REVIEW ARTICLE

Effects of cannabidiol on metabolic modulation and improving sports performance: a systematic review

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Abstract

Introduction: In the sports scenario, cannabidiol (CBD) is a phytocannabinoid that has been accumulating important scientific evidence in various metabolic and metabolomic effects. Δ9 tetrahydrocannabinol (Δ9-THC) may be responsible for some adverse effects on sports performance and this makes cannabis unattractive for athletes. Extracellular vesicles (exosomes and microRNAs) induced by exercise emerged as potential mediators of tissue crosstalk. **Objective:** It was to carry out a systematic review study to highlight the main outcomes of cannabidiol in metabolic modulation and microRNA signaling in increasing sports performance. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from March to May 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 127 articles were found. A total of 87 articles were evaluated in full and 62 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 5 studies with a high risk of bias and 11 studies that did not meet GRADE. It has been shown that cannabidiol exerts some physiological, biochemical, and psychological effects with the potential to benefit athletes. For example, there is preliminary supporting evidence for the anti-inflammatory, neuroprotective, analgesic, and anxiolytic actions of cannabidiol and the possibility that it may protect against gastrointestinal damage associated with inflammation and promote healing of traumatic skeletal injuries. 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 cannabidiol. The central observation is that there is a lack of studies that directly investigate cannabidiol and sports performance. Furthermore, we identified a specific repertoire of microRNAs that are regulated by cannabinoids, at rest (vigilant), and in microglia activated by lipopolysaccharides. Modulated microRNAs and their target genes are controlled by TLR, Nrf2, and Notch cross-signaling and are involved in the immune response, cell cycle regulation, as well as cellular stress and redox homeostasis.

Keywords: Cannabidiol. microRNAs. Metabolism. Sports performance.

Introduction

In the sports scenario, cannabidiol (CBD) is a phytocannabinoid that has been accumulating important scientific evidence on various metabolic and metabolomic effects, impacting mood, sensation, perception, tension, appetite, and pain **[1]**, as well as

acting as an anxiolytic, antipsychotic, neuroprotective, anti-inflammatory and antiemetic predictor [2,3]. 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 were also discovered as part of the endocannabinoid system (ECS) in the brain [4].

In the sporting domain, cannabis has been banned by the World Anti-Doping Agency (WADA) in all competitive sports since 2004. However, athletes can use it outside of competition for social, recreational, or performance-enhancing purposes [2]. Δ9 tetrahydrocannabinol (Δ9-THC) may be responsible for some adverse effects on sports performance and this makes cannabis unattractive to athletes [1].

Unlike Δ9-THC, CBD is not intoxicating, but it exhibits pharmacological properties that are interesting for medical use. Some preclinical and clinical data have demonstrated anxiolytic, anti-inflammatory, or neuroprotective effects for this compound with a relatively safe adverse event profile [3,4]. WADA has removed CBD from the list of banned substances since 2018.

In commerce, CBD can be found in different products such as oil solutions, sprays, pills, tinctures, liquids, or balms [3] and the route of administration influences the pharmacokinetics of CBD. Maximum plasma concentrations and total drug exposure in time are dose-dependent. Intravenous injection, smoking, or inhalation allow higher maximum plasma concentrations to be reached more quickly [5,6].

Although CBD has a low affinity for the orthosteric binding sites of cannabinoid receptors, CB1 and CB2, it can modulate their activities, either by acting as a negative allosteric modulator [7] or by increasing endogenous levels of the endocannabinoid anandamide (AEA) [8]. The endocannabinoid system is not the only target of CBD. Among other effects, it has been demonstrated that this compound is capable of activating the serotonin 5-HT1A receptor [9], the TRPV1 vanilloid receptor [8], and the peroxisome proliferator-activated receptor γ (PPARγ) [10].

Added to this, tissue crosstalk induced by a single exercise session (acute exercise) or long-term exercise may play an important role, through myokines secreted by skeletal muscle. More recently, exercise-induced extracellular vesicles (exosomes and microRNAs) have emerged as potential mediators of tissue crosstalk. Furthermore, extracellular vesicles are heterogeneous particles, linked to the lipid bilayer, released by cells into the extracellular environment. Extracellular vesicles are released mainly by direct budding from the plasma membrane (microvesicles) or by the fusion of multivesicular bodies with the plasma membrane (exosomes) [11].

In this context, all cells are probably capable of producing extracellular vesicles, and these have been found in different body fluids it has been demonstrated that their concentration changes in some pathological conditions, such as obesity, metabolic syndrome, and cardiovascular diseases. Thus, extracellular vesicles represent important biomarkers, as well as being able to modulate the genetic expression of cells [11].

In this sense, extracellular vesicles influence cell-cell and tissue-tissue communication. They have surface molecules that allow them to target specific cells, and they carry molecules with signaling abilities, such as proteins, metabolites, and nucleotides such as miRNAs. Once bound to recipient cells, extracellular vesicles can influence biological processes by inducing cell signaling at the plasma membrane. Furthermore, extracellular vesicles are implicated in a wide range of biological or pathological processes, such as coagulation, immune responses, cancer metastasis, insulin resistance, and regeneration/sports performance [10,11].

Given this, the present study aimed to carry out a systematic review study to highlight the main outcomes of cannabidiol in metabolic modulation and microRNA signaling to increase sports performance.

Methods

Study Design

The systematic review rules of the PRISMA Platform Available at: www.prismastatement.org/ were followed. Accessed on: 06/15/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Cannabidiol. MicroRNAs. Metabolism. Sports performance". The research was carried out from March to May 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

The quality of the studies was based on the GRADE instrument, prioritizing studies with scientifically rigorous methodology, randomized clinical studies, and clinical and/or pre-clinical studies with a significant sample size. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Findings

A total of 127 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 103 articles. A total of 87 articles were evaluated in full and 62 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 5 studies with a high risk of bias and 11 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.
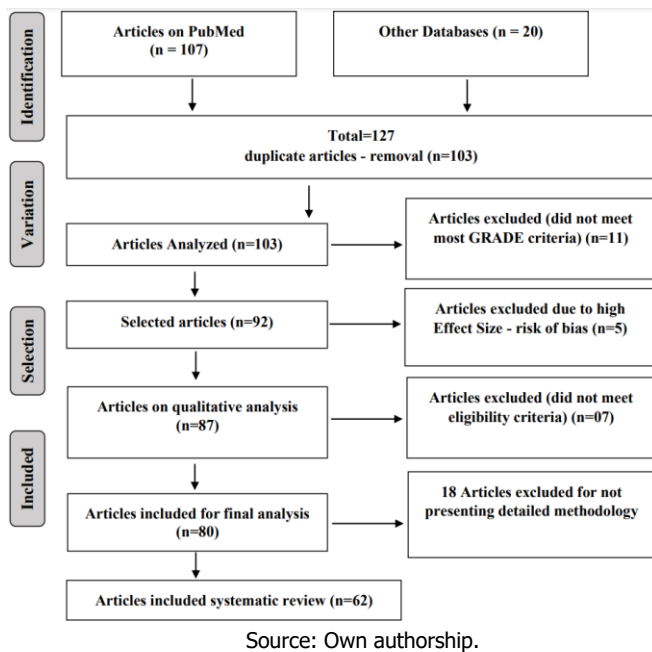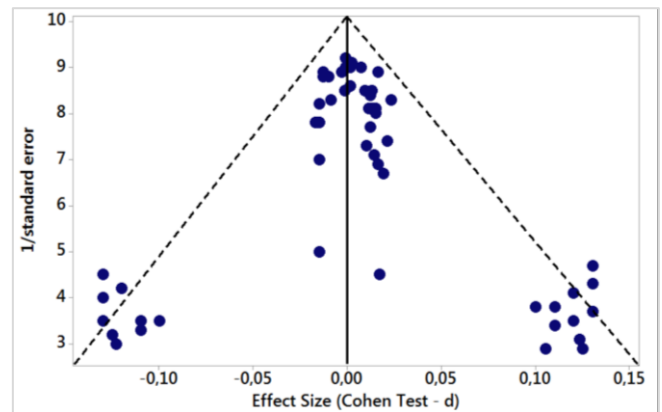

Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Magnitude of the difference (Effect size) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the 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=62 studies evaluated in full in the systematic review).

Source: Own authorship.

Cannabidiol and Metabolic Modulation in Sports

For more than 50 years, studies have accumulated scientific evidence demonstrating the anti-inflammatory action and analgesic properties of CBD. Early *in vitro* reports showed that CBD acts on cells and mediators involved in inflammatory processes and hyperalgesia processes [12,13]. Briefly, CBD modulates, directly or indirectly, receptors involved in inflammation, such as CB2 [14], TRPV1 [15], PPARγ [16], or Adenosine (A2A), a receptor that can negatively regulate overly reactive immune cells [17].

In this context, CBD reduces different markers of inflammation such as cytokines, prostaglandin E2 (PGE2), cyclooxygenase activities, production of nitric oxide (NO) and oxygen-derived free radicals, and reduces edema [18,19]. CBD also exerts promising analgesic effects in different models of inflammatory and chronic pain, regulating proinflammatory agents and affecting targets involved in nociception, such as 5-HT1A and TRPV1 receptors [9,20,21].

In this regard, athletes can benefit from this phytocannabinoid to control pain, inflammation, and swelling processes associated with injuries and CBD can become an alternative to non-steroidal anti-inflammatory drugs, opioids, or corticosteroids [22]. Despite the lack of studies on the use of CBD in the management of sports injuries, some data suggest its potential usefulness in osteoarthritis, delayed-onset muscle soreness (DOMS), and overuse injuries associated with neuropathic pain and concussion.

Furthermore, in an animal model of osteoarthritis, intra-articular injection of CBD was able to reduce the acute phase of inflammation, significantly decreasing rolling and adherent leukocytes and synovial hyperemia [20]. Furthermore, CBD was also able to inhibit the mechanosensitivity of joint nociceptors, reducing spontaneous pain induced by joint degeneration or inflammation, and allodynia or hyperalgesia due to central sensitization after neuropathic pain. The anti-inflammatory effect involved CB2 and TRPV1 receptors,

while analgesia appeared to be partially dependent on the TRPV1 receptor [20]. Indeed, as already shown in a rat model, CBD is capable of binding and desensitizing this mediator of hyperalgesia [8].

Sensitization of TRPV1 expressed in thin muscle fiber afferents is also involved in DOMS which is characterized by muscle fiber damage, inflammation, oxidative stress, and hyperalgesia [23]. Thus, the swelling, oxidative stress, and inflammation during DOMS can be alleviated by CBD's anti-inflammatory properties, causing a decrease in muscle pain induced by strenuous exercise.

In this sense, the use of CBD can alleviate chronic inflammation, production, persistence of reactive oxygen species [24], and, sometimes, chronic or neuropathic pain [25]. Preclinical studies suggest that CBD has therapeutic potential in different types of neuropathic pain, acting on TRPV1 and 5-HT1A receptors involved in pain pathways [26-29].

In these studies, the use of CBD was able to reduce allodynia or hyperalgesia associated with neuropathic pain by acting on the density of microglia in the dorsal spinal cord [29] and modulating the activity of the periaqueductal gray matter [30]. Furthermore, the affective dimension of pain can be reduced by CBD at the level of the rostral anterior cingulate cortex [28] and the dorsal raphe nucleus [9].

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, almost no clinical data is available on the use of CBD in the context of exercise performance. Therefore, although CBD seems like an interesting molecule with a wide range of potentially useful properties for athletes, one must consider some objections as only a few studies are available on the use of CBD in adults and the recent approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) of botanical CBD as a therapeutic medicine against some types of intractable pediatric epilepsy does not justify its indiscriminate use as a dietary supplement or for other therapeutic indications not yet proven in humans [3].

Furthermore, regarding the different properties presented in this paper and the reports mentioned, no study has so far compared CBD with conventional medications or therapies already approved and used by athletes. It is possible that CBD is less effective or induces undesirable side effects compared to these medications, although it appears relatively safe in humans [4]. The most commonly reported side effects in clinical studies were tiredness, diarrhea, and changes in appetite/weight. Additionally, CBD may modulate other physiological processes or systems that can directly or indirectly affect negative or positive performance, such as food intake [31], metabolism [32], and the cardiovascular [33] or musculoskeletal [34] systems [35].

Added to this, it is important to consider dosage and administration issues. The desired effects (anxiolytic, neuroprotective, anti-inflammatory, antalgic, etc.) clinical studies will have to define the correct dose and route of administration for the expected therapeutic effects, mainly because few data are available on the pharmacokinetics of CBD [6]. Additionally, it is important to keep in mind that CBD can interact with conventional medications by affecting drug-metabolizing enzymes or drug transporters [4]. Therefore, at least for now, CBD should not be used together with conventional medications to avoid undesirable effects or alteration of its therapeutic effects.

Also, the regulation of non-standard CBD products currently available over the counter is very poor. Not clinically approved or not sufficiently controlled preparations purported to contain CBD, which is increasingly present on the market, often report inaccurate data on the actual purity and quantity of this compound or the concomitant presence of Δ9-tetrahydrocannabinol (THC). These products do not always contain the concentration of CBD stated on the label and may contain higher amounts of THC [36], which can lead to intoxication or a positive drug test. Furthermore, the chemical components present in CBD products may not be safe. For example, approximately 8% of stabbing injuries associated with vaping were after CBD tinctures [37].

Therefore, the global regulatory status of CBD is complex and constantly changing. Although CBD is legal in many countries as a component of medicines, it may simultaneously be illegal as a component of unapproved Cannabis extracts containing >0.2% or 0.3% THC [3]. Therefore, the use of CBD can be legal or illegal depending on the laws of the country where the athlete works, even though WADA has removed this compound from the list of prohibited substances.

Cannabidiol, microRNAs, and Sports Performance

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. The psychoactive cannabinoid THC and non-psychoactive CBD differ in their anti-inflammatory signaling pathways. Using lipopolysaccharide (LPS) to stimulate BV-2 microglial cells, a clinical study looked at the role of cannabinoids in the expression of microRNAs.

Sequencing analysis revealed that 31 microRNAs 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 microRNAs studied. The results link the effects of LPS and cannabinoids to inflammatory signaling pathways. LPS upregulated the expression of pro-inflammatory microRNAs associated with Toll-like receptor (TLR) and NF-κB signaling, including miR-21, miR-146a, and miR-155, while CBD inhibited LPSstimulated 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. Thus, a specific repertoire of microRNAs was identified that are regulated by cannabinoids, at rest (vigilant) and in LPS-activated microglia. The modulated microRNAs and their target genes are controlled by TLR, Nrf2, and Notch cross-signaling and are involved in the immune response, cell cycle regulation, as well as cellular stress and redox homeostasis [38].

In this scenario, plasma levels of miR-106b-5p have been described as a predictor of exercise performance in male amateur runners, although there is no information available on female athletes. One study analyzed the predictive value on sports performance of plasma miR-106b-5p levels in elite female and male kayakers at the beginning and end of a training macrocycle, as well as the potential underlying molecular mechanisms. A total of 8 elite canoeists (26.2 ± 3.6 years) and 7 elite canoeists (17.4 ± 0.5 years) from the Spanish team. Two fasting blood samples were collected, the starting point of the season (A) and maximum fitness level (B). Circulating plasma levels of miR106b-5p were analyzed by RT-qPCR. The maximum 500 m performance was recorded in B. miR-106b-5p levels showed no differences between A and B in either women or men. In men but not women, miR-106b-5p levels showed a significant negative correlation with B performance, which highlights its predictive value for performance. However, in women, progesterone emerged as a determinant and the miR-106b5p/progesterone ratio showed a significant negative correlation with performance. Thus, miR-106b-5p emerges as a biomarker of athletic performance in men and women, considering the menstrual cycle [39].

In this regard, miRNAs are involved in the generation and progression of musculoskeletal pain, a condition that causes significant clinical, economic, and social burdens. In runners, the presence of musculoskeletal pain related to an inflammatory state or ongoing underlying tissue damage can result in poor training capacity and performance [40].

Added to this, a study evaluated the effects of whole cannabis, THC, and CBD on athletic performance and recovery. Although investigations of whole cannabis and THC generally show no detrimental effects on exercise performance in strength and aerobic-type activities, studies with sufficient rigor and validity to conclusively declare ergogenic or ergolytic potential in athletes are lacking. The ability of cannabis and THC to disrupt cardiovascular homeostasis warrants further investigation into the mechanisms by which performance may be affected across different exercise modalities and energy demands. In contrast to cannabis and THC, CBD has been extensively scrutinized for its potential to aid recovery. The beneficial effects of CBD on sleep quality, pain, and mild traumatic brain injury may be of particular interest to certain athletes [41].

Despite this, the legalization and consequent production and commercialization of CBD may increase its intake among sports professionals. This commercialization of cannabinoids has fueled a race to study their properties, benefits, and risks for the health and performance of athletes. Although there is evidence that suggests some beneficial properties such as anxiolytics, antidepressants, anti-inflammatories, and antioxidants, among others, the evidence presented so far is neither clear nor conclusive. There are significant gaps in knowledge of the physiological pathways that explain the role of CBD in sports performance [42].

In this vein, however, one study investigated the effects of a single CBD supplementation in a six-arm placebo-controlled crossover study following resistance training on muscle performance and damage. Before and after resistance training, one repetition maximum back squat (1RM BS), countermovement jump (CMJ), and serum creatine kinase (CK) and blood myoglobin (Myo) concentrations 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 h (p < 0.01), but not after 48 and 72 h. A significant difference between groups was detected after 72 h. In the CMJ, no significant changes were observed. CK and Myo concentrations increased significantly after 24 h, 48 h, and 72 h. After 72 h, significant differences between groups were observed for both biomarkers of muscle damage. The results showed significant effects on muscle damage and recovery of squat performance after 72 h [43].

A pilot study investigated the effects of acute oral CBD treatment on physiological and psychological responses to aerobic exercise to determine its practical utility in the sporting context. On two occasions, nine endurance-trained men (mean ± SD V̇O2 max: 57.4 ±

4.0 mL•min-1•kg-1) ran for 60 min at a fixed intensity (70% $\dot{V}O_2$max) (RUN 1) before completing an incremental run to exhaustion (RUN 2). Participants received CBD (300 mg; oral) or placebo 1.5 h before exercise in a randomized, double-blind design. Respiratory gases ($\dot{V}O_2$), a respiratory exchange rate (RER), heart rate (HR), blood glucose (BG), and lactate (BL) concentrations, and ratings of perceived exertion (RPE) and pleasure-displeasure were measured at three moments (T1-3) during RACE 1. $\dot{V}O_2$max, RERmax, HRmax, and time to exhaustion (TTE) were recorded during RACE 2. Venous blood was collected at baseline, pre- and post-RACE 1, post-RACE 2, and 1 h post-RUN 2. CBD appeared to increase $\dot{V}O_2$, enjoyment ratings, and BL during RUN 1 compared to placebo. No differences in HR, RPE, BG, or RER were observed between treatments. CBD appeared to increase $\dot{V}O_2$max and RERmax during RUN 2 compared to placebo. No differences in TTE or HRmax were observed between treatments. Exercise increased serum concentrations of interleukin (IL)-6, IL-1β, tumor necrosis factor-α, lipopolysaccharide, and myoglobin, i.e., baseline vs. baseline. Post-RUN 1, Post-RUN 2, and/or 1-h Post-RUN 2. Therefore, CBD appears to alter some of the key physiological and psychological responses to aerobic exercise without impairing performance [44].

A narrative review study explored several physiological and psychological effects of CBD that may be relevant to the sport and/or exercise context and identified key areas for future research. Preclinical studies have observed robust anti-inflammatory, neuroprotective, and analgesic effects of CBD in animal models. Preliminary preclinical evidence also suggests that CBD may protect against gastrointestinal damage associated with inflammation and promote the healing of traumatic skeletal injuries. However, more research is needed to confirm these observations. Early-stage clinical studies suggest that CBD may be anxiolytic in "stress-inducing" situations and in individuals with anxiety disorders. Although some case reports indicate that CBD improves sleep, robust evidence is currently lacking. Cognitive function and thermoregulation appear to be unaffected by CBD, while effects on food intake, metabolic function, cardiovascular function, and infection require further study. CBD can exert a range of physiological, biochemical, and psychological effects that have the potential to benefit athletes. However, studies in athlete populations are needed to further define the usefulness of CBD in supporting athletic performance [45].

In this context, exercise, particularly when strenuous, unfamiliar, and/or involving an eccentric component, can cause ultrastructural damage to skeletal muscle myofibrils and the surrounding extracellular matrix [46,47]. This exercise-induced muscle damage (EMID) impairs muscle function and initiates an inflammatory response [47]. Although inflammation is an integral part of EIMD repair, regeneration, and adaptation, excessive inflammation can contribute to prolonged muscle soreness and delayed functional recovery [48].

In this sense, CBD modulates inflammatory processes [49]. In preclinical models of acute inflammation, CBD has been reported to attenuate the accumulation of immune cells (e.g., neutrophils, lymphocytes, macrophages) [50-53], stimulate the production of anti-inflammatory cytokines (e.g., interleukin (IL) -4, IL -10) [54,55] and inhibit the production of pro-inflammatory cytokines (e.g., IL-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α) and reactive species of oxygen [56]. Models demonstrating these effects include chemical treatment-induced lung injury and hypoxia-ischemia (HI); hepatic injury induced by ischemia-reperfusion and alcohol feeding, myocardial and renal ischemia-reperfusion injuries, surgically induced oral injuries, chemically induced osteoarthritis, spinal cord contusion injury, and colitis [57].

Anti-inflammatory effects are generally observed at higher doses of CBD *in vivo* (e.g., ≥ 10 mg.kg-1); although, lower doses (e.g., ~1.5 mg • kg-1) have indicated efficacy in some studies [56]. However, research investigating the effects of CBD on inflammation in humans is limited and inconclusive [57].

In terms of muscle-specific inflammation, a preclinical study investigated the effect of high-dose CBD (i.e., 60 mg•kg-1•d-1) on the transcription and synthesis of pro-inflammatory markers (i.e., receptors of IL-6, TNF-α, TNF-β1, and inducible nitric oxide synthase) in the gastrocnemius and diaphragm of dystrophic MDX mice (a mouse model of Duchenne muscular dystrophy). In this investigation, CBD attenuated the mRNA expression of each marker and reduced plasma concentrations of IL-6 and TNFα. Improvements in muscle strength and coordination, as well as reductions in tissue degeneration, have also been reported at this dose. Lower but still relatively high doses of CBD (20–40 mg • kg-1 • d-1) had no functional benefits [58].

Furthermore, CBD is widely marketed to athletes due to effects such as reducing anxiety, extinguishing fear memories, anti-inflammatory properties, pain relief, and post-exercise recovery. Specifically non-medicinal CBD products, so-called full-spectrum cannabis extracts, may contain significant levels of these substances, but also tetrahydrocannabinol (THC) contaminations (> 2.5 mg/day in > 30% of products on the German market) potentially leading to positive doping tests. Labeled

claims about CBD content and absence of THC are often false and misleading. Contaminations with psychoactive THC can result in adverse effects on cognition, and in general, the safety profile of CBD concerning its toxicity is a controversial topic of discussion. For these reasons, the use of over-the-counter CBD products is currently advised against **[59]**.

As scientific evidence, one study investigated the effect of CBD oil on the perception of muscle pain, inflammation, and strength performance after eccentric elbow flexor exercise (EEC). Thirteen untrained men (mean ± SD age: 21.85 ± 2.73) performed 6 sets of 10 maximal ECC isokinetic muscle actions of the elbow flexors as part of a double-blind crossover design. Non-invasive measurements (perceived pain, arm circumference, suspension joint angle (JA), and peak torque (PT)) were performed PRE, POST, 24 hours, 48 hours, and 72 hours after EEC. All subjects completed the supplement (CBD: 150 mg POST, 24-h, 48-h) and placebo (PLC: POST, 24-h, 48-h) condition separated by 2 weeks. As a result, there was no condition x time interaction or main effect of condition (p> 0.05) for perceived pain, arm circumference, JA, or PT. There were main effects for the time of perceived pain. Thus, the current dose of 150 mg of CBD oil at POST, 24 hours, and 48 hours did not affect non-invasive markers of upper extremity muscle injury **[60]**.

Furthermore, one study determined whether there are age-related differences in cannabis use patterns and subjective effects in adult athletes. The age was over 21 years old. Of the 1161 participants, 301 (26%) athletes currently used cannabis. Younger athletes compared to older athletes reported significantly more positive and adverse subjective effects of cannabis. Younger athletes used cannabis concurrently with exercise more frequently than older athletes and consumed edibles, vaped, and smoked more than older athletes. Therefore, age-related patterns of cannabis use and subjective effects of cannabis were found. Concerns about cannabis misuse and abuse in athletes may be exaggerated with the potential benefits (improved sleep, decreased anxiety, less pain) outweighing the adverse effects (increased anxiety, increased appetite, difficulty concentrating) **[61]**.

Still in this context, the effects of chronic cannabis consumption on the physiological parameters of athletic performance are investigated to determine whether it negatively affects athletic performance, whether it improves performance, potentially through enhanced recovery, or whether it has no effect. Resting heart rate was the only physiological measurement that differed significantly between groups and only in one of the four studies included here. The strongest predictors of athletic performance (VO₂Max and performance) were not significantly different between groups in any of the included studies. Chronic cannabis consumption had no significant effect on athletic performance. The included studies did not evaluate other elements, such as recovery or resistance. Therefore, no evidence of ergogenic or ergolytic effects of chronic cannabis consumption was observed **[62]**.

Conclusion

It has been shown that cannabidiol exerts a series of physiological, biochemical, and psychological effects with the potential to benefit athletes. For example, there is preliminary evidence supporting the anti-inflammatory, neuroprotective, analgesic, and anxiolytic actions of cannabidiol and the possibility that it may protect against gastrointestinal damage associated with inflammation and promote the healing of traumatic skeletal injuries. 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 cannabidiol. The central observation is that there is a lack of studies that directly investigate cannabidiol and sports performance. Furthermore, a specific repertoire of microRNAs was identified that are regulated by cannabinoids, at rest (vigilant), and in microglia activated by lipopolysaccharides. The modulated microRNAs and their target genes are controlled by TLR, Nrf2, and Notch cross-signaling and are involved in the immune response, cell cycle regulation, as well as cellular stress and redox homeostasis.

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Conflict of interest
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