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Article

Anti-Inflammatory and Immunomodulatory Potential of Cannabidiol in Rheumatoid Arthritis: Integrative Review

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RESUMO

A artrite reumatoide (AR) é uma doença inflamatória crônica, autoimune e sistêmica que afeta predominantemente as articulações periféricas, ocasionando dor, rigidez matinal, fadiga e manifestações extra-articulares. A patogênese envolve fatores genéticos, hormonais e imunológicos, com participação de citocinas pró-inflamatórias e mediadores metabólicos. O tratamento convencional inclui a administração de anti-inflamatórios não esteroides (AINEs), glicocorticoides e drogas modificadoras do curso da doença (DMARDs), sendo o metotrexato a principal escolha. Contudo, esses fármacos apresentam limitações devido aos efeitos adversos e ao uso prolongado. Nesse contexto, os canabinoides, particularmente o canabidiol (CBD), emergem como alternativa terapêutica promissora devido as suas propriedades analgésicas, anti-inflamatórias, ansiolíticas e imunomoduladoras, sem os efeitos psicoativos associados ao Δ-9-tetra-hidrocanabinol (THC). A literatura demonstra um interesse científico e clínico crescente na utilização de derivados da *Cannabis sativa* L., incluindo medicamentos como o Sativex® e o Epidiolex®, bem como compostos sintéticos, para o tratamento da dor e a regulação do sistema imunológico em doenças inflamatórias como a AR.
Palavras-chave: artrite reumatoide; canabidiol; Δ-9-tetra-hidrocanabinol.

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, autoimmune, systemic inflammatory disease that predominantly affects the peripheral joints, causing pain, morning stiffness, fatigue, and extra-articular manifestations. Its pathogenesis involves genetic, hormonal, and immunological factors, with the participation of pro-inflammatory cytokines and metabolic mediators. Conventional treatment

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includes the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs), with methotrexate being the primary choice. However, these drugs have limitations due to adverse effects and prolonged use. In this context, cannabinoids, particularly cannabidiol (CBD), emerge as a promising therapeutic alternative due to their analgesic, anti-inflammatory, anxiolytic, and immunomodulatory properties, without the psychoactive effects associated with Δ-9-tetrahydrocannabinol (THC). The literature shows growing scientific and clinical interest in the use of *Cannabis sativa* L. derivatives, including drugs such as Sativex® and Epidiolex®, as well as synthetic compounds, for the treatment of pain and regulation of the immune system in inflammatory diseases such as RA.
Keywords: Rheumatoid arthritis; Cannabidiol; Δ-9-tetrahydrocannabinol.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that damages the joints, most often affecting the hand, wrist, and ankle in the early stages (Durez et al., 2022). The preferential involvement of peripheral joints is widely documented; however, in more severe cases, an inflammatory process can be observed in the synovial portion of the spinal joint (Oláh et al., 2020; Di Muzio et al., 2023). Additionally, it is recognized as a systemic pathology with extra-articular manifestations and currently affects about 1.0% of the world population (Kim, 2023).

It has an evident autoimmune character and predominantly affects females, with a ratio of three women for every man, a fact explained by the influence of hormonal, environmental, and immunological factors (Loscalzo et al., 2024). The etiology of the disease remains unclear, with possible manifestation in all age groups, although with a higher prevalence in the fourth and fifth decades of life (Venetsanopoulou et al., 2023).

Several molecules have already been identified and play crucial roles in the prevention of RA. Protein targets such as IL-4, IL-10, IL-15, IL-17, IL-18, IL-23, tumor necrosis factor alpha (TNF-α), and IL-6, as well as molecular metabolites including prostaglandins (PGs), nitric oxide (NO), reactive oxygen species (ROS), lipoxins (LXs), platelet-activating factor (PAF), and leukotrienes (LTs), have significant implications in the pathophysiology of the innate and adaptive immune response in RA.

Rheumatoid arthritis has been demonstrated to have a strong genetic component, which has been shown to make people up to 60% more susceptible to contracting the condition (Dedmon LE, 2020). At present, pharmacological treatment for this condition is comparable to that of other autoimmune diseases (AIDs). It involves the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) (Radu e Bungau, 2021)

One of the alternative medications for arthritis has been Cannabis sativa, specifically cannabidiol (CBD), which is a phytocannabinoid extracted from the plant. CBD has been demonstrated to be distinct from the psychoactive compound Δ-9-tetrahydrocannabinol (THC) in terms of its potency and addictive potential. The anxiolytic and panic-relieving properties of CBD have been shown to mitigate the adverse psychoactive effects of THC, while concurrently potentiating the effects of opioids, which may lead to a reduction in opioid consumption. The following essay will provide a comprehensive overview of the relevant literature on the subject (Aran et al., 2021).

The pharmacodynamics of cannabidiol (CBD) are characterized by their binding to type 2 cannabinoid receptors (CB2), which may aid in regulating the immune system. A correlation has been identified between the endocannabinoid system and the immune system. Conversely, type 1 cannabinoid receptors (CB1) must have their effects blocked by antagonists, such as CB1, when activated, can stimulate the inflammatory response. The following essay will provide a comprehensive overview of the relevant literature on the subject (Roseti et al., 2024).

As mentioned above, RA mainly affects the peripheral joints, and in its acute phase, patients complain of severe pain associated with swelling and morning stiffness in the affected areas. Symptoms may include more sensitive joints, increased local temperature, and joint stiffness after periods of rest. Because it is a systemic disease, many patients also experience significant fatigue, fever, loss of appetite, and weight loss (Scherer; Häupl; Burmester, 2020). Approximately 40% of people with RA may experience symptoms that are not localized in the joints, such as skin, eyes, lungs, heart, kidneys, salivary glands, nerve tissue, bone marrow, and veins. These symptoms can vary depending on severity, with periods of increased disease activity (flare-ups) alternating with periods of relative remission (without pain and swelling) (Bullock et al., 2018).

Among the main characteristics observed in patients with RA are: symmetrical arthritis affecting both sides of the body; morning stiffness responsible for lack of flexibility in the joints during the first hour after waking up; polyarthritis which is evidenced by inflammatory involvement in five or more joints); a preference for small joints, especially the proximal interphalangeal and metacarpophalangeal joints; and rheumatoid nodules that are painful, hardened in consistency, and usually appear in extensor areas, such as palms, elbows, and buttocks (Jahid et al., 2023; Diaz et al., 2023; P Shah e J Trivedi, 2024). Marked edema in the wrist and metacarpophalangeal (MCP) joints are caused by synovial proliferation, and rheumatoid nodules commonly form near the extensor surface of the elbow. They may be attached to the underlying periosteum or remain freely mobile (Conti et al., 2024).

Treatment of arthritis

The treatment of arthritis is individualized for each patient, depending on the severity of the disease, with the main objective being complete remission of the disease to prevent joint damage, functional disability, fatigue, and the development of extra-articular manifestations of RA (Lin; Anzaghe; Schulke, 2020). Among the pharmacological options for the treatment of RA, the most used are DMARDs, glucocorticoids, NSAIDs, and analgesics. Studies show that the drug of choice for RA is DMARDs, especially methotrexate (MTX), along with glucocorticoids, which are used in more severe cases of pain and for a very short period (Bullock et al., 2018).

NSAIDs and analgesics

In the past, these two classes of drugs were the first choice for treatment, but in the long term, they did not perform as expected and, instead, presented high toxicity to the cardiovascular and gastrointestinal systems. However, they were effective in reducing pain in the case of analgesics and in reducing pain and stiffness in the case of NSAIDs (Figure 1). Over the years, they have been replaced by DMARDs and are currently used only as adjuvant therapy for a short period of time (Lopes, 2019).

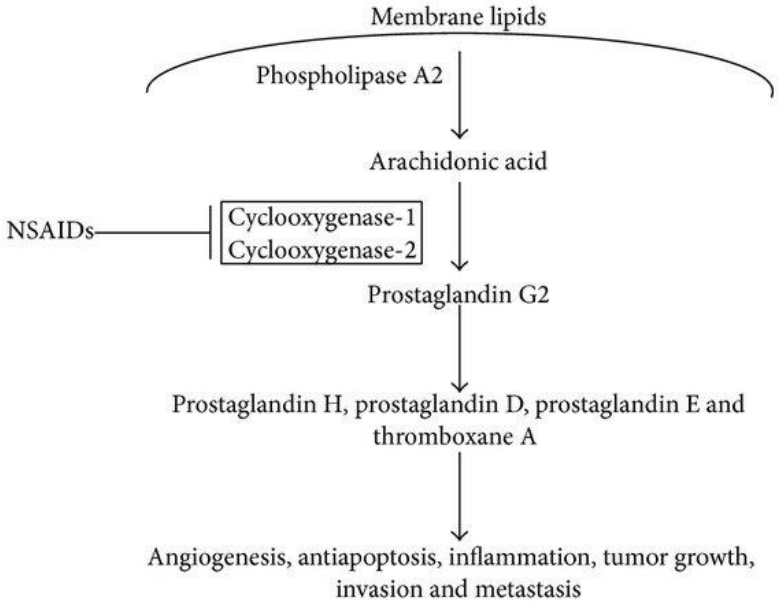

Figure 1 – Mechanism of action of NSAIDs. Source: (ResearchGate 2024).

Glucocorticoids

This class of medication is widely utilised for the management of pain, swelling, and stiffness; however, it has been demonstrated to have no impact on the long-term progression of the disease. However, it is important to note that these medications can have various adverse effects, including bone thinning, weight gain, immunosuppression, diabetes, and fluid retention. Therefore, their use is recommended for a limited duration, always in conjunction with DMARDs (Lopes, 2019). The most recommended approach is intra-articular, a technique that can be employed at any stage of treatment, particularly in patients with minimal joint limitations and during acute episodes of RA. Consequently, patients using glucocorticoids are advised to cease their use abruptly. It is imperative to note that the process of weaning should be executed in a gradual manner, with the objective of averting hypothalamic-pituitary-adrenal axis insufficiency (Bullock et al., 2018).

DMARDs

As previously stated, methotrexate (MTX) is currently regarded as the primary treatment for rheumatoid arthritis (RA). It is widely regarded as the primary treatment option for RA. It is a folic acid analog that competitively inhibits the binding of dihydrofolic acid to the enzyme that converts dihydrofolic acid to folinic acid, resulting in the inhibition of polyamine and amino acid production (Figure 2) (Lopes, 2019). Glucocorticoids are recommended at the commencement of treatment due to their rapid anti-inflammatory effect, as methotrexate (MTX) has a slow mechanism that will take 4 to 8 weeks to initiate remission of rheumatoid arthritis (RA). Frequently, treatment with methotrexate (MTX) is discontinued due to its adverse effects, which include, but are not limited to, nausea, alopecia, stomatitis, diarrhea, fatigue, hepatotoxicity, and bone marrow deterioration (Lin; Anzaghe; Schulke, 2020). In order to mitigate the occurrence of adverse effects, folic acid is administered orally on the morning following the ingestion of the medication. However, with the recent discovery of biological DMARDs, Anti-TNF-α is the most widely used of this new class. The combination of biological DMARDs is frequently employed due to their enhanced therapeutic efficacy in comparison to monotherapy (Plasencia-Rodríguez et al., 2024; Furer e Elkayam, 2023).

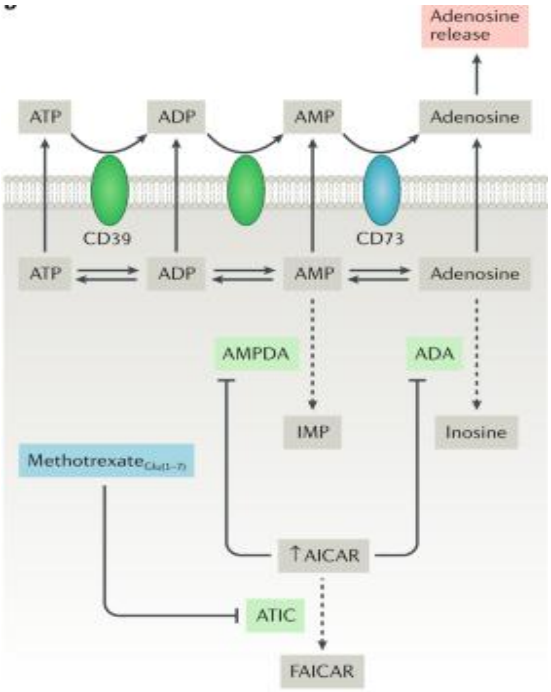

Figure 2 - Methotrexate regulates essential biochemical reactions. Source: (Cronstein & Aune 2020).

Rheumatoid factor

Rheumatoid factor (RF) is the primary antibody linked to rheumatoid arthritis (Togashi et al., 2025). It is important to note that RF is a class of immunoglobulin capable of binding to a subset of IgG, playing a key role in the pathogenesis of RA, making its presence conducive to diagnosis (Van Delft & Huizinga, 2020; Nicolo et al., 2020). The classification of RF is dependent upon the isotype, with the IgM category being the most prevalent in serological analysis. However, it has been demonstrated that RF does not initiate the inflammatory process of the disease; rather, it perpetuates and amplifies the process (Nicolo et al., 2020). This phenomenon can be attributed to the capacity of an antigenic stimulus to instigate the emergence of atypical IgG, consequently leading to the formation of RF (Mergaert et al., 2022).

In principle, RF is widely used to differentiate RA from other chronic arthritides, as it is found in 60% to 80% of RA cases, usually in high titers (Sobhy et al., 2022). It is important to note that other diseases, including but not limited to systemic lupus erythematosus (SLE), Sjögren's syndrome, chronic active hepatitis, leprosy, and certain parasitic infections, have been observed to yield positive results and low titers for this antibody (Cruz et al., 2023; Cheng et al., 2020).

History of cannabis

In 2737 BC, the first reports of the use of marijuana for medicinal purposes appeared, mainly in China, by Emperor Shen Nieng, who prescribed this tea for various diseases, such as gout, rheumatism, and memory problems. With the growing popularity of marijuana, it spread throughout Asia, the Middle East, and the East Coast of Africa, where it was used for all kinds of ailments, from earaches to labor pains, and the adverse effects of excessive use were impotence, blindness, and demonic apparitions (hallucinations) (Pisanti; Bifulco, 2019). In the 70s AD, according to the work Materia Medica by the Greco-Roman Pedanius Dioscorides, used as the main source of information on medicines, with more than a thousand substances described, marijuana was the most effective for joint pain and inflammation (Grosso, 2020).

In 1808, cannabis spread to Brazil thanks to African slaves brought from the colonies, becoming common among indigenous people and, later, among white people, and even queens became accustomed to drinking cannabis tea (Carlini; Rodrigues; Galduróz, 2005).

In 1839, with the presentation of William O'Shaughnessy's thesis, the plant arrived in England and began to be studied. Through William's observations, he was able to record some of the effects of marijuana, such as euphoric happiness, increased appetite, and other feelings of well-being. Soon, its therapeutic use began to be noticed, which led to animal testing to observe its effects. After these observations, it was noted that the plant did not present a risk of toxicity, and so tests were carried out on humans. In some of the cases described, the doctor identified Cannabis as an important alternative for seizures in children, and as the main analgesic for pain relief in some diseases such as cholera, rabies, tetanus, and rheumatism (Ryan et al., 2021; Laaboudi et al., 2024).

Even without knowledge of the cannabinoid system, the benefits that this plant could offer for numerous treatments were observed. According to Birch, in 1889, the world saw the application of *Cannabis sativa* for the treatment of opium addiction, acting as an antiemetic, becoming an established medicine in the US and Europe (Pantoja-Ruiz et al., 2022).

In the 2000s, several studies focused on the endocannabinoid system, defined as cannabinoids produced by the human body itself. The endocannabinoids identified were anandamide (AEA), 2-arachidonoylglycerol (2-AG), as well as the discovery of CB1 and CB2 receptors and their enzymes. After several investigations into its clinical potential, promising results were observed in several areas, such as the central nervous system (CNS) and the immune system (Gallego-Landin et al., 2021; Piomelli e Tagne, 2021; Simankowicz e Stępniewska, 2025).

Since the early 2000s, there has been a growing medicinal use of CBD, and several clinical reports have been published with significant improvements in pathologies. The story of Charlotte Figi, a 5-year-old girl with Dravet syndrome, who started therapy with the phytocannabinoid and saw a great improvement in her epilepsy, as well as that of Anny Fisher, a 5-year-old girl with CDKL5 syndrome, who also had a successful case in controlling her seizures with the use of CBD, where she was the first patient to obtain the drug in court, showing this alternative way of combating seizures. The widespread dissemination of these results mobilized neuroscientists to discuss the reclassification of CBD and the regulation of *Cannabis sativa* by ANVISA (Sousa; Costa, N; Costa, 2021).

In 2015, Judge Marcelo Rebello Pinheiro ordered ANVISA to remove THC, a substance found in marijuana, from the list of prohibited substances in Brazil. Therefore, although the importation of medicines containing CBD and THC was provisional, their purchase was permitted. In 2016, congressmen overturned the governor's veto on CBD, making the Federal District the first state to guarantee phytocannabinoids to SUS patients (Sousa; Costa, N; Costa, 2021).

Cannabis belongs to the Cannabaceae family, genus Cannabis, and has three species: Cannabis sativa, Cannabis indica, and Cannabis ruderalis. Cannabis sativa originates from tropical regions such as Mexico, Thailand, and Colombia and is known for its tall plants with long, narrow leaves. It has a high concentration of THC, resulting in a stimulating effect that is predominantly found in the female plant (Lapierre; Monthony e Torkamaneh, 2023; Ren et al., 2021).

Cannabis indica is native to mountainous regions such as Afghanistan, India, and Pakistan and has the characteristics of a short, compact plant with broad, dense leaves. It is known for its relaxing effects and has a high concentration of CBD (Murovec et al., 2022).

Cannabis ruderalis, native to cold regions such as Russia, where it was discovered, is the least known of the three and is characterized by its compact size, small leaves, and flowering regardless of photoperiod (Table 1) (Lapierre; Monthony e Torkamaneh, 2023).

Table 1: Botanical and chemical characteristics of *Cannabis* species

Species	Origin	Habitat	Morphology	Cannabinoid concentration
Cannabis sativa	Central Asia, Mexico, Thailand, and Colombia	Temperate and tropical regions	Tall, slender plant with long, narrow, sparsely densely packed leaves	High THC concentration
Cannabis indica	Afghanistan, India, and Pakistan	Mountainous regions	Short, compact plant with broad, dense leaves	High CBD concentration
Cannabis ruderalis	Russia	Cold regions	Smaller, compact plant, wild-growing and fast flowering	Similar concentrations of THC and CBD

Source: (Author, 2025).

Cannabinoids

CBD is a phytocannabinoid extracted from the *Cannabis sativa L.* plant, as is THC, and has been investigated as a therapeutic alternative for the treatment of arthritis. Commercially, it can be found in formulations such as Sativex®, which consists of an equimolar mixture of THC and CBD obtained from plant extracts, and Epidiolex®, a medicine based on isolated CBD.

The physiological processes associated with cannabinoids primarily occur within the hepatic system, wherein they undergo metabolic transformation into active metabolites that exhibit a comparable degree of activity to that of the original substance. Alternatively, these processes may result in the formation of inactive metabolites that lack the capacity to sustain the same level of activity as the original substance. The following essay will provide a comprehensive overview of the relevant literature on the subject (Marinho; Silva, 2023).

Cannabinoid receptors are classified as G protein-coupled receptors. The CB1 gene, which is encoded by the CNR1 gene and predominantly located in the central nervous system, where they are detected in glutamatergic, GABAergic, serotonergic, noradrenergic, and cholinergic neurons. This receptor plays a key role in regulating critical neurobiological processes, including learning, memory, mood, sleep, pain, and appetite (Sousa & Fernandes, 2024).

The CB2 receptor, on the other hand, is encoded by the CNR2 gene and its predominantly located in peripheral tissues, especially in the immune system and hematopoietic cells, but have also been identified in specific regions of the central nervous system, mainly in pathological conditions. CBD acts as a negative allosteric modulator of CB2 receptors, which means that it can alter the receptor's response to its endogenous ligands without necessarily activating it directly. This modulation can result in the regulation of inflammatory and neurodegenerative processes, making CBD a promising candidate for the treatment of diseases such as multiple sclerosis, Alzheimer's, and other neuroinflammatory conditions. In addition, the activation of CB2

receptors is not associated with psychoactive effects, which increases the safety of CBD's therapeutic use (Hakami e Alshehri, 2025; Tomaszewska-Zaremba; Gajewska e Misztal, 2025).

Table 2 – Main characteristics of cannabinoid-based drugs

Compound/Drug	Origin	Composition	Proposed therapeutic indication	Commercial form
CBD (Cannabidiol)	Phytocannabinoid from *Cannabis sativa L.*	Isolate	Alternative for arthritis, refractory epilepsy, neurological and inflammatory disorders	Epidiolex® (isolate)
THC (Tetrahydrocannabinol)	Phytocannabinoid from *Cannabis sativa L.*	Isolated or in combination	Chronic pain, spasticity, nausea, and chemotherapy-induced vomiting	Present in combination formulations such as Sativex®
Sativex®	*Cannabis sativa L.* extract	Equimolar mixture of THC and CBD	Spasticity in multiple sclerosis, chronic pain, and under investigation for arthritis	Oromucosal spray
Epidiolex®	Derived from *Cannabis sativa L.*	CBD isolate	Refractory epilepsy (Lennox-Gastaut and Dravet syndromes); in a study for inflammatory diseases at	Oral solution

Source: (Author, 2025).

The two receptors show approximately 44% homology at the protein level. Furthermore, their binding sites have a superimposable three-dimensional structure, which allows agonists to cross-bind to each receptor (Sousa & Fernandes, 2024).

CBD, however, does not bind directly to CB1 with high affinity, but acts as a negative allosteric modulator, reducing the effectiveness of ligands such as THC and thus attenuating their psychoactive effects. CBD also acts as an allosteric modulator, but with a focus on regulating inflammatory and immune processes (Mujahid et al., 2025). This distinction is crucial, as it allows CBD to exert therapeutic effects such as anti-inflammatory, neuroprotective, and immunomodulatory action without causing cognitive or behavioral changes, making it a promising alternative for the treatment of various clinical conditions without the adverse effects associated with THC use (Valentino e Volkow, 2024; Schouten et al., 2024).

CBD can reduce the adverse cognitive-behavioral effects of THC on CB1, as it acts as an antagonist of CB1 and CB2 receptors (Schouten et al., 2024). In addition, it has anxiolytic, analgesic, and antiemetic properties, mechanisms that are mediated by binding to serotonergic receptors, especially $5HT_{1A}$ (Pacher, Kogan, Mechoulam, 2020).

Given the growing scientific and clinical interest in the therapeutic effects of cannabinoids, especially CBD and THC, it is essential to understand their applications and impacts in the treatment of various health conditions. Table 3 presents an overview of the diseases and effects associated with CBD and THC. This information reinforces the potential of CBD and THC as promising pharmacological alternatives, especially in contexts where conventional treatments have limitations or significant adverse effects (Marinho; Silva, 2023).

Table 3 - Diseases and effects associated with CBD and THC

Category	CBD	THC
Diseases in which it aids treatment	Epilepsy; Anxiety disorders; Parkinson's disease; Chronic pain; Schizophrenia; Migraine; Arthritis; Sleep disorders; Bipolar disorder.	Muscle spasticity; Glaucoma; HIV; Dystonia; Cachexia; Fibromyalgia; Autism; Neuropathic pain; Cerebral palsy
Effects	Antioxidant; Muscle relaxant; Anxiolytic; Antipsychotic; Neuroprotective; Anti-inflammatory; Antiepileptic.	Cardiac tachycardia; Sedation; Anxiety; Hallucinogenic; Chemical dependency; Euphoria; Conjunctival hyperemia

Source: (Author, 2025).

Synthetic Cannabinoids

Nabilone (Cesamet® or Canemes®), a synthetic analogue of THC, has been approved in selected countries for the treatment of intractable nausea and vomiting in cancer patients (Häuser et al., 2023). Dronabinol (Marinol® or Syndros®), a synthetic THC, has been approved for similar therapeutic use in some countries (Häuser et al., 2023). Levonantradol, a potent synthetic THC, is currently available only for research purposes and not as a licensed therapeutic drug in any country.

Anandamide (AEA) is an amphipathic molecule that plays a significant role in neurophysiological functions due to its endogenous agonist effect on CB1 and CB2 receptors. Some studies have shown that AEA can act independently of receptors, potentially through its interaction with phospholipids (Guerra, 2019).

As documented in the literature, the synthesis of the AEA molecule is initiated by the N-arachidonoylation of a constituent of the phospholipid bilayer, phosphatidylethanolamine, resulting in the formation of N-arachidonoyl phosphatidylethanolamine (NAPE). This product is formed from the activity of the enzyme N-acyl transferase, followed by the hydrolysis of NAPE by another enzyme called selective phospholipase D. This process gives rise to N-arachidonoylethanolamine (anandamide) (Guerra, 2019). AEA has been shown to play a significant role in both the central nervous system (CNS) and peripheral activities over several years. This capacity of AEA requires the presence of numerous receptors, which interact with the CB1, CB2, vanilloid transient potential receptor-1 (TRPV1), G-coupled receptors 55 (GPR55) and 119 (GPR119), and peroxisome proliferator-activated receptors (PPARs) (Guerra, 2019). The pharmacological effects of AEA and THC are highly analogous; however, AEA has reduced in vivo efficacy when compared to THC. This discrepancy can be attributed to the rapid enzymatic degradation of AEA (Maccarrone et al., 2023).

In view of the above, this study aims to conduct an integrative review of the use of cannabidiol in the treatment of rheumatoid arthritis. In this regard, the research will focus on the mechanisms of action of cannabidiol in the endocannabinoid system, its comparison with conventional therapies, and a discussion of the consistency of the available evidence. The objective is to identify gaps and starting points for future investigations.

Methodology

This study was conducted as an integrative literature review, with a methodological approach that allows for the collection, critical evaluation, and synthesis of evidence from different research designs, enabling a comprehensive and multifaceted view of the use of cannabidiol (CBD) in the treatment of rheumatoid arthritis (RA). This selection is particularly appropriate in emerging areas, where the scarcity of consolidated clinical trials is notorious, but the abundance of preclinical, observational studies, and secondary reviews is evident (Peters et al., 2021; Pollock et al., 2024).

Search Strategy

The search strategy was carefully adjusted to meet the specific requirements of each database (PubMed®, Scopus™, Web of Science™, LILACS, Science Direct, and Google Scholar), including adaptations in quotation marks and the use of terms in the plural and singular to ensure comprehensive results.

The Boolean operator "OR" was used to group the synonyms of each term, and the blocks were connected by the operator "AND," composing the final search strategy. The Boolean operator "OR" was used to group synonyms for each term, and the blocks were connected by the operator "AND," composing the final search strategy. The keywords were organized into three main blocks related to the following guiding terms: "rheumatoid arthritis," "cannabidiol," and "treatment/therapy," as shown in Table 4.

Table 4: Keywords included in the electronic search strategy

Blocks	Keywords used
#1 Disease	"rheumatoid arthritis" OR "RA" OR "artrite reumatoide"
#2 Intervention	"cannabidiol" OR "CBD" OR "cannabinoids" OR "canabinoides" OR "cannabis" OR "medical cannabis"
#3Treatment/Approach	"treatment" OR "therapy" OR "therapeutics" OR "intervention" OR "pharmacological treatment"
Search String	(#1) AND (#2) AND (#3)

Source: Authors (2025).

Eligibility Criteria

This integrative review considered relevant studies that addressed the effects, mechanisms of action, and potential benefits of cannabidiol (CBD) in the treatment of rheumatoid arthritis (RA), published between 2019 and 2025. Studies that met at least one of the previously defined exclusion criteria were excluded. The eligible studies were checked to confirm whether the evidence is valid or if any retractions were recorded using the

Scite tool (https://scite.ai) (M. B. Costa et al., 2024; Ribeiro et al., 2024). This tool is used to verify the validity of the evidence and identify any retractions, improving the accuracy and reliability of the analysis (Nicholson et al., 2021; Pérez-Neri et al., 2022). Therefore, to be considered eligible, articles had to meet all of the following inclusion criteria:

The Inclusion Criteria Were As Follows:

(i1) published between 2019 and 2025; (i2) in English or Portuguese, with full text available; (i3) directly addressing the use of CBD in rheumatoid arthritis, whether in preclinical models, clinical trials, observational studies, or secondary reviews; (i4) published in peer-reviewed journals.

The Following Items Were Excluded:

(e1) duplicate articles; (e2) editorials, comments, letters to the editor, conference abstracts, and isolated case reports; (e3) publications not directly related to the topic or without access to the full text; (e4) studies that have been retracted.

Selection Process

The process followed PRISMA 2020 in four phases: identification of records in the selected databases; removal of duplicates; screening by title and abstract; and full-text reading to apply eligibility criteria. Eleven studies addressing rheumatoid arthritis and evaluating the anti-inflammatory effects of cannabidiol (alone or in cannabinoid formulations) were included in the summary of results. Although several other articles were located and cited throughout the manuscript, only these eleven formed the analytical basis of the review and were considered in the qualitative synthesis of the findings. The selection and extraction were conducted carefully by two reviewers, with disagreements resolved by consensus.

Results

This integrative review analyzed 11 studies that investigated the therapeutic potential of cannabidiol (CBD) and other phytocannabinoids in the management of rheumatoid arthritis (RA). The synthesis of the results was organized into three main areas: preclinical studies, clinical evidence, and literature reviews. The experimental results demonstrated anti-inflammatory and immunomodulatory effects of CBD. In a murine model of collagen-induced arthritis, Maayah et al. (2020) observed a significant reduction in joint inflammation, oxidative stress, and bone erosion.

Similar results were described by Aswad et al. (2025), who used a CBD-rich extract (CBD-X), demonstrating a reduction in IL-1β, IL-6, and TNF-α, inhibition of the NF-ϰB/Akt pathways, and promotion of a pro-resolution phenotype in macrophages. In synovial fibroblasts from RA patients, Lowin et al. (2020) reported selective apoptosis of activated cells and decreased IL-6, IL-8, and MMP-3, mechanisms mediated by TRPA1.

In addition, Grogan et al. (2023) identified synergistic effects of the combination of CBD + cannabichromene (CBC), with positive modulation of the serum cytokines profile. Together, these findings support the biological plausibility of CBD as an agent capable of attenuating inflammation and preserving joint integrity. Publications involving humans, although limited, suggest symptomatic benefits of CBD in pain management and life quality.

Schubert et al. (2023), in an observational study with Australian patients with chronic pain, including cases of RA, reported significant improvement in pain and overall well-being scores, with predominantly mild adverse

events such as drowsiness and dry mouth. Similarly, Frane et al. (2022) found that 83% of patients with arthritis who used CBD experienced pain relief, and 60% reduced or discontinued the use of NSAIDs and opioids. Despite the heterogeneity in formulations and dosages, these studies reinforce the adjuvant potential of CBD in the treatment of RA. Critical reviews have highlighted both the promise and limitations of the current evidence.

Fitzcharles, Clauw, and Häuser (2023) pointed out the scarcity of RA specific randomized clinical trials evaluating CBD, despite robust preclinical data. Mujahid et al. (2025) highlighted CBD's ability to modulate immune cells, with an increase in IL-10 and a reduction in TNF-α and IL-6, confirming its potential. Mujahid et al. (2025) also highlighted CBD's ability to modulate immune cells, with increased IL-10 and reduced TNF-α and IL-6, confirming its immunomodulatory potential.

Britch and Craft (2023) analyzed the role of minor phytocannabinoids, highlighting methodological heterogeneity but reinforcing the safety and clinical relevance of CBD as an adjuvant. Although not the main focus, some included studies explored phytocannabinoids other than CBD. Lowin et al. (2023) reported anti-inflammatory properties of cannabigerol (CBG) in synovial fibroblasts from RA patients. Vanegas et al. (2024), evaluating Δ8-THC in a murine model of collagen-induced arthritis, observed a reduction in inflammation, edema, and bone erosion, with results comparable to dexamethasone. These findings broaden the perspective that multicomponent formulations may enhance therapeutic effects in the management of RA.

Discussion

The results of this integrative review demonstrate that cannabidiol (CBD) has consistent anti-inflammatory and immunomodulatory effects in preclinical models of rheumatoid arthritis (RA). Experimental studies have identified relevant mechanisms of action, including the induction of selective apoptosis in activated synovial fibroblasts, the modulation of pro-inflammatory pathways mediated by NF-ϰB/Akt, and the reduction of cytokines such as IL-1β, IL-6, and TNF-α (Maayah et al. 2020; Lowin et al. 2020; Aswad et al. 2025).

These findings reinforce the biological plausibility that CBD may act on central cellular and molecular targets of RA pathogenesis, contributing not only to the reduction of inflammation but also to the preservation of joint integrity. In animal models, CBD has been shown to reduce oxidative stress and prevent structural damage, characteristics that position it as a promising adjuvant candidate. However, when transposed to the clinical setting, the findings remain limited. Observational studies suggest that CBD may reduce pain, improve life quality, and decrease the use of analgesics, NSAIDs, and opioids (Schubert et al. 2023; Frane et al. 2022).

Despite this, the heterogeneity in formulations, dosages, and routes of administration, associated with the absence of randomized controlled clinical trials, prevents the generalization of results. Thus, it is still premature to consider CBD as a consolidated intervention for the management of RA. The analyzed reviews complement this overview. Fitzcharles, Clauw, and Häuser (2023) highlight the scarcity of rigorous clinical trials that directly evaluate CBD in RA, while Mujahid et al. (2025) point out that preclinical data support a robust immunomodulatory profile, with an increase in IL-10 and a reduction in TNF-α and IL-6.

Britch and Craft (2023), in turn, emphasize the methodological heterogeneity and the consequent difficulty in formulating standardized clinical recommendations, even though they recognize the safety and therapeutic potential of CBD. Another emerging aspect is the investigation of phytocannabinoids beyond CBD. Recent evidence suggests that compounds such as cannabichromene (CBC), cannabigerol (CBG), and Δ8-THC may have synergistic or complementary effects. Grogan et al. (2023) observed that the combination of CBD + CBC potentiated inflammatory reduction in murine models.

Lowin et al. (2023) identified anti-inflammatory properties of CBG in human synovial fibroblasts, while Vanegas et al. (2024) reported that Δ8-THC reduced inflammation and bone erosion in an experimental model of arthritis, with efficacy comparable to dexamethasone. These findings broaden the debate on the usefulness of multicomponent formulations in the management of RA, although they still lack clinical validation.

Despite advances, critical gaps remain in literature. The absence of randomized, multicenter, long-term clinical trials compromises the consolidation of clinical evidence. The lack of standardization in formulations, concentrations, and dosage regimen hinders the comparability of results and prevents the definition of consistent therapeutic protocols. Most clinical studies evaluated only self-reported outcomes, without including laboratory markers, imaging tests, or validated disease activity scores. Long-term safety also remains uncertain, especially in patients on polypharmacy with DMARDs and biologics, a frequent context in the treatment of RA.

In summary, although preclinical results are promising and initial clinical data indicate symptomatic benefits, the use of CBD in rheumatoid arthritis should still be considered exploratory. Significant advances will depend on the conduct of high-quality clinical trials, the standardization of formulations, and the development of studies that integrate clinical and laboratory biomarkers, in addition to the systematic investigation of synergies between different phytocannabinoids.

Conclusion

Cannabidiol is emerging as a promising therapeutic alternative for rheumatoid arthritis, particularly in pain control, inflammation reduction, and quality of life improvement. However, the available evidence is still incipient and does not allow for its adoption as a substitute for conventional pharmacological therapies. To date, CBD should only be considered as an adjunctive resource, under medical supervision and within individualized protocols. The consolidation of its clinical use depends on the conduct of randomized, multicenter, long-term clinical trials capable of establishing clear parameters of efficacy, safety, and dosage standardization. Overcoming these gaps is essential to transform CBD into an effective and widely recommended therapeutic tool in the management of rheumatoid arthritis.

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