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Efficacy and Safety Study of Medicinal Cannabis in Migraine: a Literature Review

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Abstract. Migraine is a multifactorial disease that affects adults aged 22 to 55 years; the most common symptoms are severe to moderate, unilateral, pulsating pain. It may or may not be accompanied by nausea, vomiting, photophobia, and phonophobia. In addition, these symptoms persist for 4 to 42 hours. Currently, the search for alternative therapies for the management of migraine pain, such as the use of medicinal cannabis, has grown due to the undesirable side effects of conventional therapy and due to the legalization of medicinal cannabis in the United States. Therefore, the objective of this study was to conduct a literature review to evaluate the efficacy and safety of the use of medicinal cannabis, that is, medicinal marijuana as an alternative treatment for migraine. The methodology used in this research was an exploratory search for narrative review and systematic review articles through the MEDLINE (PubMed), LILACS (BVS Salud), Scielo and Google Scholar databases. The following keywords were used to conduct these searches: adults, migraine, efficacy, safety and medicinal cannabis. The results obtained by research were that treatment with medicinal cannabis helped in the reduction and frequency of migraine attacks, and its adverse effects were drowsiness, dizziness, vertigo, cough, dry mouth, dry eyes, anxiety and feeling of imbalance. It is concluded that the use of medicinal cannabis for the treatment of migraine can be effective and safe; however, more clinical studies are still needed. It was observed in the studies listed in this review that the adverse effects of medicinal cannabis are mild and tolerable by patients.

Keywords: Pathophysiology. Medicinal Cannabis. Migraine. Efficacy. Safety.

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Estudo de Eficácia e Segurança da Cannabis Medicinal na Enxaqueca: uma Revisão da Literatura

Resumo. A enxaqueca é uma doença multifatorial que acomete a população adulta na faixa etária dos 22 a 55 anos; os sintomas comumente observados são dor de gravidade intensa a moderada, unilateral, de qualidade pulsátil. Ela pode ser acompanhada ou não de náusea, vômito, fotofobia e fonofobia. Além disso, estes sintomas persistem de 4 a 42 horas. Atualmente, tem crescido a busca por terapias alternativas para o manejo da dor da enxaqueca, como o uso da cannabis medicinal, devido aos efeitos colaterais indesejados da terapia convencional e devido à legalização da cannabis medicinal nos Estados Unidos. Logo, o objetivo deste estudo foi realizar uma revisão da literatura para avaliar a eficácia e segurança do uso da cannabis medicinal, isto é, a maconha medicinal como um tratamento alternativo

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para enxaqueca. A metodologia utilizada nesta pesquisa foi a busca exploratória por artigos de revisão narrativa e revisão sistemática através das bases de dados MEDLINE (PubMed), LILACS (BVS Salud), Scielo e Google Acadêmico. Para a realização destas buscas foram utilizadas as palavras-chave: adultos (adults), enxaqueca (migraine), eficácia (efficacy), segurança (safety) e cannabis medicinal (marijuana medicinal). Os resultados obtidos pela pesquisa foram que o tratamento com a cannabis medicinal ajudou na redução e frequência dos ataques de enxaqueca e seus efeitos adversos foram sonolência, tontura, vertigem, tosse, boca seca, olhos secos, ansiedade e sensação de desequilíbrio. Conclui-se que o uso da cannabis medicinal para tratamento da enxaqueca pode ser eficaz e seguro; contudo, ainda são necessários mais estudos clínicos. Foi observado nos estudos elencados nesta revisão que os efeitos adversos da cannabis medicinal são leves e toleráveis pelos pacientes.

Palavras-chave: Fisiopatologia. Cannabis Medicinal. Enxaqueca. Eficácia. Segurança.

Estudio de Eficacia y Seguridad del Cannabis Medicinal en la Migraña: una Revisión de la Literatura

Resumen. La migraña es una enfermedad multifactorial que afecta a la población adulta entre 22 y 55 años; los síntomas comúnmente observados son dolor severo a moderado, unilateral y de tipo pulsátil. Puede o no estar acompañado de náuseas, vómitos, fotofobia y fonofobia. Además, estos síntomas persisten durante 4 a 42 horas. Actualmente, la búsqueda de terapias alternativas para el manejo del dolor de la migraña, como el uso de cannabis medicinal, ha crecido debido a los efectos secundarios no deseados de la terapia convencional y también debido a la legalización del cannabis medicinal en Estados Unidos. Por tanto, el objetivo de este estudio fue realizar una revisión de la literatura para evaluar la eficacia y seguridad del uso del cannabis medicinal, es decir, la marihuana medicinal como tratamiento alternativo para la migraña. La metodología utilizada en esta investigación fue una búsqueda exploratoria de artículos de revisión narrativa y revisión sistemática a través de las bases de datos MEDLINE (PubMed), LILACS (BVS Salud), Scielo y Google Scholar. Para realizar estas búsquedas se utilizaron las siguientes palabras clave: adultos, migraña, eficacia, seguridad y cannabis medicinal. Los resultados obtenidos por la investigación fueron que el tratamiento con cannabis medicinal ayudó a reducir la frecuencia de los ataques de migraña y sus efectos adversos fueron somnolencia, mareos, vértigo, tos, sequedad de boca, ojos secos, ansiedad y sensación de desequilibrio. Se concluye que el uso de cannabis medicinal para el tratamiento de las migrañas puede ser efectivo y seguro; sin embargo, aún se necesitan más estudios clínicos. Se observó en los estudios enumerados en esta revisión que los efectos adversos del cannabis medicinal son leves y tolerables por los pacientes.

Palabras clave: Fisiopatología. Cannabis Medicinal. Migraña. Eficacia. Seguridad.

INTRODUCTION

Migraine is a multifactorial neurovascular disorder that typically occurs in the age group of 22 to 55 years, with a prevalence of occurrence in the female population (Rajapakse, L. *et al*., 2019). “In the US and world populations, prevalence of migraine is two to three times higher in women” (Ahmad, Sarah R. *et al*., 2022). In addition, women are more likely to have disability related to grade IV headache, according to the Migraine Disability Questionnaire Assessment – MIDAS (Ahmad, Sarah R. *et al.*, 2022).

The Migraine Disability Assessment Questionnaire (MIDAS), as illustrated in Table 1, assesses the disability associated with migraine through questions that assess the number of days missed from work, school or reduced productivity at school, home or work. Through this data points are given for each day missed; at the end of the questionnaire the points are added up, and this sum of points reflects a degree of severity (Manson, Kofi Frimpong. *et al.*, 2024).

Table 1 – Migraine Disability Assessment Questionnaire (MIDAS)

1. How many days in the last 3 months have you missed work or school because of your headaches?		
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches?		
3. How many days in the last 3 months have you not done household chores because of your headaches?		
4. How many days in the last 3 months has your productivity in housework reduced by half or more because of your headaches?		
5. How many days in the last 3 months have you missed family, social or other activities? professionals because of their headaches?		
A- How many days in the last 3 months have you had a headache?		
B- On a scale of 0 to 10, how painful were these headaches on average?		
Grade I	Little or no disability	0 – 5 points
Grade II	Mild disability	6 – 10 points
Grade III	Moderate disability	11 – 20 points
Grade IV - A	Severe disability	21 – 40 points
Grade IV - B	Very severe disability	>40 points

Source: MANSON; KOFI FRIMPONG, *et al.*, 2024.

Migraine is a disease that can be considered a public health problem because it affects 58.2% of the world's population, thus affecting 1.16 billion people; and is considered the third leading cause of years lived with worldwide disability (Zhao, Yine Shaoru. *et al.*, 2024). “In Brazil, it is estimated that the prevalence of migraine is 15.8% of the population.” (Nacazume, Jéssica. 2019).

Migraine is characterized by the appearance of a headache moderate to severe intensity, lasting 4 to 72 hours, with unilateral location and pulsatile. It may be accompanied by nausea or vomiting and photophobia (which is the aversion to light) or phonophobia (which is the aversion to sound). In addition, it can manifest itself with an aura or without an aura (Sherpa, Mingma L. *et al*., 2022). Chronic migraine is defined as having a headache for at least 15 days a month or for three months, with at least eight days per month with headache characteristics (INTERNATIONAL HEADACHE SOCIETY, 2018).

Cannabis has been used throughout time for medicinal and recreational purposes by adults (Poudel, Sujan. *et al*., 2021). Around 800 AD, it was used via intranasal in the treatment of migraine by Arabs; its use is described in the first Arab list of medicines, Al-Agrabadhin Al-Saghir (Duarte, Robert A. *et al*., 2021).

Cannabis has been used to treat acute pain, anxiety, aches and pains oncological conditions, depression, chronic pain and headaches. It can be extracted from three plant species: *Cannabis indica*,

Cannabis ruderalis and *Cannabis sativa. Cannabis sativa* is popularly known as marijuana and has more than 400 constituents (Poudel, Sujan. *et al.*, 2021). Its main constituents' active chemicals are ÿ9-tetrahydrocannabinol (THC), cannabidiol (CBD), flavonoids and terpenes. They can act on the endocannabinoid system, reducing the nociception and frequency of migraine symptoms (Santiago, Natally Marques. *et* al., 2023). Terpenes are believed to be involved in the on of the anti-inflammatory and analgesic properties of cannabis (Zahra, SMN. *et* al., 2023).

THC concentration is higher in *C. sativa* and lower in *C. ruderalis* (Rajapakse, L. *et al*., 2019). Therefore, this happens due to the type of cannabis species, soil, climate, cultivation technique (harvest season and time), and efficiency of the process of drying and preparing the extracts that formed the plant drug to be used in pharmaceutical forms.

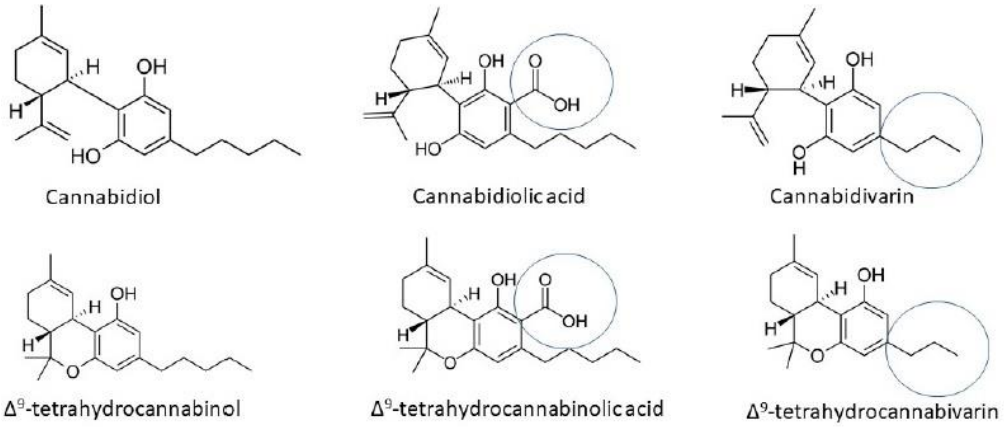
In recent years, the number of research studies involving medicinal cannabis *(*MC*)* has grown due to the search for alternative therapies for pain management due to the undesirable effects of conventional therapy for the treatment of migraine and due to the legalization of MC for medicinal use in the United States (Mechtler, Laszlo L. *et al.*, 2021; Okusanya, Babasola O. *et al.*, 2022). Therefore, the pharmacist can contribute to conducting studies that evaluate the efficacy and safety of medicines produced from medicinal cannabis.

The aim of this study was to conduct a literature review to assess the efficacy and safety of the use of MC, that is, medical marijuana as an alternative treatment for migraine. In addition, we sought to understand. What is the pathophysiology of migraine, its triggering factors, symptoms and stages of the disease, as well as what is the probable mechanism of action of *Cannabis sativa* for this disease.

THEORETICAL FRAMEWORK

In this theoretical framework, the pathophysiology and symptomatology of migraine will be presented. In addition, presentation of the possible mechanism of action of some phytocannabinoids, such as CBD and THC (figure 1), in migraine.

Figure 1. Structures of the main phytocannabinoids



Source: STASIÿOWICZ-KRZEMIEÿ, ANNA. *et al*., 2024.

PATHOPHYSIOLOGY OF MIGRAINE

The vascular theory was proposed by Graham and Wolff, it was the first postulate that attempted to explain the pathogenesis of migraine. It was proposed that serotonin released by platelets into blood vessels was the causal molecule. Node However, after the reuptake or metabolization of serotonin, the blood vessels previously contracted, they dilate and produce headaches (Shibata, Yasushi., 2022). According to Iversen *et al.* (1989 apud Manson; Kofi Frimpong, *et al*., 2024), the oxide nitric oxide is a potent vasodilator; it is one of the main contributors to maintenance of vascular theory.

According to Shibata Yasushi (2022), the trigeminovascular theory was proposed by Moskowitz. According to this theory, it was believed that trigeminal nerve stimulation causes vascular dilation and neurogenic inflammation. When this pathway is activated, there is a release of neuropeptides, such as peptide related to gene of calcitonin (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), at the level of the dura mater (Puledda, Francesca. *et al.,* 2023). These neuropeptides are responsible for causing neurogenic inflammation and consequently onset of headache (Kuburas, Adisa. *et al.*, 2023).

According to the neurovascular theory, the hypothalamus is the site of origin of the attack of migraine. It is responsible for stimulating the trigeminal nucleus caudalis, which in turn stimulates the trigeminal ganglion. In light of this activation, CGRP is released from trigeminal C fibers that surround the pial and dural vessels and, through interaction with the receptors themselves, leads to dilation of the meningeal vessels and nociception (Biscetti, Leonardo. *et al*., 2021).

Recent studies report that the orexinergic system, which is known to regulate arousal and nociceptive processing, as well as, thermoregulation and autonomic functions is involved with the attacks and/or sustaining of migraine (May, Arne. *et al.,* 2020).

It is believed that the glymphatic system could be involved in the pathogenesis of migraine. However, its mechanism of action has not yet been fully elucidated. However, there are three potential hypothetical mechanisms: neuroinflammation, calcitonin gene-related peptide (CGRP) dysregulation and depression of cortical spreading (Vittorini, Maria Grazia. *et al*.,2024).

Mast cell degranulation also contributes to appearance of migraine because it causes vasodilation and sensitization of trigeminal ganglion, consequently activating nociceptive pathway of trigeminovascular system (Biscetti, Leonardo. *et al*., 2023; Manson, Kofi Frimpong. *et al.*, 2024; D'agnano, Daniela. *et al*., 2024).

SYMPTOMS OF MIGRAINE

Migraine manifests itself in two ways: migraine with aura and without aura (Khan, Johra. *et* al., 2021). When it occurs without an aura, it is characterized by the presence of two of the following symptoms: headaches of moderate to severe intensity, one-sided, throbbing pain, it is aggravated by routine activities, such as walking or climbing stairs. In addition, the patient presents the following symptoms: nausea or vomiting and photophobia or phonophobia. The duration of the symptoms is 4 to 72 hours in the absence of treatment or ineffectiveness of therapy (INTERNATIONAL HEADACHE SOCIETY, 2018).

Migraine with an aura is manifested by the appearance of one or more of the following symptoms: visual, sensory, motor, retinal and language disturbances or speech. In addition, aura symptoms may manifest gradually within 5 minutes, with two or more symptoms occur in succession; each aura symptom lasts from 5 to 60 minutes; one of the symptoms is unilateral, the aura may be accompanied or followed within 60 minutes by a headache; and your symptoms may be positive (INTERNATIONAL HEADACHE SOCIETY, 2018).

MECHANISM OF ACTION OF PHYTOCANNABINOIDS IN MIGRAINE

The endocannabinoid system is currently believed to mitigate migraine through several glutamatergic, inflammatory, opiate and serotonergic mechanisms both centrally and peripherally (Tassorelli, Cristina. *et al.*, 2019; Poudel, Sujan. *et al*., 2021). This system is responsible for modulating the pain, sleep, mood, and memory among other functions. Peripherally, the endocannabinoids may affect immune-mediated neuroinflammation trigeminovascular in the meninges through its stabilizing effect on mast cells (Tassorelli, Cristina. *et al.*, 2019).

"The endocannabinoid system consists of receptors (CB1 and CB2), ligands of endogenous endocannabinoid receptors (endogenous cannabinoids) N- arachidonoylethanolamide (anandamide or AEA) and 2-arachidonoylglycerol (2-AG) and degradation enzymes" (Santiago, Natally Marques. *et al*., 2023).

CB1 receptors are expressed in the hypothalamus, nerve terminals peripheral and central presynaptic systems; CB2 appears mainly in hematopoietic and immunological systems. Studies indicate that endocannabinoids inhibit the trigeminovascular nociceptive processing and affect serotonin in neurons in the dorsal raphe nucleus of the brainstem (Duarte, Robert a. *et al.,* 2021).

Other studies indicate that migraine is caused by a deficiency of endocannabinoids (Duarte, Robert A. *et al.,* 2021). and that inflammation observed in these patients is caused by excessive platelet activity (Santiago, Natally Marques. *et* al., 2023). In addition, cannabinoids inhibit the release of 5HT from platelets during migraine. In migraine patients, anandamide levels are decreased in the cerebrospinal fluid, and CGRP and nitric oxide are higher when compared with patients without migraine (Santiago, Natally Marques. *et al*., 2023). However, endocannabinoids may have a vasoconstrictor effect by inhibiting vasodilation caused by CGRP in dural vessels (Tassorelli, Cristina. *et al.,* 2019).

THC is a psychoactive compound that acts as a partial agonist of CB1 and CB2 receptors; therefore, it acts by binding to the same site as AEA and 2-AG (Zorrilla, Erik. *et al.,* 2024). Its properties are antiemetic, analgesic, antioxidant and immunosuppressant (Duarte, Robert A. *et al.,* 2021). In addition, it also acts on opioid receptors and GPR55 (Mechtler, Laszlo L. *et al*., 2021). Studies show that in high doses it acts as a dopamine agonist (Sherpa, Mingma L. *et al*., 2022).

CBD acts primarily as a negative allosteric modulator in CB1 receptor and acts on the CB2 receptor as a partial agonist (Zorrilla, Erik. *et al.*,2024; Duarte, Robert A. *et al.,* 2021). At very high concentrations this phytocannabinoid acts on CB1 receptor by making orthosteric bonds; on the other hand, in normal concentrations it does not activate CB1 receptor by itself. Therefore, the combination of CBD and THC can reduce psychotropic effects of THC (Zorrilla, Erik. *et al.,* 2024).

Additionally, CBD appears to be involved in the modulation of receptors 5HT1 (anxiolysis), ion channels, cyclooxygenase and lipoxygenase cycle (Duarte, Robert A. *et al.,* 2021). When this phytocannabinoid acts on the 5HT1 receptor, it promotes anxiolysis, and when it acts on COX, it promotes anti-inflammatory. Other research has shown that this phytocannabinoid and terpenes are involved in analgesia.

One of the ionotropic effects of CBD is the stabilization of the lipid membrane connected to sodium channels due to decreased current. CBD can act as an agonist of the G glycoprotein-coupled receptor 55 (GPR55), promoting increased inhibition of neural transmission and consequentlyng as an

anticonvulsant. In addition, this effect promotes a feeling of calm in brains of patients suffering from migraines and seizures (Mechtler, Laszlo L. *et al*., 2021; Sherpa, Mingma L. *et al*., 2022).

CBD may reduce inflammatory and neuropathic pain by acting on the serotonin receptor 1A (5-HT1A) and TRPV1 channels; it also suppresses the release of cytokines and chemokines, decreases the production of reactive oxygen species, and modulates the immune system (Tassorelli, Cristina. *et al.*, 2019).

THC-GPR55 interaction increases intracellular calcium, increases excitatory neuronal signaling and may have pronociceptive effects at certain doses. Both THC and CBD interact with the opioid receptor promoting signaling opioid receptors; this decreases the unwanted effects of opioids, such as depression respiratory and opioid abuse. Furthermore, repeated exposure to CBD in low doses increases the firing of 5-HT (increases available serotonin), producing anxiolytic and antinociceptive effects. Due to the lipophilic nature of this phytocannabinoid, it interacts directly with cell membranes, maintaining sodium channels closed and inactivated, inhibiting ionic and excitatory conduction of electrical signals from neuronal to synaptic terminals; thus, they mimic sodium channel blockers, commonly used in the prophylactic treatment of migraine, including amitriptyline and topiramate (Mechtler, Laszlo L. *et al*., 2021).

METHODOLOGY

An exploratory search for review articles was carried out through the databases MEDLINE (PubMed), LILACS (BVS Salud), Google Scholar and Scielo. Searches were performed in these databases using the descriptors in English according to MeSH medical terms – adults, efficacy, safety, migraine and marijuana medicinal. The filters used during the searches were articles published in the period from 2019 to 2024, Portuguese or English language, free articles, reviews and systematic revisions. In addition, the following boolean operators were used AND and OR.

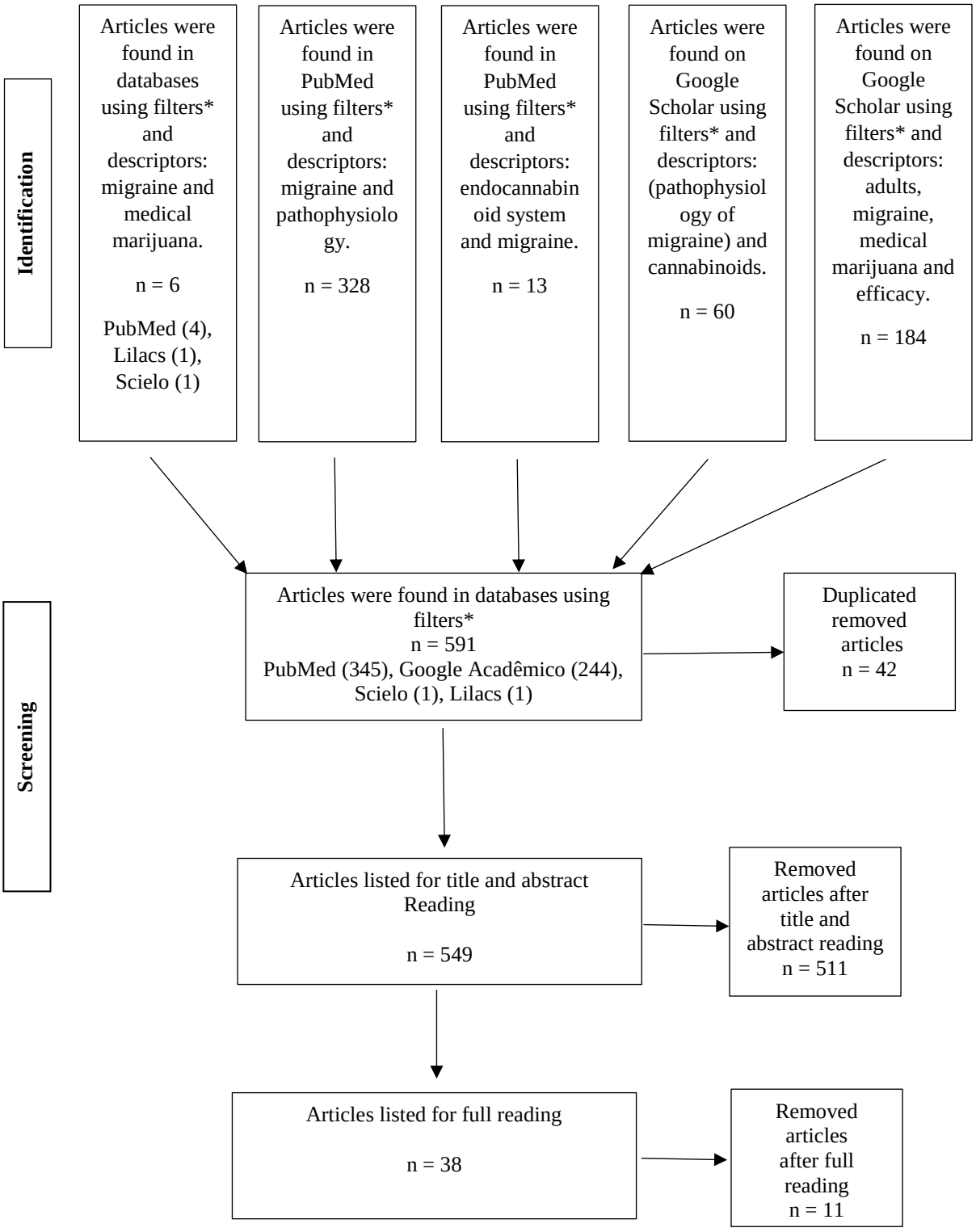
Inclusion factors were articles reporting patients diagnosed with migraine between the ages of 18 and 60 who received treatment with marijuana medicinal and articles published in English and Portuguese. Exclusion factors were duplicate publications, paid publications and those that were not related to the topic, such as pediatric population, migraine cluster type and tension migraine.

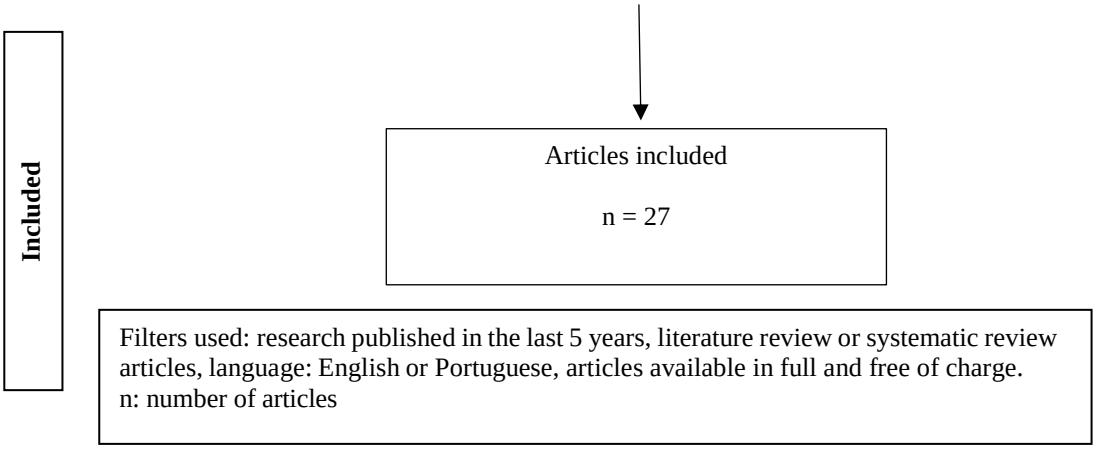
The studies were initially screened by reading the title and abstract. Articles that were in accordance with the theme and eligibility criteria of this research were listed for reading in full. After reading the full articles, the included studies had their data extracted.

RESULT AND DISCUSSION

After removing duplicates, searching the PubMed databases, Lilacs, Scielo and Google Scholar returned 549 articles. After reading titles and abstracts, 38 articles were listed in this review for full reading. Of these studies, only 27 were included for extraction. The flowchart 1 illustrates how the research has been done and their results.

Flowchart 1. Database and research results





Source: own authorship, 2024.

Symptoms of Migraine

Migraine can manifest itself in two ways: without aura and with aura. Symptoms of migraine without aura are unilateral, pulsating pain, worsening of pain with physical activity and moderate or severe intensity. Besides, others symptoms that some patients present are nausea or vomiting, photophobia or phonophobia; headache usually lasts 4 to 72 hours if left untreated or ineffectiveness of treatment. In addition, aura symptoms are visual, sensory, motor, retinal or language; these symptoms appear within 5 minutes and can last from 5 to 60 minutes. Patients may present only symptoms headache without aura or manifest headache with aura (INTERNATIONAL HEADACHE SOCIETY, 2018; Braga, Maria Izabel. 2024).

Pathophysiology of Migraine

The pathophysiology of migraine involves the trigeminal pathway, hypothalamic pathway, thalamus, cortex, neuropeptides, nitric oxide and interleukins. Migraine begins due to an imbalance in the homeostasis of the hypothalamus (Shibata, Yasushi. 2022); this sensitizes the trigeminal system via the dopaminergic pathway and produces the sensation of pain. Pathways of the trigeminal system when active produce neuropeptides, such as CGRP and PACAP, resulting in neurogenic inflammation, which generates vasodilation and protein leakage, and consequently headache (Puledda, Francesca. *et al.*, 2023; Biscetti, Leonardo. *et al.*, 2023).

Furthermore, studies indicate that in hypothalamus region there is system orexinergic which is responsible for migraine attacks and/or maintenance (May, Arne. *et al.*, 2020). The occipital cortex is associated with visual symptoms of migraine such as light sensitivity, visual aura and visual snow (Puledda, Francesca. *et al.*, 2023).

According to Kuburas, Adisa. *et al.* (2023), CGRP receptors can be found in neurons of the trigeminal ganglia and satellite glia, in these locations this neuropeptide causes peripheral sensitization of migraines. PACAP can be found in the extracranial parasympathetic sphenopalatine ganglion and when it stimulates this pathway, it causes autonomic symptoms of migraine. And then, this author found studies that indicate that fibers containing CGRP from the trigeminal ganglia connect within ganglia sphenopalatine. Therefore, he suggested the hypothesis of interaction between system sphenopalatine and trigeminal. Also, this author also suggested that within meninges, CGRP and PACAP may contribute to neuroinflammation.

According to Vittorini, Maria Grazia. *et al.* (2024), another mechanism discovered recently that could explain pathogenesis of migraine is impairment of glymphatic system involving neuroinflammation, excess CGRP and depression cortical spreading. However, these authors found conflicting results in the studies involving the pathophysiology of migraine and this system in studies with humans. Therefore, more studies involving this topic are needed.

Migraine can become chronic when there is prolonged activation of the trigeminovascular pathway due to the increase in neuropeptides such as CGRP. Furthermore, PACAP may be elevated during migraine and appear to induce vasodilation of the middle cerebral and superficial temporal arteries in patients with migraine. Nitric oxide contributes to the vasodilation of meningeal vessels and sensitizes trigeminal fibers (Biscetti, Leonardo. *et al.*, 2023). Therefore, understanding how these neuropeptides and nitric oxide work in patients with migraine compared to healthy patients can help in development of potential drugs against this disease.

Mechanism of Action of Medicinal Cannabis in Migraine

Research suggests that the endocannabinoid system mitigates migraines through various pathways of central and peripheral nervous systens. Its main receptors are CB1 and CB2; CB1 receptors can be found in hypothalamus, peripheral and central nerve terminals, while CB2 receptors are found in hematopoietic and immunological system. Its main endogenous endocannabinoid ligands are anandamide and 2-arachidonoylglycerol. Endocannabinoids can affect trigeminovascular system-mediated neuroinflammation in meninges through their mast cell stabilizing effect (Tassorelli. *et al*., 2019; Poudel, Sujan. *et al.*, 2021; Duarte, Robert A. *et al.*, 2021; Santiago, Natally Marques. *et al.*, 2023).

Medicinal cannabis contains phytocannabinoids that act on endocannabinoid system, some of which are THC and CBD. THC is a partial agonist of CB1 and CB2 receptors (Zorrilla, Erik. *et al.*, 2024; Frimpong-Manson *et al.*, 2024); it also acts on GPR55 receptor increasing the influx of calcium into the

intracellular environment, thus generating an increase in neuronal signaling and effect pronociceptive. Both THC and CBD act on opioid receptors, increasing signaling of them, as consequence, it decreases the side effects and unwanted effects of opioids (Mechtler, Laszlo L. *et* al., 2021). A study pointed out that this phytocannabinoid may help decrease cortical spreading depression, and consequently, headache was reduced (Tassorelli, Cristina. *et al*., 2019).

CBD acts on the allosteric site of CB1 receptor and on CB2 receptor, it acts as a partial agonist (Duarte, Robert A. *et al.*, 2021; Zorrila, Erik. *et al.*,2024; Braga, Maria Izabel. 2024). In addition, it acts on 5HT1 and GPR55 receptors, ion channels and cyclooxygenase cycle. When it acts on 5HT1 receptor and TRPV1 channels, it promotes the reduction of pain resulting from neuroinflammation and decrease in anxiety; when it acts on cyclooxygenase cycle, it promotes anti-inflammatory effects. When it acts on GPR55 receptor it promotes increased neural transmission and anticonvulsant effect (Tassorelli, Cristina. *et al*., 2019; Duarte, Robert A. *et. al.*, 2021; Mechtler, Laszlo L. *et al.*, 2021; Sherpha, Mingma L. *et al.*, 2022).

Furthermore, due to the lipophilic nature of CBD, it can act almost as in the same way as sodium channel blockers commonly used in migraine prophylaxis; it acts on sodium channels inhibiting ionic conduction and excitatory transmission of neuronal electrical signals to synaptic terminals; therefore, it reduces the pain caused by migraine (Mechtler, Laszlo L. *et al.*, 2021).

Efficacy of Medicinal Cannabis in The Treatment of Migraine

In 2022, Sherpa, Mingma L. *et al.* conducted a literature review using systematic reviews for analyze efficacy, safety, dose and side effects of using medical marijuana (MM) for treatment of migraines. They found that MM contributes to the reduction of frequency and intensity of migraine. In addition, they found research conducted by Aviram *et al.* in 2020, which said that migraine patients who started using MM decreased the use of traditional medications used for chronic pain, such as opioids.

In 2021, Poudel, Sujan. *et al.* conducted a literature review study whose objective was to identify whether medicinal cannabis could be used as an alternative treatment in the management of headache or migraine. They found that medicinal cannabis is not indicated as first or second line treatment for these diseases; however, when it is used together with other medications, it helps to reduce the frequency and duration of migraines. In addition, they found that synthetic cannabis compounds are dose dependent, and that dronabinol and nabilone are effective in controlling pain.

According to Chayasirisobhon Sirichai (2019), a retrospective study of analysis of medical records of 121 adult patients with migraine who used medical marijuana prescribed for treatment and prophylaxis of migraines pointed out a decrease in migraines frequency from 10.4 to 4.6 headaches per

month. In addition, this study also showed that 14 patients (11.6%) stopped feeling headaches.

Studies have shown that THC reduced migraine pain after microinjection of a dural TRPA1 agonist in a time- and dose-dependent manner. Another study found that this phytocannabinoid can reduce spreading depression cortical (Tassorelli, Cristina. *et al.,* 2019).

The study of effectiveness of using dried cannabis flowers administered by inhalation (pipe/steam) for headache and migraine treatments, conducted by Sarah S. Stith *et al.* (2020), incorporated data from 699 participants who were using Releaf app between June 10, 2016, and June 12, 2016, and February 2019. The study assessed changes in pain intensity on a VAS scale from 0 to 10 before and after cannabis use. The results showed that 94% of users felt relief within a two-hour window, and on average, symptoms dropped 3.3 points on a VAS scale of 0 to 10. Besides, the effectiveness of treatment may have been different due to way cannabis is used, THC and CBD content present in sample or age and gender of participants (Stasiÿowicz-Krzemieÿ, Anna. *et al*., 2024).

Otherwise, there being no conclusive scientific evidence, medicinal cannabis is often used by migraine sufferers as self-treatment of last resort. A retrospective study evaluated the effects of medicinal cannabis in 121 patients who had episodic migraine; they attended two medical marijuana clinics in Colorado (United States), the result of the study was an overall decrease in frequency of migraine (Locastro, Flavia. *et al*., 2021).

According to Okusanya; Babasola O. *et al.* (2022), medicinal cannabis (MC*)* significantly reduced nausea and vomiting associated with migraine attacks after 6 months of use. In addition, MC reduced the number of migraine days after 30 days and the frequency of migraines per month. MC was 51% more effective in reducing migraines than cannabis-free products.

The authors Okusanya; Babasola O. *et al.* (2022), found in their research a randomized clinical study with 79 patients with migraine; this study compared the efficacy of MC using a control group with amitriptyline. The patients in the intervention group received the THC+CBD treatment. The result obtained was a 40.4% reduction in migraine attacks in the intervention group in compared to control group, which had a 40.1% decrease in seizures migraines. Futhermore, using 200 mg of cannabinoids as an adjunct in patients using amitriptyline provided an additional reduction in intensity of headaches to 43.5% among patients in the control arm. In the study conducted by Rhyne *et al.* (2016), 39.7% of headache patients had their medication discontinued symptoms.

Safety of Medicinal Cannabis in The Treatment of Migraine

According to Sherpa, Mingma., *et al.* (2022), the side effects of using medicinal cannabis during treatment were drowsiness, psychosis, cognitive deficits, stomach problems, euphoria and

worsening of migraine symptoms. However, these effects appear to have been caused by an overdose of cannabinoids, mainly due to THC. Furthermore, they found the study published by Mechtler *et al.* (2022), which stated that the use of this drug is not recommended in pregnant women, infants and children under 12 years of age. Women who smoked marijuana during pregnancy had babies with low birth weight (Tassorelli, Cristina. *et al.*,2019).

According to Poudel, Sujan., *et al.* (2021), the adverse effects presented by patients who used medicinal cannabis to treat migraines experienced dizziness, nausea, vomiting, dry mouth or dry eyes, and psychosis. According to Rajapakse *et al.* (2021), the use of medicinal marijuana in patients with cardiovascular problems is not recommended because it can cause increased blood pressure, angina and vasodilation. In addition, it can contribute to the risk of acute myocardial infarction.

The study conducted by Rajapakse *et al.* (2021) showed that some of the short-term side effects of medicinal cannabis on the respiratory system are increased airway resistance, worsening of chronic bronchitis symptoms, risk of inflammation and emphysema. In the long term, this drug can cause pulmonar tissue damage.

CBD has high lipophilicity, so it is quickly distributed in the brain, adipose tissue and other organs. It can also bind to proteins and is hydroxylated by the cytochrome P450 isoenzyme family (CYP3A and CYP2C). Its half-life is approximately 18-32 hours. THC is also metabolized in the liver by cytochrome P450 isoenzymes CYP2C and CYP3A; their half-life plasma life is 1 to 3 days in infrequent users and 5 to 13 days in chronic marijuana users. Cannabis is primarily excreted in feces and very little in the urine (Chayasirisobhon Sirichai, 2019).

According to Okusanya; Babasola O. *et al.* (2022), adverse events were mostly mild and occurred in 43.75% of patients who used preparations of oral cannabinoids. Furthermore, another study found that tolerance to the effect of medicinal cannabis was indicated by a significant increase in dose over the time per session of cannabis use ($p = 0.001$) and this may lead to the use of higher dosages of MC. They found further evidence in the study conducted by Rhyne *et al.* (2016), that 11.6% of patients presented negative effects to treatment with medicinal cannabis. These patients presented drowsiness and difficulty controlling the movement and intensity of the dose with the use of edible cannabis.

According to Okusanya, Babasola O. *et al.* (2022), adverse effects of medical marijuana in general are mild; however, some studies have shown that medication overuse headaches, such as medication overuse syndrome cerebral vasoconstriction, can lead to stroke (Burch, Rebecca. 2019). Therefore, this demonstrates the need for rigorous experimental studies to evaluate the efficacy and safety of medicinal cannabis for treating migraine in adults.

The phytocannabinoids CBD and THC are metabolized in the liver by cytochrome P450 isoenzymes CYP2C and CYP3A are excreted more in the feces than urine, and have a long plasma half-

life (Chayasirisobhon, Sirichai. 2019). Additionally, CBD appeared to inhibit cytochrome CYP3A4 isoenzyme P450, which is responsible for the metabolism of 60 to 70% of human drugs.

Therefore, based on these data, it seemed necessary to have a therapy guided by doctors, carrying out therapeutic monitoring, which can be carried out by clinical pharmacists, medicinal cannabis and drugs co-metabolized by CYP3A4 (Mechtler, Laszlo L. *et al.*, 2021); and it is necessary to conduct further studies involving investigation of possible interactions between medicinal cannabis and other medications used to treat migraines.

CONCLUSION

Migraine is characterized by unilateral, pulsating pain, accompanied or not by nausea, vomiting, photophobia, phonophobia and aura symptoms; it usually lasts for 4 hours or days (INTERNATIONAL HEADACHE SOCIETY, 2018). The pathogenesis of migraines is complex and needs further study. However, based on the pathophysiology of migraine it is possible to identify possible therapeutic targets for the development of new drugs in the future.

CBD and THC are two phytocannabinoids that act on the endocannabinoid system, more precisely in the CB1 and CB2 receptors. In addition, when they act at opioid receptors, they promote analgesia due to increased signaling of these receptors and reduce side effects, such as respiratory depression (Tassoreli, Cristina. *et al.*, 2019; Duarte, Robert A. *et al.*, 2021; Mechtler, Laszlo L. *et al.*, 2021; Sherpha, Mingma L. *et al.*, 2022). Besides, treating migraines with medicinal cannabis appears to be promising because it was 51% more effective in reducing migraines than products without cannabis (Okusanya, Babasola O. *et al.*, 2022).

We could observe mild and tolerable adverse effects in patients who used medicinal marijuana to treat migraines. In addition, using medical marijuana for migraine treatment may be effective and does not cause serious side effects. Nevertheless, it is necessary to study more about the efficacy and safety of medical cannabis in the treatment of migraine due to the low number of studies found.

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