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Research Article

Potential of Cannabinoids for the Treatment of Endometriosis

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Abstract

Endometriosis is a painful disorder that affects many women characterized by the growth of endometrial tissue outside the uterine cavity, being closely related to infertility. Endometriosis can be challenging, regarding both diagnosis and treatment. Recently, researchers suggest the relationship between new signaling pathways and endometriosis, which includes the endocannabinoid system (ECS). The ECS is constituted by a set of receptors, lipid ligands (i.e., cannabinoids), and enzymes with a wide distribution from the Central Nervous System (CNS) to the peripheral tissues, controlling physiological processes of nociception, inflammation, cell growth, anxiety, and memory, among others Thus, scientists actively seek to study novel possible pharmacological approach to endometriosis and stablish the mechanism of action of the cannabinoids. This study aimed to update associations among the Endocannabinoid System, Endometriosis, and Cannabinoids for summarizing evidence of possible pharmacological therapies using cannabinoids for the treatment of endometriosis. It is a literature review, in which we highlight the evidence found by clinical trials regarding the use of cannabinoids for the treatment of symptoms associated with endometriosis. The study was carried by conducting a literature search for original articles and bibliographic reviews.

Research objects were selected according to the reliability, relevance, quality, and originality through searches in the following databases: PubMed, Lume, Scielo, Health agencies websites, MEDLINE, and Web of Science. Those papers referring to endometriosis and the endocannabinoid system covered the years from 1927 to 2022. As for the search between the parallel Endometriosis X Endocannabinoid System and the new possibilities of treatments with cannabinoids, materials from 2017 to 2022 were used. Up to this date, there is no complete cure for endometriosis other than complete esterification. Moreover, patients report problems achieving precise diagnosis and adequate pain control and serious side effects related to hormone-based therapy, revealing that endometriosis treatments often provide limited efficacy and patient compliance. Our results showed that ESC is closely related to the pathogenesis of endometriosis itself and is responsible for exacerbating pain perception. Indeed, there is a considerable amount of evidence demonstrating that cannabinoids can prevent the evolution of endometriosis by mechanisms that involve reducing lesion expansion, modulating and improving pain, decreasing tissue inflammation, and blocking cell migration and apoptosis. In addition, the use of CBD together with other analgesics makes it possible to reduce the dose of these compounds, which are less tolerated, and the abuse behavior. Such results corroborate the ever-growing body of evidence of ECS role in endometriosis and the pharmacological potential, yet underexplored, of the cannabinoids.

Introduction

Endometriosis affects many women in the 21st century. Although it was first reported in 1860 by Von Rokitansky [1] it is considered one of the modern female diseases, as after decades of its discovery, it continues to present great challenges for scientists, physicians, and a high rate of new patients. It is a multifactorial disease, heterogeneous in its formation and evolution, and with common causes to the current woman's standard way of living, such as later pregnancies and early menarche [2,3].

In addition to the challenges of research on development and treatment, precise diagnosis is also not easy. The whole process of investigation, treatment, and healing or ammelioration of the symptomatic conditions can take years [4]. This long process leads to a decline in the quality of life of patients for a large part of their adult life and to underreporting of the pathology. Since the delay in endometriosis resolution leads many women to give up the investigation and live with the symptoms for decades [5,6]. Besides the time until a final diagnosis, the procedures are expensive, leading to data often biased by socioeconomic status and access to health [1].

The search for a better understanding of endometriosis and alternatives of treatment, new research have emerged seeking to clarify the physiological systems and possible new therapeutic targets. As a result, the endocannabinoid system (ECS) has emerged as potentially involved in endometriosis development [7].

The ECS was discovered in the mid-80s [8], after the understanding of the biological effects of *Cannabis sativa L*. The therapeutic use of this plant had already been mentioned hundreds of years ago through the Chinese Pharmacopoeia [9]. In these compendiums, the first reports for the treatment of rheumatic pain, intestinal disorders, malaria, and problems in the female reproductive system can be found. from *C. sativa* [10].

CB1 was the first cannabinoid receptor identified [11], through the screening of metabotropic receptors. Later, CB2 receptors were identified [12]. Both CB1 and CB2 are receptors coupled to G protein [9,11].

Once the ECS was identifies, the research efforts were devoted to understand its action in human physiology and the way in which ligands (i.e., cannabinoids) are related to homeostasis and different pathologies. For instance, the relationship between the ECS and the pain signaling pathways, the inflammatory system, hormonal regulations, and cell growth has been reported [7]. Comparing with the female reproductive system, ECS representatives are found in the uterus, endometrium, myometrium, ovarian cortex, and uterine tubes and play an important role in regulating the menstrual cycle and gestational phases [13]. In addition, ECS has been shown to affect important mechanisms for the establishment and maintenance of endometriosis [7], being related to cell migration, proliferation, survival, inflammation, and on nerve fibers found in the ectopic endometrium [14].

Methods

The study was carried out in the year 2022, through the search for original articles and bibliographic review. Research objects were selected according to their reliability, relevance, quality, and originality through searches in PubMed, Lume, Scielo, Ministry of Health, MEDLINE, and Web of Science. In this way, works related to the theme were selected, by reading the initial title and abstract, and those that best suited the search were carried out by reading the complete compendium. In this way, essential information about the relationship between ESC and endometriosis and its student references were extracted, in order to better understand the exposed text.

The articles referring to endometriosis and the endocannabinoid system covered the years from 1927 to 2022, a filter was used for seeking the historical context of the research and the years of the relevance of the subject. It was followed as exclusion criteria: the permanence of the use, as well as a reference in the latest articles. As for the search between the parallel Endometriosis X Endocannabinoid System and the new possibilities of treatments with cannabinoids, materials from 2017 to 2022 were used. The following terms were used for the search strategy: endometriosis, the endocannabinoid system, endocannabinoid, chemical structure, Anandamide, 2-arachidonoylglycerol, Palmitoylethanolamine, N-oleoylethanolamine, cannabinoid, phytocannabinoids, capsaicin, β-caryophyllene, cannabis sativa, therapeutic targets, and treatment.

Endometriosis

Endometriosis is a gynecological condition characterized by the presence of functional endometrial tissue outside the uterine cavity and endometrium [4]. The abnormal cell growth induces chronic inflammatory reactions and is related to cyclic estrogen variations [1,15]. Socially, endometriosis is considered a benign pathology [5], however, it is the greatest responsible for female infertility and the causative agent of the decrease in women's quality of life [16].

Despite the benign classification given to endometriosis, diseased women have been associated with the double risk of developing comorbidities than healthy women (SURREY, *et al.*, 2020). The presence of ectopic endometrium may be related to the development of ovarian cysts, uterine fibroids, a pelvic inflammatory disorder, interstitial cystitis, irritable bowel syndrome, constipation, and ovarian and endometrial cancer (SURREY, *et al.*, 2018) [17].

Due to the hormonal influence, endometriosis is more frequent during the female reproductive period. Besides, the most affected sites include the ovaries, peritoneum, bladder, rectum, and portions of the digestive tract [5]. The most common symptoms are associated with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility (FEBRASGO, 2010) [18].

It is currently known that several factors are related to the occurrence of endometriosis, such as favorable hormonal environment, failures in the immune mechanism, genetic inheritance, retrograde menstruation and pregnancy, early menarche, and favorable anatomy [4,19]. Sampon's theory is the most commonly accepted to define the evolution of the pathology, it argues that retrograde menstruation associated with immunological imbalances is the main cause of the pathology [7,20].

During the development of ectopic endometrial tissue, the immune disorder fails to eliminate cells in foreign locations, which, concomitant with a favorable metabolic environment and exacerbated inflammatory responses, triggers the chronic inflammatory response. The presence of ectopic endometrium in different locations and with different patterns of extension lead to the classification of endometriosis into 3 different phenotypes (MORETTO *et al.*, 2021) [4]: (i) superficial peritoneal lesions and ovarian cysts, (ii) clusters of ectopic endometrial tissue with ingrowth to the ovary and (iii) infiltrations that usually cause deeper extra pelvic lesions in the uterine ligaments and organs surrounding the uterus.

In addition, according to the American Society for Reproductive Medicine (ASRM) (NEVALAINEN, 1996) [21], endometriosis can be classified into four possible stages, considering the location, extension, and depth of the lesions in the pelvic and adjacent structures, evidencing the severity of the disease. Being them (MORETTO *et al.*, 2021) [4]: Stage I: minimal disease, involving small points of superficial and isolated adhesions; Stage II: mild disease, superficial adhesions and some deeper (up to 5 mm); Stage III: moderate disease, including isolated endometrioma, or with other adhesions, which may be present in a more superficial or dense form; Stage IV: severe disease, the sum of previous manifestations occurs with the involvement of other pelvic and abdominal structures.

Regarding the most common clinical manifestations, chronic pain is associated with the location, extension, and depth of the lesions, being the most reported symptom among patients and those who have greater discomfort with living with the disease (COSTA *et al.*, 2018). Currently, it is believed that the pain mechanism involved in this process is linked to neuropathic and inflammatory characteristics since pain sensitivity is intrinsically related to the local production of estradiol and inflammatory mediators [22]. Dysmenorrhea, another symptom of high incidence, may be related to the exacerbated production of prostaglandin from endometrial implants [4].

Besides the important symptoms, a serious consequence of endometriosis is infertility generated in many women (MISTRY *et al*., 2021) [23]. This is a delicate point of the disease, since the peak of ectopic endometrial growth occurs precisely in the female reproductive phase, thus leading many patients to infertility [4].

The relationship between the disease and the inability, or difficulty, of a healthy pregnancy, is caused by a decline in ovarian reserves, reduced implantation and survival of the embryo in the uterine environment, the toxic effect of inflammatory responses on the embryo and/or sperm and increased levels of cytokines, growth factors, and activated immune cells [14,15].

Given the causes of endometriosis and its signs and symptoms, the most common diagnostic approaches remain clinical evaluations and imaging exams, such as transvaginal ultrasound and nuclear magnetic resonance imaging [24] or the measurement of biological markers, such as CA 125, associated with prolactin levels [4].

Endometriosis and Its Economic Role

It is estimated that approximately 10% of women in the reproductive phase have endometriosis at some stage (TANAKKA *et al*., 2019), In this context, the development of the disease, the delay in diagnosis, and the pain caused have significant economic consequences for the patient and for society (SURREY, *et al*., 2020) since most symptomatic women are in their productive and economically active age.

A study conducted in Europe, the UK, and the US concluded that the total cost per woman with endometriosis per year was €9,579, most of which was caused by absence from work during the most critical days of the symptoms [25]. The authors showed that the economic burden follows the increase in pain severity since the productivity of women with endometriosis drops substantially. This factor is generated by the discomfort caused by the symptoms and consequently absences from work [26]. In this way, the pathology affects not only the life of the patients but also the society that surrounds them. Therefore, the improvement in women's conditions and, consequently, in their quality of life, has an impact not only on them but also on those around them, as they become more willing and motivated to carry out day-to-day activities. In addition, the economic gain is an important point, as it affects not only the woman, but the entire society that surrounds her (AS-SANIE, *et al*., 2019), and a reduced burden to the health system.

It is widespread and well-accepted that menstruation is commonly considered a painful event that should be normalized in the routine of women of reproductive age. In addition, the complaints of women with severe pain are not seriusly considered by most of the healthcare professionals, as the reported symptoms are often trivialized [27]. Women also tend to be reluctant to reveal irregularities related to the menstrual cycle, in order to avoid the stigmatization of female vulnerability. Taken together, these facts delay diagnosis, treatment, and female quality of life [6].

Therefore, even though endometriosis shows a high prevalence and high socioeconomic costs, research involving endometriosis remains underfunded and underexplored, limiting deep scientific understanding of the disease, and delaying much-needed innovation in diagnostic and treatment options (AS-SANIE, *et al*., 2019).

Classic Treatments for Endometriosis

To this date, there is no cure for endometriosis other than total esterification. Currently, the mainstream treatment is based on the symptomatology of endometriosis, by either pharmacological or surgical approaches or with their combination. (TANAKKA *et al*., 2019). The procedures aim at slowing down the symptoms and preventing the advancement of ectopic endometrial growth. The choice of treatment should take into account the severity of the symptoms, extent, location of the disease, desire for pregnancy, patient age, adverse effects of medications, rates of surgical complications, previous treatments, and cost [28].

Regarding the pharmacological treatment, a non-hormonal approach can be selected, with the oral administration of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), or hormones, such as combined contraceptives and/or progesterones [1,19].

Analgesics and NSAIDS act by inhibiting cyclooxygenase (COX), reducing prostaglandins, and inhibiting the arachidonic acid chain, thus acting on pain mechanisms and cell replication. However, they can produce several adverse effects, such as dependence, liver damage, coma due to hypoglycemia, nausea, vomiting, abdominal pain, kidney failure, headache, dizziness, tinnitus, hearing and vision changes, sweating, thirst, hyperventilation, diarrhea, gastric ulcer, mental confusion, changes in concentration and agitation, and its use should be limited and controlled [18,29].

Besides analgesic drugs, combined contraceptives and progesterone are the first line treatment of for women in the early stages of the disease, with the aim to delay the progression of lesions, in addition to regulating the estrogen cycle [5]. Synthetic estrogens, the main components of combined contraceptives, cause effects on the liver's metabolism, increasing the hepatic production of several proteins, which may lead to increased thrombosis, among other problems [30].

Progesterones, on the other hand, antagonize the effects of estrogens and produce a more prolonged effect [31]. Even at therapeutic doses, the prolonged use of these substances can cause undesirable effects, such as unbalanced triglycerides and a drop in HDL concentration [32,29], cystic endometrial hyperplasia, mammary hyperplasia, resulting in tumors mammary glands, pseudocyesis, retention, and fetal death [33].

As a second line for hormone-based treatment, analogues of gonadotropin-releasing hormone (GnRH) agonists are used, and the mechanism of action involves negative feedback on the pituitary gland, generating hypogonadism that causes anovulation [4]. However, such approach is related to undesirable effects, such as intense hot flashes, vasomotor symptoms, vaginal dryness, changes in libido, and loss of bone mass, among others [34].

An alternative treatment can be conducted with Danazol, which is able to reduce pelvic pain, pain to evacuate, and low back pain in patients with level 4 endometriosis [5]. However, the lowest possible dose should be used due to the possibility of major adverse events such as lipid alterations, liver damage, decrease in breast volume, cramps, increased appetite, weight gain, hoarseness, acne, and edema [35,36].

Surgical treatment is the last treatment option, as it occurs when the disease is at a more advanced stage, and in it, there may be cauterization of specific points of the endometrium or total esterification of the woman (MORETTO *et al.*, 2021) [4]. It is most often associated with pharmacological treatment after the procedure (COSTA *et al.*, 2018).

Despite the existence of pharmacological and surgical treatments, these have a high rate of adverse effects and there is a need for frequent alternation of the therapy type, in order not to harm a certain system for a long time and generate inefficiency in the treatment of certain symptoms, such as pain [4,35].

Therefore, the search for a more specialized way to treat endometriosis is of great importance. In addition, the use of natural alternatives with fewer adverse effects is a possible key to continued treatment and good acceptability among patients (RICCI, *et al.*, 2012; MARESMAN, *et al.*, 2021; MACHAIRIOTIS, *et al.*, 2019).

Endocanabinoid System (ECS)

The ECS is one of the largest neurochemical systems found in the human organism [9].

It is currently known that the structure of this system is composed of receptors, synthesizing and degrading metabolic enzymes, lipid signaling molecules, and membrane transporters (TANAKKA *et al.*, 2019). The ECS physiology consists of the neuromodulation of the CNS through the binding of neurotransmitters to postsynaptic receptors (PEREIRA, 2020). The interaction of these structures stimulates cell depolarization, leading to an increase in intracellular calcium and consequently stimulating the neuron to produce endogenous ligands, i.e., endocannabinoids, by enzymatic action (CORRÊA *et al.*, 2020). These substances, in turn, are released into the synaptic cleft and bind to presynaptic receptors [9].

The transport of endocannabinoids across the plasmatic membrane can occur by simple diffusion, due to its lipophilic character, or through a putative endocannabinoid membrane transporter (EMT) [37], facilitating bidirectional flow (MAIA *et al.,* 2020). Endocannabinoids then, activate their primary CB1 and CB2 receptors, as well as their secondary targets.

Receptors

Two classic cannabinoid receptors, CB1 and CB2, are found throughout the ECS and modulate different physiological processes in the body [10,15]. These are located in the plasmatic membrane, associated with the G protein and their activation promotes a homeostatic balance in biochemical pathways in the organism (MISTRY *et al.*, 2021).

Despite having similar pathways, cannabinoid receptors locate at different sites of action in human tissues. CB1 receptor is associated with the Central Nervous System, mainly in presynaptic sites, being one of the most abundant receptors in the CNS [38]. It can be detected mainly in the cerebral cortex, hippocampus, basal ganglia, and cerebellum [10]. In the peripheral systems, it is evidenced in the cardiovascular, gastrointestinal, respiratory, reproductive, and skeletal systems [39,40].

CB1 acts as a CNS neuromodulator and its function is mainly linked to memory, analgesia, and motor function [38,40]. Its central activation is beneficial in inflammatory diseases, depression, anxiety, neuropathic pain, multiple sclerosis, and intestinal diseases [10]. In the periphery, CB1 is located in nociceptive terminals and inhibits the transmission of stimuli, acting directly on the release of neurotransmitters involved in pain transmission [41,42].

CB2 receptor is present mainly in peripheral tissues, such as the intestine, lung, uterus, skin, and pancreas, and in the immune system [9]. In cells of the immune system, it is expressed mainly in B and T lymphocytes, mast cells, and macrophages, and are found in tissues that regulate the production of these cells [10]. Its presence in immune cells interferes in the release of endorphins, which act on opioid receptors in primary afferent neurons, thus inhibiting nociception [41,42].

The modulation of these receptors has been the subject of studies since intervention in their peripheral action has demonstrated beneficial effects in various pathological conditions (ZOU *et al.*, 2018). Initially, it was believed that endogenous cannabinoid ligands were related only to classic receptors. However, it is currently known that these substances interact with other membrane receptors [10], which are considered constituents of the ECS. They include orphan receptors coupled to G protein, such as the GPR55, GPR18, and GPR119 receptor [23,43,44,45], the receptors peroxisome proliferator-activated receptors (PPAR) [10,44] and the transient receptor potential of the vanilloid receptor (TRPV) (TANAKKA *et al.*, 2019).

The orphan receptors, GPR55, GPR18, and GPR119, play their role in cell proliferation phenomena (TANAKKA *et al.*, 2019). On the other hand, representatives of TRPV constitute a class of Ca 2+ -dependent ion channel receptors, which can be related to environmental-related responses [10]. In the case of TRPV1, the main player involved in the endocannabinoid pathway, signaling can be triggered by mechanical pressure, heat, and chemical influences [19].

Ligands

Endocannabinoids

The endogenous ligands of the ECS pathway, are called endocannabinoids. These are derivatives of arachidonic acid and have a lipophilic character since they are synthesized from membrane phospholipid precursors [9].

The first recognized endocannabinoid was Arachidonoylethanolamine, also known as Anandamide (AEA), which consists of an ethanolamide of arachidonic acid [8]. Few years later, another derivative of arachidonic acid was isolated and identified, receiving the name of 2-arachidonoylglycerol (2-AG) [46]. Both show interesting different affinities for cannabinoid receptors in the body, thus providing different physiological effects.

The first research data regarding the production of endocannabinoids defended the idea that they were synthesized by physiological demand and were not stored in vesicles like the classic neurotransmitters [23]. However, in 2014, a study carried by Fezza *et al*. suggested that endocannabinoids are synthesized by both mechanisms. Most of them are produced according to physiological demand, but they can also be stored in intracellular lipid droplets, called adiposomes (MACARRONE, 2009; FEZZA *et al*., 2014), thus providing a more constant performance of the endocannabinoid system.

AEA is a CB1 agonist and CB2 partial agonist, due to its high affinity for CB1 and low affinity for CB2 [47]. Its biosynthesis is initiated from the influx of Ca 2+ into the neuronal cell [10].

2-AG is the second preponderant endocannabinoid in ECS, being the main endo cannabinoid in the CNS. It is a full agonist of CB1 and CB2, with low affinity for both of them [10]. Its biosynthesis is very similar to that of AEA, also being initiated through the entry of Ca 2+ into cells (MURATAEVA *et al*., 2014) [48].

After biosynthesis and interaction with receptors, both endocannabinoids act by triggering the activation of inhibitory G protein. This, in turn, inhibits the activity of adenylylcyclase and, consequently, prevent the conversion of ATP into cAMP (PEREIRA, 2020). This phenomenon causes a decrease in neuronal excitability and consequently suppresses the release of neurotransmitters [9].

In this way, the activities of endocannabinoids are related to biological responses to cell damage, regulate proliferation, differentiation, migration, and cell death, in addition to modulating neuronal functions, such as pain perception, motor, and cognitive functions (ZOU *et al*., 2018). At the same time, because they have representatives in the immune system, the inhibition of G protein can modulate the production of pro-inflammatory cytokines, providing an anti-inflammatory effect and promoting antioxidant activity, protecting the CNS (VIEIRA, 2019; CORRÊA *et al*., 2020). In peripheral organs, endocannabinoids act on blood pressure, heart rate, and energy balance via glucose homeostasis, and their role in the female reproductive system is related to gametogenesis, decidualization, implantation, and placentation [23].

In addition to those classic ligands, there are structural analogues known to play a role in this pathway, such as Palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA) (BEN-SHABAT *et al*., 1998). These compounds can be considered as alternative substrates for fatty acid amide hydrolase (FAAH) and aminoacylglycerol lipase (MAGL), enzymes responsible for the hydrolysis of endocannabinoids. Thus, their presence causes an increase in the potency of endocannabinoids at their sites of action (TANAKKA *et al*., 2019).

Phytocannabinoids

In addition to the study of endogenous signalers, the discovery of ECS stimulated studies of exogenous ligands, the so-called phytocannabinoids, found in different plant species. The major botanical representative of these compounds is Cannabis sativa, with the first phytocannabinoid ever found being cannabinol (CBN) in 1899. The studies of these compounds were increasingly stimulated since then, which led to the identification of the two most known phytocannabinoids, i.e., cannabidiol (CBD), in 1940, and tetrahydrocannabinol (THC), in 1942 [9,49].

CBD has been the focus of the most proeminent research efforts, due to its outstanding medicinal properties without showing psychoactive effects. CBD has been reported to show anticonvulsant, anti-inflammatory, analgesic, intraocular pressure reducer, and antitumor activities. Besides, it has been popularly used to mitigate the side effects of chemotherapy (MIRANDA, 2016; SELTZER *et al*., 2020; BELGO *et al*, 2021). CBD has also shown positive effects in managin anxiety, depression, insomnia, and neurodegenerative disorders, such as Alzheimer's and Parkinson's. Through the activity on TRPV receptors, CBD can promote analgesia and decreased perception and tolerance of pain, including neuropathic pain (CAMARGO *et al*., 2019; VIEIRA; MARQUES; DE SOUSA, 2020).

CBD has a low affinity for both CB1 and CB2 receptors. It acts as a negative allosteric modulator of CB1 receptors, which allows it to attenuate the effects of THC on CNS [9]. THC, in turn, is one of the main representatives of the class of CB1 agonists. The interaction of these two most proeminent cannabinoids is of great pharmacological value (RAMIREZ, 2021). In addition to the actions described, CBD inhibits the enzyme responsible for AEA degradation, increasing the levels of this endocannabinoid and prolonging its activity (COSTA, 2011; OLIVEIRA; LIMA, 2016; MATOS *et al*., 2017).

In addition to phytocannabinoids extracted from C. sativa, many other plants can produce secondary metabolites that can interfere with the ECS. β- caryophyllene (BCF), for instance, is a sesquiterpene of pharmacological importance and the main active ingredient in Copaíba trees (Copafera spp) [50] and one of the main agents responsible for the anti-inflammatory activity of the essential oil of the baleeira herb (Cordia verbenacea) (FERNANDES, *et al*., 2007). BCF also possesses antifungal, antibactericidal, anti-insecticidal, antitumor, and cytotoxic activity.

Capsaicin is considered the main phytocannabinoid, found in peppers, and being associated with the physiological processes of cell replication, inflammation, and pain. Physiologically, capsaicin acts as a TRPV1 agonist and its use is mainly associated with the treatment of acute or chronic pain [10,51]. Capsaicin promotes receptor activation, triggering calcium influx and activating receptors and endocannabinoid synthesis enzymes (GOMES, 2009).

Endocannabinoid System End Endometriosis

During the last decade, a strong relation between the development of endometriosis and ESC has been stablished, based on the reports of ECS constituints found in the female reproductive system [15]. In this way, there are representatives of the ECS in the uterus, endometrium, myometrium, ovarian cortex, and uterine tubes (TANAKKA *et al*., 2019). Regarding the feminine reproductive system, the ECS can influence homeostasis-related processes, such as hormones regulation and cicles, gametogenesis, decidualization, ovarian maturation, embryonic implantation, and placentation [13,23].

Drawing a parallel between the way in which the ECS acts in the body and the characteristics of endometriosis, hypotheses are raised about its influence on the pathology and its intersection pathways (DMITRIEVAA *et al*., 2010; TANAKKA *et al*., 2019). Thus, this work will highlight the relationship between endometriosis and ECS in processes such as variation in ECS action during the menstrual cycle, availability and performance of cannabinoid receptors, the concentration of signals and enzymes, modulation of inflammation, cell

proliferation, and apoptosis, and in the presence of cannabinoid receptors in lesions caused by endometriosis (DMITRIEVAA *et al*., 2010) [15]. All of these processes are critical to the disease, and they can contribute to diagnosis and treatment.

ESC action during the menstrual cycle is highlighted in the decidualization process (OKADA *et al*., 2018). In this process, endometrial stromal cells proliferate and differentiate into decidual cells. This specialized tissue has the two main cannabinoid receptors and the metabolic enzymes of the AEA (HABAYEB *et al*., 2004; ALMADA *et al*., 2016). However, the process can be interrupted through activation of the CB1 receptor, or high concentration of AEA, causing dysregulation of the cell cycle and inhibition of endometrial proliferation (ALMADA *et al*., 2016).

Another common feature in patients with endometriosis is variation in the action and concentration of cannabinoid receptors. In patients with endometriosis, CB1, and CB2 receptors are seen in smaller amounts during the menstrual cycle. Its agonists induce apoptosis and reduce the proliferation of Ishikawa cells (endometrial gland cells) [52]. Such action affects the regulation of endometrial tissue, decreasing its susceptibility to endocannabinoids, and reflecting the relevance of ECS in the pathogenesis of endometriosis (TANAKKA *et al.,* 2019) [19]. TRPV1 receptors, on the other hand, act positively on ectopic tissues and are associated with the pain symptomatology of the pathology [19].

Regarding the inflammatory pathways, the upregulation of CB2 is linked to the inflamed tissues of the ectopic endometrium (IUVONE *et al*., 2008). In these, it is possible to observe high levels of AEA and low concentration of PEA in fibroids. In fibroid tissues, there is lower expression of fatty acids and GPR55 and CB1 receptors (AYAKANNU *et al*., 2019). In addition, pro-inflammatory molecules increase the mRNA expression index, which negatively affects the biochemical activity of CB1 receptors and stimulates TRPV1 and TRPA1 in sensory nerves, triggering inflammatory responses [53] and relating to the severity of symptoms of pain, dysmenorrhea, and dyspareunia. Furthermore, cytokines and growth factors are found in higher concentrations in the blood and peritoneal fluid of women with endometriosis [23,54].

Regarding enzymatic interference, alteration in the concentration of enzymes such as FAAH and N- acyl - phosphatidylethanolamine (NAPE-PLD) is more evident in endometriotic tissues, interfering in the synthesis and degradation of endocannabinoids, impacting epithelial and stromal cells during the pathogenesis of the disease [52]. At systemic levels, the expression of the endocannabinoids AEA, 2-AG, and OEA are higher in the secretory phase than in the proliferative phase of the uterine cycle of patients with endometriosis (TANAKKA *et al*., 2019), while in healthy patients, there is no difference significant in the concentration of these compounds. A possible justification for the increase in the levels of these endocannabinoids is the higher concentration of NAPE-PLD and the drop in the level of FAAH (SANCHEZ *et al*., 2016).

In addition, the expression of enzymes involved in ESC is influenced by changes in steroid hormones (RIBEIRO *et al*., 2009, MAIA *et al*., 2017) [13], which leads to a variation in endocannabinoid levels throughout the menstrual cycle. In this case, there may be an increase in AEA levels in the ovary (EL-TALATINI *et al*., 2009), when compared to the follicular and luteal phase (HABAYEB *et al*., 2004).

In endometriosis, the endocannabinoids AEA, 2-AG, and PEA are found in greater amounts in ectopic endometrium (SANCHEZ *et al*., 2016) [55]. Such high concentration is related to the pain associated with endometriosis [19]. ESC imbalance is not only related to the pathogenesis of endometriosis itself, but also to changes in pain perception, which is more exacerbated in this context.

Using a rat model of endometriosis, Dmitrieva *et al*. (2010) demonstrated that the CB1 receptor is expressed in sensory and sympathetic fibers, which innervate endometriotic lesions, and in the body of sensory and sympathetic neurons. This finding indicates that CB1 are located in such a way as to influence the innervation of lesions in patients with endometriosis and that they may be related to pain. This same study showed that CB1 agonists decrease endometriosis-associated hyperalgesia, while antagonists increase it, evidencing an opportunity for a novel treatment approach.

The findings described above provide a rich scenario and point to the great contribution of the ECS not only to the mechanisms of pathogenesis but also to the peripheral innervation of abnormal growths in terms of pain associated with endometriosis. Thus, ESC emerges as a new therapeutic target, fostering new research for the development of innovative and extremely necessary treatments for endometriosis (DMITRIEVA *et al*., 2010).

Cannabinoids as an Alternative to the Treatment of Endometriosis

The exogenous cannabinoids act by mimicking endocannabinoids and are involved in homeostasis of physiological systems. Currently, the use of these substances is associated with the treatment of CNS-related pathologies such as epilepsy, neuropathic pain, nephropathy, Alzheimer's, and schizophrenia (DI MARZO, 2018) [9,10] and more recently in endometriosis. In general, cannabinoids are associated with pain relief through the activation of CB1 and CB2 receptors [56], and also through the interaction with opioid, vanilloid, serotonergic and anti-inflammatory receptors (VUCKOVIC, *et al*., 2018). These effects alone can justify their application for the treatment of endometriosis since pelvic pain is the main symptom reported by many womens.

The use of *C. sativa* is an ancient tradition for the treatment of gynecological and obstetrical problems. Its history of scientific research has been built for years through clinical, epidemiological, and botanical comparisons (RUSSO, 2002). Consequently, their cannabinoids are better elucidated in several lines of research. The clinical use of *C. sativa*-derived cannabinoids is related to their role as agonists or antagonists of CB receptors with activity in pain, inflammation, and angiogenesis processes (BOUAZIZ, *et al*., 2017).

A survey carried out in Australia in 2017 addressed women between 21 and 45 years old with diagnoses of endometriosis who sought self-management of their symptoms through secondary treatment alternatives. The study was carried out through a questionnaire, in which women listed from 0 to 10 the efficiency of certain treatments for pain relief. About 13% of the women already used Cannabis or CBD oil as an association with classic pharmacological treatment, and among these, the use of these compounds was identified as one of the best strategies for reducing pain associated with the pathology. According to the scale used, Cannabis presented a relief of 7.6 and CBD of 6.3. Table 1 was extracted from the work in question, and presents the 10 alternatives that obtained the best results in modulating pain caused by endometriosis.

Table 1: *Level of pain relief by self-management, listed from greatest to least pain reduction*

Modality used for self-management of pain	Pain Relief
Cannabis	7.6
Heat	6.5
Gluten-free and/or vegan diet	6.4
Hemp oil/CBD oil	6.3
Acupressure	6.3
Cold	5.5
Massage	5.5
Rest	5.3
Exercise	4.9
Herbal medicines	4.8

Fonte: Adapted from MIKE, *et al.*, 2019 [57]

Two years later, Reinert and Hilber, conducted a clinical study with 364 endometriosis patients, who answered a questionnaire with 55 to 75 questions about the use of *Cannabis* and CBD in the management of pelvic pain associated with the disease. Their results showed that approximately 37% of patients reported having tried *Cannabis*, with the majority of them (85.5%) rating it as very or moderately effective. Furthermore, around 34% of participants reported having tried CBD, of which approximately 78% responded that CBD is very or moderately effective [58].

Concomitantly with this significant improvement in pain, Mike *et al.*, showed that endometriosis patients reported that the use of these alternative therapies helped to reduce the amount of classic medications, improving or avoiding the adverse effects caused by them. Their results showed that 56% of women using cannabis and one-third of CBD users reported that they decreased their endometriosis-related medication by 50% or more [57].

CBD acts as a negative allosteric modulator of CB1 and CB2, potent TPV1 agonist, GPR55 antagonist, and contributes to indirectly increasing the availability of AEA and other endocannabinoids through FAAH inhibition. A point of attention is CBD relationship with the PEA, as they share several biological effects. CBD causes the modulation of GPR55, causing the inhibition of factors involved in inflammation and pain [19].

Alejandra Escudero-Lara and colleagues evaluated the effects of THC in female mice with surgically induced endometriosis. In these, the main symptoms associated with the presence of endometrial lesions were pelvic pain, anxiety, and memory deficits. The treatment with THC reduced the pain caused by endometrial cysts; altered uterine innervation by decreasing receptor points linked to pain transmission; restored cognitive function; and, unexpectedly, inhibited the growth of cysts and the development of new nodules. In this way,

the work presented the observed findings in a graphic and visual way. Introducing the decrease of uterine cysts, their innervation points, the decrease in pain caused by the cysts, and the return of cognitive functions after treatment with THC. These findings highlight the interest of clinical trials in women with endometriosis in order to investigate the benefits of THC on female physiology [49].

THC modulates the production of cytokines through the positive response of CB2 receptors, preventing the degranulation and release of pro-inflammatory mediators from macrophages. In addition, by binding to CB1 and/or CB2 receptors, THC inhibit the migration and survival of vascularized endothelial cells as part of their antiangiogenic action [59], which is an important point in the growth of lesions. However, due to its strong known psychoactive action, THC is less pharmacologically explored and its use is being associated with CBD, which delays CNS-related effects (SANCHEZ *et al*., 2012; BATISTA. *et al*., 2021; POLINETO *et al*., 2022) [9,15,56].

BCF has been increasingly investigated against endometriosis. BCF provides a selective CB2 agonist function, causing analgesic effects [19]. Therefore, its use is associated with the relief of chronic pelvic pain in women, as in endometriotic conditions.

In a study carried out in mice, endometriotic tissue fragments were implanted in adult female rats and the development of endometriosis followed. After 21 days, BCF-based treatment resulted in the suppression of the growth of pathogenic tissues by 52.5%, compared to controls. Furthermore, BCF produced apoptosis of lesions and endothelial cells of blood vessels. In this way, the research findings foster the promising expectation of BCF-based therapy for patients with endometriosis [60].

Discussion

When it comes to endometriosis, capsaicin has shown to regulate the cell cycle and inhibit non-apoptotic proteins (GOMES, 2009), interfering with cell migration and proliferation since they affect the receptors responsible for such demand (KOOSHKI, *et al*., 2018). Wu, Starzinski-Powitz, and Guo reported the use of capsaicin as a therapeutic target for endometriosis. After clinical trials, it was found that capsaicin inhibited the proliferation of endometriotic epithelial cells in a concentration-dependent manner. In addition, it was observed that endometriotic cells are more sensitive to treatment with capsaicin than the others, thus being an important candidate for the treatment of endometriosis due to its selectivity.

From the discoveries of phytocannabinoids and their pharmacological action in pathologies, synthetic representatives were developed, such as WIN 55212-2 (BOUAZIZ, *et al*., 2017). Leconte and colleagues evaluated the *in vitro* effect of WIN 55212-2, a CB agonist, on cell lines extracted from patients with endometriosis. *In vitro* treatment with WIN 55212-2 decreased cell proliferation, production of reactive oxygen species, and expression of smooth muscle α-actin. The *in vivo* effects were evaluated in mice implanted with human endometriotic lesions. WIN 55212-2 decreased endometriotic tissue growth [61].

Based on the results presented, and considering the promising scenario, cannabinoids feature several positive effects for the treatment of endometriosis, which, with further research, can be evidenced as an alternative solution for mitigating symptoms and also, as a possible treatment to enable regression of the lesions.

Conclusion

Despite being socially and cultured considered a benign disease, endometriosis produces a significant impact on women, affecting their quality of life, interpersonal relationships, future planning, and socioeconomic status, and can lead to infertility, besides many psychic and nutritional sequelae. Endometriosis also produce relevant social consequences, as it causes high costs to the health system and a decrease in women's labor productivity at different stages of adult life. Because of this, endometriosis should be considered a public health problem and the search for its most studied signaling and treatment pathways should be sought. Currently, the early detection of the disease, the management of symptoms, the attempt to prevent cell replication processes, and the growth of lesions constitute the best alternative for endometriosis therapy.

Since the ECS is found to be spread through various organs and impacting on several physiological processes of the female reproductive system, it is important in the way of elucidating the diagnosis and pharmacological treatment of endometriosis. Cannabinoids emerge as an innovative promising treatment because they can reduce the expansion of lesions, modulate and improve pain perception, decrease tissue inflammation, and prevent cell migration and apoptosis.

In addition, the use of CBD together with other analgesic drugs makes it possible to reduce the dose of these compounds, which are less tolerated, and the abuse behavior. In addition to the direct action on the mechanisms of endometriosis, cannabinoids produce anxiolytic, antidepressant, mood stabilizer, and sleep modulators effects. These effects are useful as adjuvants in the treatment of the pathology, since comorbidities are frequent among patients with endometriosis.

In this way, the need for in-depth studies on the subject is extremely valuable, and the results presented here suggest a new, and promising, direction for the treatment of the pathology through cannabinoids. Therefore, the work stresses the importance of an interdisciplinary approach, in addition to raising awareness among health professionals and the public about endometriosis. Since these measures are necessary to end the stigma of pain associated with menstruation and in order to emphasize the importance of seeking an early diagnosis, optimal treatment, and stimulating new scientific advances.

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