



Action of cannabidiol in interaction with microRNAs and exosomes in modulation of inflammatory and immune processes in athletes: a systematic review

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Abstract

Introduction: The correct interaction between 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. In addition, 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.

Objective: It was to develop a systematic review study to highlight the main aspects of cannabidiol in the interaction with microRNAs and exosomes in the modulation of inflammatory and immunological processes in athletes. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from February to April 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 228 articles were found, and 84 articles were evaluated in full and 33 were included and developed in this systematic review study.

Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 90 studies that did not meet GRADE. 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 the anti-inflammatory, neuroprotective, analgesic, and anxiolytic actions of CBD and the possibility that it may protect against gastrointestinal damage associated with inflammation and promote the healing of traumatic skeletal injuries. The combination of Δ^9 -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. However, it is important to recognize that these findings are very preliminary, sometimes inconsistent, and largely derived from preclinical studies. These studies are limited in their generalizability to athletes and often administer high doses of CBD. The central observation is that there is a lack of studies that directly investigate CBD and sports performance.

Keywords: Sports nutrition. Cannabidiol. Cannabis. microRNAs. Exosomes. Metabolism. Inflammatory processes. Immunological processes. Athletes.

Introduction

Cannabidiol (CBD) has effects that impact mood, sensation, perception, tension, appetite and pain [1]. Also, CBD has shown anxiolytic, antipsychotic, neuroprotective, anti-inflammatory, and antiemetic properties [2,3]. 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 [5]. Outside the brain, the SEC 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 GABAergic 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 Δ^9 -tetrahydrocannabinol. CBD is another well-known phytocannabinoid present in dried or heated cannabis preparations. Unlike Δ^9 -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].

Given this, the present study aimed to develop a systematic review study to highlight the main aspects of cannabidiol in the interaction with microRNAs and exosomes in the modulation of inflammatory and immunological processes in athletes.

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: 08/14/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 08/14/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Sports nutrition. Cannabidiol. Cannabis. MicroRNAs. Exosomes. Metabolism. Inflammatory processes. Immunological processes. Athletes*". The search was carried out from February to April 2023 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.

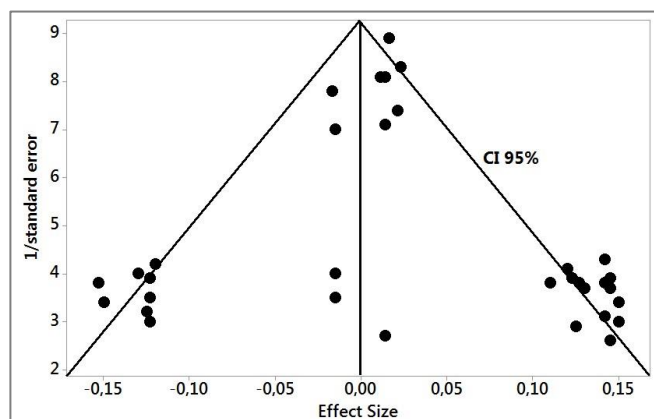
Quality of Studies and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

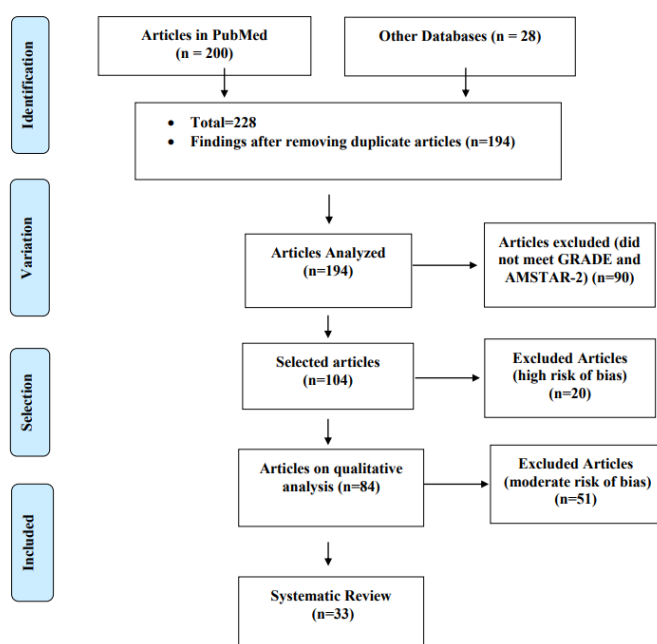
Summary of Findings

A total of 228 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 104 articles. A total of 84 articles were evaluated in full and 33 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 20 studies with a high risk of bias and 90 studies that did not meet GRADE.



Source: Own Authorship.

Figure 1. Selection of the articles.



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=33 studies evaluated in full in the systematic review).

Main Scientific Evidence - Cannabidiol and microRNAs/Exosomes

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, several important implications in inflammation and the immune system that are induced by the activity of cannabinoid receptors stimulated by delta-9-tetrahydrocannabinol (Δ^9 -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 (Δ^9 -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- κ B), 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 [16-21]. 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 [22-26].

The authors Juknat et al. [27] carried out a study on the interactions between CB1 and CB2 receptors with microRNAs after the activation of Δ 9-THC and CBD. To simulate pro-inflammatory conditions, they stimulated BV-2 microglial cells with lipopolysaccharide (LPS) and subsequently analyzed the effects induced by Δ 9-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- κ B 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. [28] showed a decrease in the expression of microRNA-17, microRNA-92, microRNA-421, and microRNA-374b, induced by the action of Δ 9-THC.

Finally, studies have demonstrated that Δ 9-THC modulates and reduces T cell (Th1)-mediated cytokine

biosynthesis, as well as microRNA-mediated expression of TNF- α and IFN- γ [29-32]. Added to this, Rao et al. [33] studied the effects induced by Δ 9-THC on the inflammatory profile and the activity of staphylococcal enterotoxin B (SEB). They showed a 100% increase in survival rate in mice that received Δ 9-THC treatment, in contrast to the control group where mortality was 100%. Regarding the expression of microRNAs, they reported changes in the activity of microRNA-17-92 and microRNA-18a.

Conclusion

It was concluded 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 Δ 9-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. However, it is important to recognize that these findings are very preliminary, sometimes inconsistent, and largely derived from preclinical studies. These studies are limited in their generalizability to athletes and often administer high doses of CBD. The central observation is that there is a lack of studies that directly investigate CBD and sports performance.

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No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

Peer review process

It was performed.

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