associated with a burning sensation on oral mucosal surfaces with xerostomia, dysgeusia and tingling or paresthetic sensations, although patients do not have clinically evident causative lesions. In a pilot study, Bediol cannabis sativa extract oil, composed of 6.3% THC (63 mg per gram) and 8% CBD (80 mg per gram), was effective and well tolerated in patients with primary BMS when used orally for a period of 4 weeks, with a dose titration protocol starting with 5 drops twice daily for 5 days, followed by 10 drops twice daily for 5 days, 15 drops twice daily for 5 days, and finally 20 drops twice daily for 13 days[36]. However, new studies are needed, with a larger sample, randomized, double-blind, controlled and with different therapeutic approaches.

Cannabinoids are also indicated as adjuvant therapy in cancer patients, including head and neck cancer, early in treatment, due to their analgesic, opioid-sparing and antiemetic effect[37], which contributes to the reduction of chemotherapy-induced adverse effects and improved quality of life[38]. In oncologic patients, an analgesic base with dipyrone is recommended, since

its effect involves the activation of cannabinoid and opioid receptors[39,40], which may contribute to the reduction of the dose of cannabinoids and opioids[41], and consequently of their adverse effects.

One of the most common types of chronic orofacial pain is TMD, which affects the temporomandibular joint (TMJ) and associated muscles. Preclinical studies have suggested that different types of cannabinoids have the potential to reduce pain associated with joint and muscle TMD. For example, activation of type 1 cannabinoid receptor has been shown to reduce the nociceptive response in formalin test in the TMJ_{42} and the perioral region with analgesic efficacy similar to that of morphine and superior to that of indomethacin and ketamine[43].

Other studies have shown that the peripheral application of both THC[44] and the non-psychoactive PHYTs cannabidiol and cannabinol[29] promoted a reduction in masticatory muscle pain in preclinical experimental models, without central adverse effects. These promising results culminated in a translational research that demonstrated, through a randomized, double-blind, controlled clinical study, that the application of a cannabidiol cream (with a concentration of approximately 1.46%) twice a day for 14 days on the masseter muscle of patients with muscular TMD significantly reduced (70%) the intensity of myofascial pain quantified by the Visual Analogue Scale and promoted a slight reduction in muscle activity (approximately 10%), assessed immediately after the end of treatment. Therefore, the peripheral analgesic effect of cannabidiol is not secondary to muscle relaxation.

Bruxism is a non-functional activity of the chewing muscles, controlled by CNS, characterized by teeth clenching or grinding, which can occur during wakefulness (wake bruxism) or during sleep (sleep bruxism). The fact that anxiety increases its occurrence[45] and that cannabidiol has an anxiolytic effect[46] suggests that it has the potential to reduce bruxism. However, to date, in the scientific literature, there is only one clinical case report on the efficacy of cannabidiol on severe awake bruxism, in a patient with fronto-temporal degeneration accompanied by psychiatric, behavioral and cognitive changes[47]. In this specific case, the patient was treated with a capsule containing 4.8 mg CBD and 0.31 mg THC taken in the morning. Although the effect of cannabinoids in bruxism treatment is promising, more studies are needed to prove their efficacy.

Some indications of cannabinoids in dentistry are related to their inflammation modulating and regenerative properties and include oral ulcers, mucositis, periodontitis and dental surgeries. In a randomized controlled clinical trial of patients with oral ulcers, topical application of a 0.1% CBD oral paste 3 times daily for 7 days reduced the extent and accelerate healing of oral ulcers without adverse effects[48]. Oral mucositis is a common complication during chemotherapy, characterized by ulceration, mucosal atrophy and tissue necrosis, which seriously interferes with the patients' nutritional intake and oncotherapy procedures. Although evidence is limited, the antioxidant and anti-inflammatory properties of cannabidiol suggest that it may be used in the treatment of oral mucositis[49] as demonstrated in preclinical studies[50,51] and on the healing of oral ulcers[48].

In periodontitis, randomized, placebo-controlled clinical trials have not been published to date, which represents a major challenge in terms of a realistic assessment of the effectiveness of cannabinoids, such as cannabidiol, in prophylaxis and treatment of periodontal inflammation[52]. However, the results of preclinical studies are promising and suggest that cannabinoids indeed have the potential to contribute to the treatment of periodontitis. PHYTs exhibit anti-inflammatory properties as demonstrated in a gingival fibroblast culture model[53] and cannabidiol has been shown to reduce alveolar bone loss in an experimental model of periodontitis[54]. In addition, cannabinoids exhibit antimicrobial properties that may contribute to the prevention of periodontitis and the preventive treatment of dental caries. For example, cannabinoid-infused mouthwashes (CBD, CBG) were as effective as 0.2% chlorhexidine in decreasing the bacterial content of dental plaque samples[55]. In addition, CBG has been shown to have dual antibacterial and antiplatelet activity on streptococcus mutans[56] via multiple mechanisms of action[57,58].

Some studies with synthetic cannabinoids have not shown analgesic efficacy in post-extraction third molar pain. However, in one of the studies, a single dose of the synthetic CB1/CB2 receptor agonist AZD1940 (800 μg) was used, which has an exclusively peripheral action[59], which may explain the analgesic failure. Another study also used a single dose, at this time of the synthetic CB2 receptor agonist GW842166 (100 or 800 mg)[60], suggesting that CB2 receptor activation alone is not sufficient to control acute postoperative pain.

Therefore, it is important to remember that "cannabinoid" is a broad term and before drawing erroneous conclusions about its efficacy in scientific studies it is important to consider the composition of the product, the route of administration, the dose and the duration of treatment, since all these variables influence the therapeutic outcome. In this context, it can be stated that PHYTs have the potential to be used as adjunct therapy in cases of oral and maxillofacial surgeries[61] and in implant dentistry due to their analgesic, anti-inflammatory, anxiolytic, antimicrobial and regenerative properties, contributing to a better quality of life and tissue regeneration during postoperative period. In bone tissue, cannabidiol stimulates bone regeneration[62] by increasing migration of mesenchymal stem cells to the site of injury and their differentiation into osteoblasts[63].

Cannabidiol has also been seen as a potential therapeutic target in treatment of pulp vitality. For example, low-dose cannabidiol has been shown to stimulate the proliferation of dental pulp cells and the migration and differentiation of these cells into odontoblasts[64], and to have an anabolic effect in both basal and inflammatory situations[65], suggesting a possible application of CBD in regeneration of oral tissues, including dentin/pulp and bone. Results from *in vitro* studies were promising and studies using dentin/pulp and bone regeneration models should soon confirm the anabolic role of CBD in these tissues.

Cannabinoids also have the potential to reduce anxiety and stress associated with dental procedures. A systematic review of the literature demonstrated that CBD has anxiolytic effects in healthy patients and those with social anxiety disorder[46].

CONTRAINDICATIONS

Before prescribing cannabinoids, it is important to know their contraindications, which vary depending on product composition. The contraindications associated with medical cannabis are more closely linked to THC, but products with a predominant CBD composition may contain THC.

THC is contraindicated for patients with a personal history or strong family history of bipolar disorder or schizophrenia, due to the increased risk of early onset of psychosis in those already at risk of developing schizophrenia[66], for patients with angina, and with a history of myocardial infarction or unstable cardiovascular disease, as THC can cause tachycardia and postural hypotension[67].

THC and CBD are contraindicated for patients with hepatitis C due to the risk of fibrosis/steatosis progression and for pregnant and breastfeeding women[66].

PHARMACOLOGICAL INTERACTIONS

Cannabis is metabolized in the liver by CYP 450 isoenzymes and is believed to be relatively safe when used with the vast majority of drugs. CBD is predominantly metabolized by CYP2C19 and CYP3A4 enzymes, and THC is predominantly oxidized by CYP2C9, CYP2C19 and CYP3A4 enzymes[68,69]. Therefore, drugs that act as inhibitors or inducers of these enzymes may increase or reduce, respectively, the serum levels of these cannabinoids through pharmacokinetic drug interactions.

Although both THC and CBD can affect CYP enzymes and, consequently, serum levels of other drugs metabolized by these enzymes, in many cases the relevance of experimental findings is not clinically significant. CBD and THC can also inhibit or stimulate the drug transporter P-glycoprotein[70]. Caution should be exercised with the use of oral anticoagulants together with drugs that inhibit the CYP3A4 enzyme and P-glycoprotein, such as medical cannabis; also with anticoagulants such as XARELTO® (rivaroxaban), warfarin and clopidogrel, and with drugs metabolized by CYP 2C19 enzyme, such as norclobazam (clobazam active metabolite)[71].

In contrast to pharmacokinetic interactions, pharmacodynamic interactions are more common with combined sedation, being observed with several central nervous system depressant drugs such as alcohol, antidepressants, antipsychotics, antiepileptics, benzodiazepines and opioids. However, cannabinoids can be used with benzodiazepines and opioids in order to reduce the dose of these drugs that have much more important side effects[66].

In any case, it is recommended to start treatment with low doses of cannabinoids and gradually increase the dose until the desired therapeutic effect is achieved without possible adverse effects[69].

ADVERSE EFFECTS

Adverse effects are most often dependent on the dose of THC and dissipate over time through tolerance. The most common include drowsiness/fatigue, dizziness, xerostomia, nausea, effects on cognitive function and deficits in motor function. However, they can be avoided, or at least mitigated, by starting therapy at a low dose and slow titrating. Many of these effects can be controlled with adjustments to administration factors such as product composition, dose and route of administration[69]. Randomized controlled trials and clinical studies on the adverse effects of CBD are almost all in patients with rare forms of epilepsy, using very high doses of 5-20 mg/kg daily. The most serious adverse effect in these cases was elevation of liver enzymes (i.e. alanine transaminase, aspartate aminotransferase and gamma-glutamyl transferase). However, CBD dosing regimens in other conditions, such as chronic pain, are much lower than this, with a recommendation of approximately 40 mg/day accompanied by a very favorable safety profile[71].

ENTOURAGE EFFECT

Although CBD and THC are the most studied phytocannabinoids, cannabis plant contains more than 100 PHYTs, in addition to terpenes, flavonoids, vitamins and pigments. While synergy indicates that two or more active compounds of the plant can produce a combined effect greater than their separate individual effects, the potentiation of one compound's biological effect by inactive compounds in combination has been termed "entourage effect"[72].

Cannabis-based drugs exert their effects by interacting with the ECS present in the body, which as already described consists of endocannabinoids, the enzymes responsible for their synthesis and degradation, and cannabinoid receptors. For example, 2-acyl-glycerols are inactive compounds found in the cannabis plant that increase the effect of 2-AG endocannabinoid by decreasing its degradation, representing a new mechanism of endogenous cannabinoid activity molecular regulation, which favors the therapeutic effect of cannabis extract. The advantage of the synergistic effect and entourage effect is that, thanks to it, the plant extract has greater efficacy, tolerability and patient preference, attributed to combinations of cannabinoids and other components present in the cannabis plant.

For example, it has been shown in patients with intractable cancer pain that the predominantly THC extract was not effective, while the full plant extract with THC and CBD was effective in pain control[73]. Animal studies focusing on analgesia have also shown a greater response of a full-spectrum cannabis extract compared to pure CBD[74]. Considering that the analgesic efficacy of full-spectrum products is superior to the effect of isolated compounds, they are the most indicated for chronic pain management.

CONCLUSION

The more knowledge is acquired about the ECS and the therapeutic benefits of cannabis components and derivatives, the more there is a conviction about the emergence of a new therapeutic frontier. The growing number of good outcomes, including cases of chronic orofacial pain, obtained through well-conducted studies, brings a mixture of satisfaction and excitement. However, it is important to always be in touch with the best available

evidence, so that it is possible to offer safe and effective therapy. Encouraging research, combined with adequate prior training in orofacial pain, is essential. No therapy will achieve good results without an accurate diagnosis. Thus, it is of paramount importance to comprehend the ECS, the products and derivatives of the plant, synthetic cannabinoids, their indications and effects.
It is also essential to understand a new way of thinking therapeutically, because when cannabinoids are used, individualization is the key word for therapeutic success, not only in orofacial pain. New studies are needed and, at this moment, it can be said that the prospects are very good and a new and challenging horizon is emerging.

AUTHORS' CONTRIBUTION

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