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REVIEW ARTICLE

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Nutrological modulation of cannabidiol in the inflammatory processes of athletes: a systematic review

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Abstract

Introduction: The correct interaction between the elements of the endocannabinoid system plays an important role in the development of the central nervous system. Clinical and preclinical studies suggest that cannabidiol (CBD) may be useful for athletes due to its anti-inflammatory, analgesic, anxiolytic, and neuroprotective properties and its influence on the sleep-wake cycle. Furthermore, a series of implications for epigenetic processes were also proven, through changes in the expression of exosomes and microRNAs responsible for modulating the immune and inflammatory systems. **Objective:** It was to list the main clinical considerations of the nutritional modulation of cannabidiol in inflammatory and immunological processes in athletes through a systematic review. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from January to March 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and AMSTAR-2, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 88 articles were found. A total of 36 articles were evaluated in full and 18 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 26 studies with a high risk of bias and 12 studies that did not meet GRADE and AMSTAR-2. CBD has been reported to exert a range of physiological, biochemical, and psychological effects with the potential to benefit human health. For example, there is preliminary supporting evidence for CBD's anti-inflammatory, neuroprotective, analgesic, and anxiolytic actions and the possibility that it may protect against gastrointestinal damage associated with inflammation and promote the healing of traumatic skeletal injuries. The combination of Δ9-THC and CBD can alter the activity of microRNAs responsible for increasing the biosynthesis of inflammatory mediators, leading to a reduction in the inflammatory profile. Despite these findings, there is still a lack of randomized and/or prospective controlled clinical studies with a robust sample size to better understand the safety and

effectiveness of the use of cannabidiol by medium to high-performance athletes, as well as better understand the dosages for each type of sports performance.

Keywords: Sports. Nutrology. Cannabidiol. MicroRNAs. Exosomes. Inflammatory processes.

Introduction

In the nutritional and sports practice scenario, cannabidiol (CBD) has effects that impact mood, sensation, perception, tension, appetite, and pain. Also, CBD has shown anxiolytic, antipsychotic, neuroprotective, anti-inflammatory, and antiemetic properties **[1-3]**. However, growing interest in the substance as medicine was renewed in the 1990s, with the discovery of cannabinoid receptors 1 and 2 (CB1 and CB2, respectively), endogenous ligands (endocannabinoids, N-arachidonoyl-ethanolamine (anandamide/AEA) and 2 - arachidonoyl-glycerol (2-AG)) and enzymes as part of the endocannabinoid system (ECS) in the brain **[4]**.

In this scenario, the correct interaction between all these ECS elements plays an important role in the development of the central nervous system (CNS), synaptic plasticity, motor control, memory, cognition, stress, emotional responses, reward and motivated behavior, appetite, pain, development, and homeostasis. Outside the brain, the ECS system is one of the crucial factors modulating the autonomic nervous system, immune system, endocrine system, gastrointestinal tract, reproductive system, and microcirculation **[5]**.

In this regard, endocannabinoids are one of the most important systems controlling excitatory and inhibitory neurotransmission, as well as neuroplasticity **[5]**. They serve as retrograde signaling messengers at gabanergic and glutamatergic synapses, as well as modulators of postsynaptic transmission, interacting with other neurotransmitters, including dopamine. Endocannabinoids also participate in modulating the hypothalamic-pituitary-adrenal (HPA) axis and regulating stress. The synthesis of cannabinoid receptor agonists and antagonists, anandamide uptake blockers, and inhibitors of anandamide endocannabinoid degradation have opened new treatment strategies **[6]**.

In the domain of sports, cannabis has been banned by the World Anti-Doping Agency (WADA) in all competitive sports since 2004. The few studies on physical exercise and cannabis have focused on the main compound, namely Δ9-tetrahydrocannabinol. CBD is another well-known phytocannabinoid present in dried or heated cannabis preparations. Unlike Δ9-tetrahydrocannabinol, CBD is not intoxicating but exhibits interesting pharmacological properties for medical use. The global regulatory status of CBD is complex and this compound is still a controlled substance in many countries. Interestingly, however, the World Anti-Doping Agency has removed CBD from the list of banned substances, in or out of competition since 2018. This recent decision by WADA leaves the door open for the use of CBD by athletes **[7]**.

Preclinical studies suggest that CBD may be useful for athletes due to its anti-inflammatory, analgesic, anxiolytic, and neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, little clinical data is available on CBD in the context of exercise. Furthermore, a series of implications for epigenetic processes have also been proven, through changes in the expression of microRNAs responsible for modulating the immune and inflammatory systems **[7,8]**.

Therefore, the present study aimed to list the main clinical considerations of the nutritional modulation of cannabidiol in inflammatory and immunological processes in athletes through a systematic review.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 02/20/2024. AMSTAR2 (Methodological Quality Assessment of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 02/20/2024.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (DeCS/ MeSH Terms): *"Sports. Nutrology. Cannabidiol. MicroRNAs. Exosomes. Inflammatory processes"*. The research was carried out from January to March 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Quality of Studies and Risk of Bias

According to GRADE recommendations (available at: https://www.jclinepi.com/article/S0895-4356(10)00332-X/fulltext. Accessed on 02/12/2024), the quality of scientific evidence in studies covered was classified as high, moderate, low or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses.

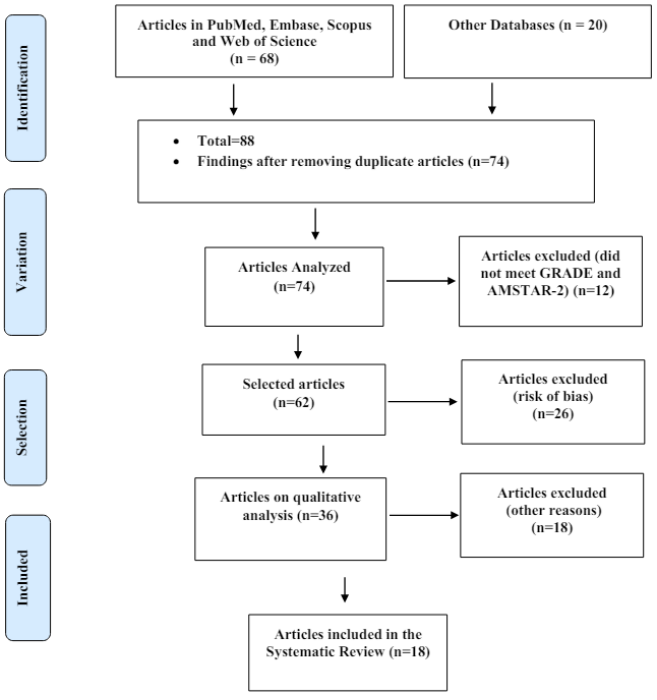
High-quality evidence was assigned using four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials; 3) Sample size greater than 20 participants; 4) Studies with statistically well-designed results; 5) Studies published in indexed journals and with a significant impact factor; 6) descriptive validity (identification of studies that clearly showed the dosage, route of delivery and follow-up of participants), interpretative (identification of advantages and disadvantages), theoretical (credibility of the methods) and pragmatic. The low quality of evidence was attributed to case reports, editorials, and brief communications. The risk of bias was analyzed according to the Cochrane instrument (Available at: https://sites.google.com/site/riskofbiastool/. Accessed on 02/12/2024) through analysis of the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 88 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was carried out, removing articles that did not include the topic of this article, resulting in 62 articles. A total of 36 articles were evaluated in full and 18 were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 26 studies with a high risk of bias and 12 studies that did not meet GRADE.

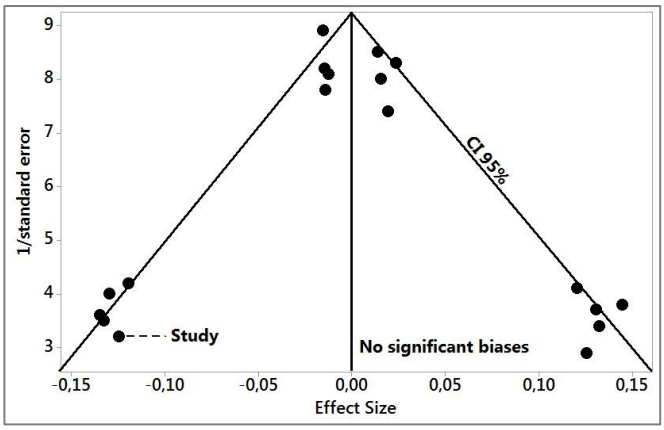
Figure 1. Flowchart. Article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph presented symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the base of the graph and in studies with a large sample size that are presented in the upper region.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal=18 studies evaluated in full in the systematic review).



Source: Own authorship.

Major Clinical Findings

One of the systems that has been intensively studied in recent years is the endocannabinoid signaling pathway, as a series of important interactions between cannabinoid receptors and biochemical pathways have been clarified. Furthermore, many important implications in inflammation and the immune system that are induced by the activity of cannabinoid receptors stimulated by delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) have been observed. One of the most important is the ability to reduce the biosynthesis of pro-inflammatory mediators and the modulation of immunological mechanisms. Different studies have reported that cannabinoids can reduce oxidative stress at the mitochondrial and cellular levels. There are important mechanisms modulated by the endocannabinoid signaling pathway, as well as molecular and cellular connections **[9]**.

Recent studies have shown the involvement of specific endocannabinoid receptors, such as the CB1

endocannabinoid receptor and the CB2 receptor, as well as their connection with important processes in sepsis, such as immune response, inflammatory response, and redox activity **[10]**. Furthermore, a series of implications for epigenetic processes have also been proven, through changes in the expression of microRNAs that are responsible for modulating the immune and inflammatory systems **[8]**.

In this sense, when stimulating CB1 and CB2 receptors through cannabinoids, such as delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), important changes occur in the main biochemical and cellular mechanisms **[11]**, with effects on the inflammatory profile. , immune response, metabolism, and metabolic status. Different research groups have also shown the impact of cannabinoids on the expression of microRNAs and the mechanisms of transcription and genetic modulation of cellular processes **[12]**.

In this scenario, it is highlighted that the molecular segment involved in modulating the immune response and the inflammatory cascade is represented by the expression of microRNAs **[13]**. The specific molecular activity of microRNAs in sepsis is complex, with numerous interactions being observed between Toll-Like receptors (TLRs) and a series of other specific biological signals, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κB), autophagy mechanisms, and apoptosis. The activity of TLRs is mediated in numerous cases by the expression of microRNAs, with subsequent modulation of molecular and biological mechanisms for the production of inflammatory mediators **[13]**.

Based on this, it can be defined that microRNAs are non-coding single-stranded RNAs that contain between 19 and 25 nucleotides **[14]**. Its biosynthesis begins in the cell nucleus through the action of RNA polymerase II on specific microRNA genes. After these reactions, the first forms of microRNAs (pri-microRNA) are obtained, which ultimately lead to the formation of mature species of microRNAs **[14,15]**.

The mature species are released from the cell as exosomes, apoptotic bodies, or high-density lipoproteins, becoming one of the pathways of intercellular communication, as well as a pathway for the modulation of specific biochemical and biological processes **[16,17]**. These epigenetic mechanisms are also involved in modulating the cannabinoid system. Furthermore, recent studies have proven the existence of certain links between THC/CBD activity and the response of CB1 and CB2 receptors by modulating the expression of microRNAs **[18]**.

The authors Juknat et al. **[19]** carried out a study on the interactions between CB1 and CB2 receptors with microRNAs after the activation of Δ9-THC and CBD. To simulate pro-inflammatory conditions, they stimulated BV-2 microglial cells with lipopolysaccharide (LPS) and subsequently analyzed the effects induced by Δ9-THC on microRNA expression. A significant increase in the expression of microRNA-21, microRNA-146a, and microRNA-155, closely linked to the TLRs and NF-κB biochemical pathways, was observed. Regarding CBD activity, they observed a decrease in the expressions of microRNA-146a and microRNA-155, as well as an increase in the expression of microRNA-34a. A similar study by Yang et al. **[20]** showed a decrease in the expression of microRNA-17, microRNA-92, microRNA-421, and microRNA-374b, induced by the action of Δ9-THC. The authors Chiarlone et al. **[21]** also reported the involvement of let-7d in the biochemical pathways that activate CB1 receptors.

In this sense, it is also highlighted that microRNAs play a critical role in modulating the response of immune cells to stimuli. Cannabinoids are known to exert beneficial actions, such as neuroprotection and immunosuppressive activities. Using lipopolysaccharide (LPS) to stimulate BV-2 microglial cells, the role of cannabinoids in the expression of miRNAs was examined. MiRNA sequencing analysis revealed that 31 miRNAs were differentially modulated by LPS and cannabinoid treatments. Furthermore, it was found that at the concentration tested, CBD has a greater effect than THC on the expression of most of the studied miRNAs. The results link the effects of LPS and cannabinoids to inflammatory signaling pathways. LPS increased the expression of pro-inflammatory miRNAs associated with Toll-like receptor (TLR) and NF-κB signaling, including miR-21, miR-146a, and miR-155, while CBD inhibited LPS-stimulated expression of miR -146a and miR -155. Furthermore, CBD upregulated miR-34a, known to be involved in several pathways, including Rb/E2f cell cycle and Notch-Dll1 signaling. The results show that both CBD and THC reduced the expression of the LPS-regulated Notch ligand Dll1. MiR-155 and miR-34a are considered redox-sensitive miRNAs, which regulate Nrf2-driven gene expression. Nrf2-mediated expression of redox-dependent genes defines a Mox-like phenotype in CBD-treated BV-2 cells **[22]**.

One study evaluated the impact of two doses of CBD oil on inflammation (IL-6), performance, and pain following an eccentric loading protocol in athletes. Participants (n = 4) participated in three conditions (placebo, low dose, and high dose) in this randomized, counterbalanced design. Each condition took 72 hours to complete, with a 1-week washout period between conditions. At the beginning of each week, participants underwent a loading protocol of six sets of ten eccentric-

only repetitions on the biceps curl. Participants consumed capsules of placebo, low dose (2mg/kg), or high dose (10mg/kg) CBD oil immediately after the session and continued every twelve hours for 48 hours. Venipunctures were performed before exercise and repeated 24, 48, and 72 hours after exercise. Blood samples were centrifuged for 15 minutes in gel and lithium heparin vacutainers. Plasma was separated from cells and stored at -80° until analysis. Samples were analyzed using an IL-6 immunometric assay (ELISA). There were no differences in inflammation between conditions or over time, handgrip strength between conditions or over time, or biceps curl strength between conditions or over time. There were no differences in pain between conditions, but there was a difference over time. However, there was a visible increase in IL-6 48 (4.88 ± 6.53) and 72 hours (3.12 ± 4.26) post-exercise in the placebo condition, which was not observed in the low dose condition (48: 0.35 ± 2.22; 72: 1.34 ± 5.6) and high (48: 1.34 ± 1.34; 72: -0.79 ± 5.34) **[23]**.

Furthermore, chronic musculoskeletal pain (CMK) is one of the most prevalent causes that bring patients to the doctor's office. The most common disorders affecting CMK structures are osteoarthritis, rheumatoid arthritis, back pain, and myofascial pain syndrome, all of which are responsible for severe pain and physical disability. While there are many known management strategies currently in practice, herbal compounds have recently begun to increase in the medical community, especially CBD. CBD plays vital roles in human health that go far beyond the classic immunomodulatory, anti-inflammatory, and antinociceptive properties. Recent studies have shown that CBD also improves cell proliferation and migration, especially in mesenchymal stem cells. Based on this, a review study analyzed the therapeutic potential of CBD in the context of regenerative medicine. Numerous studies listed in the literature indicate that CBD has a significant ability to modulate mammalian tissue to attenuate and reverse the notorious characteristics of chronic musculoskeletal disorders (MSDs). Most of the research included in this review reports common findings, such as immunomodulation and stimulation of cellular activity associated with tissue regeneration, especially in human mesenchymal stem cells. CBD is considered safe and well tolerated, as no serious adverse effects have been reported **[24]**.

A randomized, double-blind, placebo-controlled, repeat-dose clinical study tested the safety, tolerability, and preliminary effects on recovery of a formulation containing cannabidiol (CBD; 35 mg), cannabigerol (CBG; 50 mg), beta-caryophyllene (BCP; 25 mg), branched-chain amino acids (BCAAs; 3.8 g) and magnesium citrate (420 mg). Exercise-trained individuals (N = 40) underwent experimental induction of delayed-onset muscle soreness (DOMS) and completed follow-up visits 24, 48, and 72 hours after DOMS. Participants were randomized to active or placebo formulation and consumed the formulation twice daily for 3.5 days. The results showed that there was one adverse event in the active group (diarrhea) and two in the placebo group (dry mouth; rash/swollen eye). There was 100% self-reported compliance with formulation consumption in both groups. For the primary outcome of interest, the effect estimate for mean pain/discomfort ratings 72 hours post-DOMS between the active and placebo groups was -1.33 (85% confidence interval = -2.55, -0,10), suggesting moderate evidence of a treatment difference. The effect estimate for the result of ratings of interference of pain, discomfort, or stiffness with daily activities at work or home 48 hours after DOMS was -1.82 (95% confidence interval = -3.64, - 0.01), indicating a treatment difference of potential clinical importance. There was no significant effect between the active and placebo groups on objective measures of recovery, sleep quality, or mood disturbances. Therefore, the tested formulation reduced the interference of DOMS in daily activities, demonstrating its improvement in the functional aspect of recovery **[25]**.

Finally, CBD supplements are increasingly consumed by athletes to improve regeneration. However, the evidence for the pro-regenerative effects of CBD in sports is quite limited. A randomized, cross-over, placebo-controlled clinical trial investigated the effects of a single CBD supplementation following resistance training on performance and muscle damage. Before and after resistance training, one repetition maximum back squat (1RM BS), countermovement jump (CMJ), and blood serum concentrations of creatine kinase (CK) and myoglobin (Myo) were measured in healthy, well-trained participants. A total of 16 of the 21 participants completed the study and were included in the analysis. In 1RM BS, a significant decrease was observed after 24 hours, but not after 48 and 72 hours. A significant difference between groups was detected after 72 hours. No significant changes were observed in the CMJ. CK and Myo concentrations increased significantly after 24 h. After 72 h, significant differences between groups were observed for both biomarkers of muscle damage. The results showed small but significant effects on muscle damage and squat performance recovery after 72 hours **[26]**.

Despite these findings, there is still a lack of randomized and/or prospective controlled clinical studies with a robust sample size to better understand the safety and effectiveness of the use of cannabidiol by

medium to high-performance athletes, as well as better understand the dosages for each type of sports performance.

Conclusion

It was concluded that cannabidiol exerts a series of physiological, biochemical, and psychological effects with the potential to benefit human health. For example, there is preliminary supporting evidence for anti-inflammatory, neuroprotective, analgesic, and anxiolytic actions, as well as the possibility that it may protect against gastrointestinal damage associated with inflammation and promote healing of traumatic skeletal injuries. The combination of Δ9-THC and CBD can alter the activity of microRNAs responsible for increasing the biosynthesis of inflammatory mediators, leading to a reduction in the inflammatory profile.

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Informed Consent

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

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It was performed.

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