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REVIEW ARTICLE

Cannabinoid Therapy in Athletics: A Review of Current Cannabis Research to Evaluate Potential Real-World Cannabinoid Applications in Sport

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Abstract
The increasing legalization of *Cannabis sativa* plant products has sparked growing interest in their therapeutic applications. Prohibition laws established in 1937 hindered formal research on cannabis, a plant with cultural and medicinal roots dating back to 2700 BC in Chinese history. Despite regulatory hurdles, published research on cannabis has emerged; yet elite athletes remain an underrepresented population in these studies. Athletes, known for exploring diverse substances to optimize performance, are drawn to the potential benefits of cannabinoid therapy, with anecdotal reports suggesting positive effects on issues ranging from anxiety to brain injuries. This review aims to evaluate empirical published cannabis research with a specific focus on its potential applications in athletics. The changing legal landscape, especially the removal of cannabis from drug testing programs in leagues such as the National Basketball Association (NBA), and endorsements by Major League Baseball (MLB) for cannabinoid products and the National Football League (NFL) for cannabis research, reflects a shift in the acceptability of such substances in sports. However, stigma, confusion, and a lack of education persist, hindering a cohesive understanding among sports organizations, including business professionals, policymakers, coaches, and medical/training staff, in addition to athletes themselves. Adding to the confusion is the lack of consistency with cannabinoid regulations from sport to sport, within or out of competition, and with cannabis bioactive compounds. The need for this review is underscored by the evolving attitudes toward cannabinoids in professional sports and the potential therapeutic benefits or harms they may offer. By synthesizing current cannabis research, this review aims to provide a comprehensive understanding of the applications and implications of cannabinoid use in the realm of athletics.

1 Introduction

As the legal landscape continues to increase authorized access to cannabis plant products, interest in using them for therapeutic purposes is growing. Prohibition laws implemented in 1937 stifled formal research on a plant whose cultural and medicinal use traces back as far as 2700 BC to the Chinese Emperor Shen Nungin [1]. Although difficult and limited by restrictive regulations, published cannabis research has still transpired. Loosened cannabis regulations at the state level within the USA (2014) and full legalization within Canada (2018) has catalyzed the influx of new cannabis products as well as exercise and performance research in the context of cannabis products. The athletic population, who often experiment with a variety of ingredients in search of optimal health and performance enhancement, are an underrepresented population in cannabis research. With everything from anxiety to brain injury anecdotally reported to benefit from cannabinoid therapy, the attention of many athletes has been drawn to its potential as an agent that could assist with inflammation, neuroprotection, pain, and mental health as key factors that impact performance. As a substance that is growing in popularity, but that is clouded in confusion, the aim of this review is to evaluate existing published cannabis research and potential applications specific to athletics. The literature was approached by searching for relevant published peer-reviewed research to explain and expand each concept included in this review. A comprehensive literature search in PubMed, Cochrane Library, Medline, EMBASE,

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Key Findings/Implications

A review of the molecular mechanisms of the human endocannabinoid system in the context of cannabinoid therapy suggests potential therapeutic value but also potential risks of cannabis use in athletes.

Current human studies on cannabinoid therapy are limited in design and interpretability. Vast discrepancies exist on the basis of specifics of the study such as the cannabinoid(s) used, the population studied, and the administration route and dose. Study findings only apply to the specifics of that study, and caution is warranted not to misinterpret the applicability of results to non-similar populations or cannabinoids.

Health policies and regulations regarding cannabinoid use in athletics are confusing and non-standardized. More education and awareness on benefits and potential harm is needed for athletes, medical staff, and policymakers.

EBSCOhost, ScienceDirect and Google Scholar was performed. Searches were performed using keywords and subject headings for each section. Citations from previously published meta-analyses and peer-reviewed publications were also reviewed in addition to clinical trial registries. ChatGPT 3.5, an AI language model developed by OpenAI, was employed to assist with refining grammar and sentence structure, initially, and then all authors completed the final writing and editing of this manuscript.

2 Need for the Review

Changing prohibition laws and the growing anecdotal evidence of the benefit of cannabinoids has garnered recent attention from several professional sports leagues in North America. For example, in 2022, Major League Baseball (MLB) became the first professional sports league to endorse the use of cannabidiol (CBD) [2]. They signed a partnership with industry leader Charlotte's Web to become the "official CBD of major league baseball" [2]. Also in 2022, the National Football League (NFL) announced the awarding of 1 million USD in funding for research to investigate the effects of cannabinoids on pain management and neuroprotection from concussion [3]. More recently, in the 2023 collective bargaining agreement with players, the National Basketball League (NBA) removed cannabis from its drug testing program, in addition to allowing players to promote and invest in cannabis companies [4]. The National Hockey League (NHL) has not categorized cannabis or Δ^9 tetrahydrocannabinol (THC) as a banned substance since 2016; however, if a player has high THC metabolites in their urine test consistently, the league gives players the option to enter the Player Assistance Program should they think their own use has become problematic [5]. The NHL prioritizes cannabis education, treatment, and harm reduction rather than strict prohibition and punishment.

These major occurrences signal a shift in the acceptability of cannabinoid use in athletics. However, the paucity of evidence, stigma, confusion, and lack of education continue to slow a cohesive understanding among sports organizations as a whole, which include relevant corporate groups, policymakers, coaches, and medical/training staff in addition to the athletes. The inadequate knowledge of cannabis benefits and harms among healthcare providers is a particularly important concern, and patients have identified insufficient provider knowledge as a contributing factor to perceived physician discomfort with cannabis-related inquiries, creating a barrier to effective communication between patient and provider [6] and amplifying the experience of stigma [7, 8]. Further, needs assessment studies also suggest additional education could increase the confidence of providers in treatment planning and relative risk–benefit analysis [6, 7]. In Canada, 75% of Canadian physicians-in-training suggested an increase in educational opportunities would improve standard of care for patients [8]. Nonetheless, a general paucity of human evidence exists for the efficacy for cannabis-based medicines. Ethical and legal complications associated with administering cannabis to human research participants creates barriers to discoveries [9]. Legal and regulatory compliance issues, required drug research licenses, lack of approved research grade cannabis product for studies, and the high cost of clinical trials cumulatively make cannabis research in humans difficult [9]. In addition, current ambiguous evidence creates challenges in determining which assertions are adequately substantiated and which have been produced by commercial interests or those with conflicts of interest. Despite these limitations, a review of current cannabis research to evaluate and educate individuals on the potential therapeutic applications in sport is warranted and may help to improve current understandings and provide an objective assessment of existing data to inform athletes, coaches, medical staff, and policymakers.

3 The *Cannabis* Plant

A basic understanding of the cannabis plant is necessary to appreciate its potential therapeutically. Within the cannabis plant there are more than 120 recognized phytocannabinoid

molecules, along with hundreds of unique terpenes, flavonoids, and other bioactive plant metabolites [10, 11]. Plant-derived phytocannabinoids interact with human cannabinoid receptors in the endocannabinoid system (ECS) in addition to transient receptor potential ion channels (TRPV) and numerous other G-protein coupled receptors (GPCR), evoking a variety of physicochemical downstream effects potentially impacting almost any tissue in the body [12]. The phytocannabinoid Δ^9 tetrahydrocannabinol (THC) is well known for its psychoactive effects or "high," but this is only one of more than 500 bioactive molecules found in the cannabis plant. The phytocannabinoid cannabidiol (CBD) is now recognized for its non-intoxicating therapeutic benefits, but unfortunately is often confused with THC because these chemicals come from the same plant species and the distinction between specific plant molecules is often overlooked [13, 14]. Many of the lesser known phytocannabinoids, terpenes, and flavonoids have unique effects and therapeutic potential of their own, without intoxicating consequences [10]. They operate through different molecular mechanisms than THC and must be considered for their own specific biological effects. It is important to acknowledge the value of all therapeutic cannabis molecules and not make the mistake of assuming all cannabis-based medicines include identical plant component profiles.

4 The Endocannabinoid System

The endocannabinoid system (ECS) is the largest neurophysiological receptor system in the body. It is within this system that cannabis plant molecules interact, producing a myriad of downstream effects. The ECS is a compensatory system described as both a neuromodulator and an immunomodulator, responsible for achieving and maintaining homeostasis in both the nervous system and the immune system [15]. It plays a critical role in balancing the endocrine system, the musculoskeletal system, and the gastrointestinal system. The ECS was initially thought to include the basic coordination of lipophilic endogenous ligands, arachidonoylethanolamide (AEA or anandamide) and 2 arachidonoyl-glycerol (2-AG), their hydrolyzing enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), and two G-protein-coupled receptors specific to endocannabinoids, appropriately named cannabinoid receptor type-1 (CB1) and type-2 (CB2) [12]. As our understanding of the ECS continues to evolve, it is clear this relatively simple description is considerably incomplete.

Recently, the term endocannabinoidome has emerged to characterize the complexity of this receptor system [16]. In addition to the original description above, research has uncovered many other receptors, ion channels, and ligands that participate in the ECS. These include but are not limited to: G-protein coupled receptors (GPR55, GPR110, GPR119, and GPR18), transient receptor potential ion channels (TRPV1, TRPV2, TRPV4, TRPM8), peroxisome proliferator-activated receptors found in the nucleus (PPARα, PPARγ), "endocannabinoid-like molecules" N-acylethanolamine (NAE) congeners (i.e., PEA, OEA, LEA, and DHEA), 2- mono-acyl-glycerol (2-MAG) congeners (i.e., 2-OG, 2-LG), and many more [12, 17]. In its entirety, the endocannabinoidome is extremely complex and includes a multitude of overlapping pathways; as such, relevant sections and mechanisms of action will be discussed as they pertain to relevant pathologies related to sports and athletics and the therapeutic application.

5 Therapeutic Applications in Sports

Inflammation Inflammation is the athlete's natural healing response to muscle damage, microtears, and excessive neuron disturbances in their body [18]. Inflammation is a normal cascade of signals and cellular events that take place to repair damage occurring from intense physical activity such as strenuous exercise training or competition in contact sport [19]. The purpose of inflammation is not only to stimulate repair, but also to resolve the immune trigger (tissue damage/infection) and clear out the debris before the repair process starts [20].

The inflammatory response occurs as needed and is reduced once the injury has been repaired and homeostasis achieved. Inflammation proceeds as a multistep process involving numerous trigger molecules, receptors, and intracellular signaling pathways that ultimately promote the expression of either pro- or antiinflammatory cytokines, chemokines, and involved genes [21]. Inflammation is neither "good" nor "bad" but a necessary physiological progression to identify and repair a stressor and help the body return to homeostasis. Inflammation becomes problematic only when it is unable to appropriately regulate itself and persists unnecessarily [21]. Inflammation is how the various participating cells of the immune system receive their instructions to either address a problem or retreat. In fact, a certain degree of localized inflammation is necessary to initiate the cellular and molecular responses that drive muscle growth and remodeling after resistance exercise [22]. It can be used intentionally to manipulate physiology, such as invoking acute inflammation by resistance training to build muscle. [21]. However, when inflammation becomes excessive or chronic, it can significantly diminish an athlete's ability to recover from exercise training or to perform at their best [18]. Chronic inflammation can disrupt normal sleep patterns that are important for optimal performance and recovery [23]. Persistent inflammation requires energy and can result in fatigue [24, 25], impaired immune function

[26], and prolonged injury status [27]. Impeding an athlete's ability to repair and build muscle or recover from competition will reduce their ability to perform optimally when needed.

The endocannabinoid system is a homeostatic regulator tasked with controlling inflammatory triggers. The CB2 receptors of the endocannabinoid system are primarily found on peripherally circulating immune cells and tissue, although they are also found in other places [28]. They are the "non-neuronal" endocannabinoid receptor involved in inflammatory processes. CB2 receptors have been identified on cells of the thymus, tonsils, B cells, T cells, macrophages, monocytes, and natural killer cells [29]. Their wide distribution on circulating immune cells enables them to be active participants in the modulation of peripheral inflammatory processes [30]. For example, a variety of immune cell types are called upon in response to physical insult and tissue damage from body contact in sport. An increase in both endocannabinoid secretion (i.e., 2-AG and AEA) and CB2 receptor concentration occurs in response to injury [30]. In addition, effects beyond initial cell responses are influenced by the endocannabinoid system, such as alterations in chemokine and cytokine signaling in both proinflammatory and antiinflammatory ways [29]. The ECS regulates and controls immune responses and the extent of inflammation by regulating cytokine production and release at different stages of injury. The ECS ligands, anandamide and 2AG, suppress proinflammatory and enhance antiinflammatory cytokines in both innate and adaptive immune responses, demonstrating the critical involvement of the ECS in the inflammatory process [30].

Neuronal injuries also incorporate the CB1 receptor in the inflammatory process. The CB1 receptor is found primarily in the central and peripheral nervous system. It is the most abundant G-protein coupled receptor in the brain [30]. These receptors are most highly expressed at the axon on presynaptic neurons in the brain amygdala, hippocampus, cortex, basal ganglia, and cerebellum [31]. They are strongly associated with inhibitory gamma-aminobutyric acid (GABA) and excitatory glutamatergic neurons. Their activation by a cannabinoid ligand strongly influences GABA and glutamate release through potassium and calcium ion channel activity [31]. Unlike typical neurotransmitters that exist in storage vesicles waiting to be called upon, endocannabinoid ligands such as anandamide and 2-AG are made on demand and subsequently rapidly degraded [32]. They are made and released from the post-synaptic terminal as needed, in a site-specific manner, and travel in a retrograde direction to the pre-synaptic terminal where they activate the CB1 receptor [32]. Activating the CB1 receptor causes a reduction of calcium ions entering the cell, which leads to reduced neurotransmitter release. This functions as a "circuit breaker" to reduce neurotransmitter output. For example, if the excitatory neurotransmitter glutamate is over secreted and becoming excitotoxic from injury, the post-synaptic formation and release of endocannabinoid ligands will travel in the retrograde direction to activate pre-synaptic CB1 receptors (Fig. 1). This will reduce calcium influx, leading to a reduction of glutamate release, bringing the whole system closer to homeostasis. Preclinical and rodent model research has shown that activating CB1 and CB2 receptors with a cannabinoid agonist (either synthetic or from the cannabis plant phytocannabinoid) can suppress out-of-control neural and inflammatory responses, which theoretically could have benefits for athletes who regularly invoke their immune system to heal injuries from physical training and body contact if the preclinical data translate dependably to humans [33]. A recent investigation into the effects of medical cannabis use on inflammatory cytokines and chemokines in adult patients with chronic pain showed possible immunomodulatory effects on several immune markers with cannabinoid use and encouraged more research in this area [34]. Research studies are underway to evaluate this concept in humans (e.g., clinicaltrials.gov NCT06204003, NCT05066308, NCT03522103, NCT05514899)**.**

Successfully targeting the endocannabinoid system to modulate inflammatory immune response could be useful in athletics. Cannabinoid-based therapies targeting antiinflammatory, antioxidant, neuroprotective, and neurogenerative effects have been successfully demonstrated in preclinical and rodent research [35]. One avenue to accomplish this is to provide exogenous cannabinoids and terpenes that influence the ECS. An assortment of these bioactive molecules is found in the cannabis plant. Two well-researched approaches include directly agonizing or antagonizing receptors of the ECS (i.e., CB1, CB2, TRPV1, etc.) and/or inhibiting endocannabinoid degradation enzymes (i.e., FAAH and MAGL) leading to an increase in circulating secreted endocannabinoids as shown in Fig. 2, which illustrates the potential antiinflammatory cannabinoid pathways in athletic injury, pain, and concussion. While the THC molecule also has potential inflammatory effects in certain doses, the focus of this figure is strictly on the antiinflammatory potential and the reader is directed to other sources for additional information on potential inflammatory pathways and cautioned not to be misled. Specific research projects have demonstrated less immediate physiological effects using phytocannabinoid treatment as well, such as transcription factor modifications through PPAR nuclear receptors [36], gut microbiome influences [37], and bioenergetic metabolic effects [38]. Since cannabis products are increasingly available to the public for consumption, focused therapeutic applications in athletics are now possible and could be beneficial to support an overwhelmed inflammatory system.

The phytocannabinoid cannabidiol (CBD) is widely available commercially and recognized as a possible

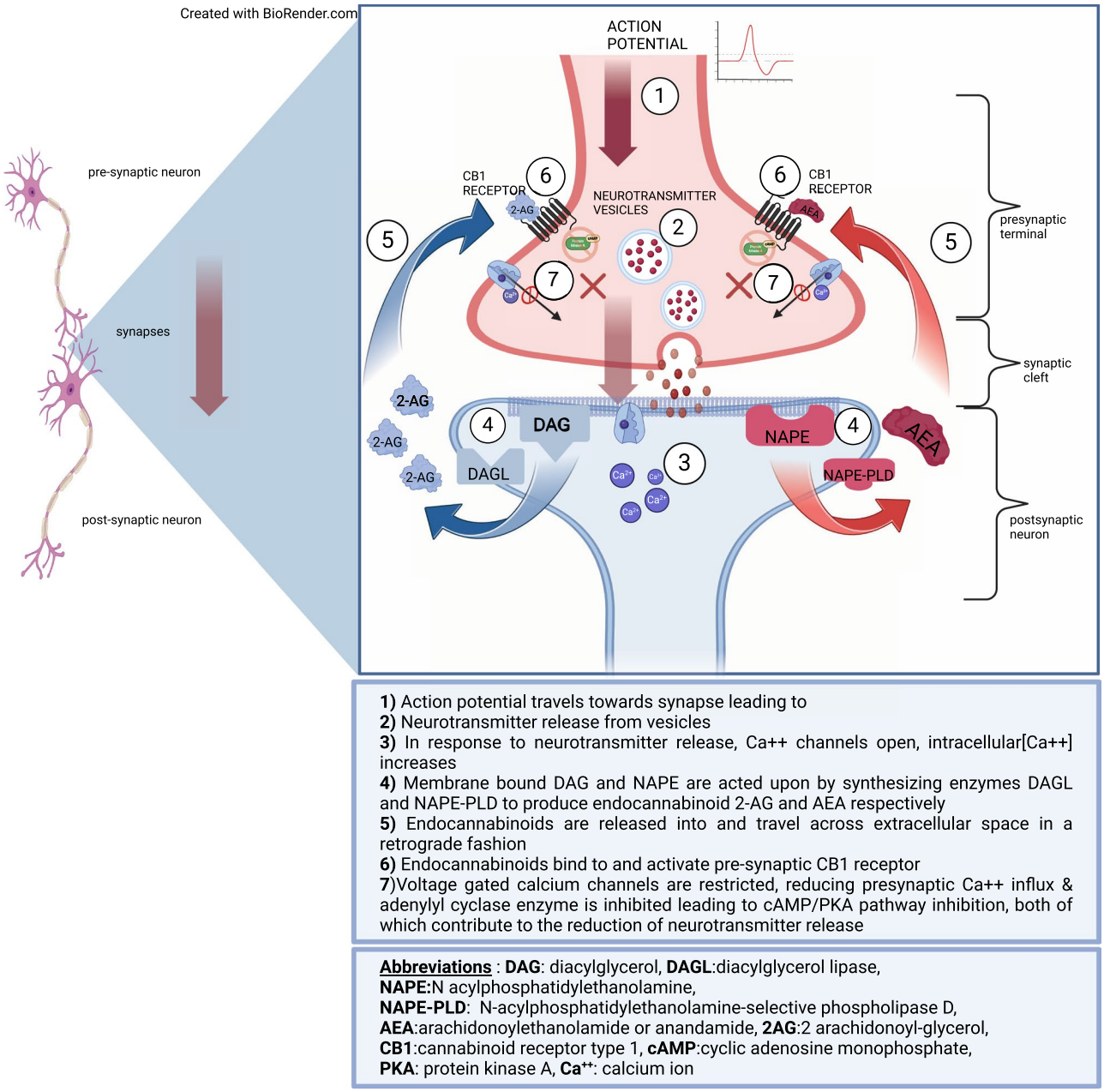
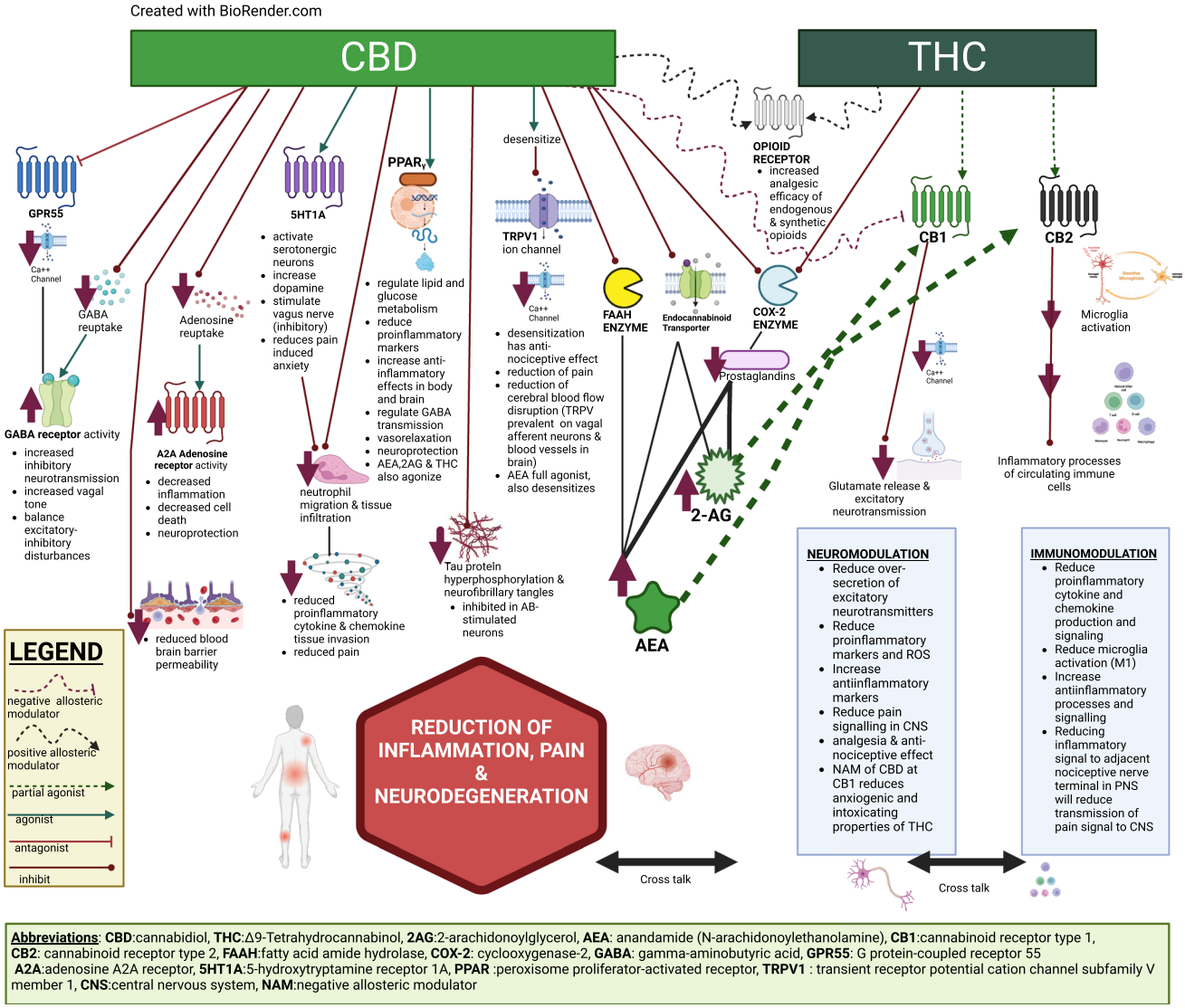


Fig. 1 Endocannabinoid system retrograde transmission

antiinflammatory agent. It has a high safety profile, which contributes to its recent popularity. Void of intoxicating effects, it is a promising therapeutic that has more than 56 recognized molecular targets [39]. Its multi-target capabilities are attractive since this single substance could be used to address multiple different conditions; however, its promiscuous nature complicates pharmacological specificity and selectivity [39]. In regard to inflammation, in vitro and in vivo research suggests CBD acts directly on cells and tissues of the immune system to decrease cytokine production and tissue infiltration [40]. One CBD research study demonstrated several effects on polymorphonuclear neutrophils (PMNs), which are the first immune cells called to the site of acute inflammation, with a potential role in chronic inflammation as well [40]. At sites of inflammation, CBD decreased PMN migration and tissue infiltration, reduced proinflammatory reactive oxygen species, and reduced proinflammatory cytokine production [40]. CBD was found to have a greater inhibitory effect on immune cells of perturbed and inflamed tissue rather than on tissue in a balanced homeostatic state [40]. This implies its activity would not push healthy tissue out of a state of balance; but rather, its



Abbreviations: **CBD**:cannabidiol, **THC**:Δ9-Tetrahydrocannabinol, **2AG**:2-arachidonoylglycerol, **AEA**: anandamide (N-arachidonoylethanolamine), **CB1**:cannabinoid receptor type 1, **CB2**: cannabinoid receptor type 2, **FAAH**:fatty acid amide hydrolase, **COX-2**: cyclooxygenase-2, **GABA**: gamma-aminobutyric acid, **GPR55**: G protein-coupled receptor 55 **A2A**:adenosine A2A receptor, **5HT1A**:5-hydroxytryptamine receptor 1A, **PPAR** :peroxisome proliferator-activated receptor, **TRPV1** : transient receptor potential cation channel subfamily V member 1, **CNS**:central nervous system, **NAM**:negative allosteric modulator

Fig. 2 Cannabinoid pathways in athletic injury, pain, and concussion

effects would mainly occur at sites experiencing inflammation. In addition, CBD can inhibit the hydrolyzing enzyme fatty acid amide hydrolase (FAAH), which is the enzyme responsible for inactivating the naturally secreted endocannabinoid anandamide (AEA) [41]. FAAH enzyme inhibition leads to increased circulating levels of AEA and subsequent interaction with the ECS that promotes antiinflammatory processes. These immunomodulating features may benefit athletes looking to reduce inflammation that occurs from daily physical exercise training (e.g., resistance and endurance), and from physical contact in sport.

The phytocannabinoid Δ^9 tetrahydrocannabinol (THC) is another popular cannabis plant molecule featured in emerging commercial cannabis products. THC content is the focus of most cannabis laws and regulations due to its intoxicating effects and history of prohibition. While not without potential harm, stigma and confusion about THC generally overshadow its potential therapeutic applications [42]. Education on the mechanisms of action and prospective therapeutic benefits of THC is severely lacking and desperately needed [43]. THC is a partial agonist at the CB1 receptor, provoking downstream effects that mimic activation by naturally secreted endocannabinoids [44]. It also has activity at the CB2 receptor, but with less affinity than at CB1. Unlike CBD, THC's activity is relatively specific for cannabinoid receptors. The notorious psychotropic effects of cannabis products are dose dependent on THC's interactions at the CB1 receptor. Research on THC has demonstrated its ability to down-regulate proinflammatory markers such as tumor necrosis factor-alpha (TNF-αβ), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), nuclear factor-kappa B (NF-κB), matrix metalloproteinase-9 (MMP-9), and vascular

endothelial growth factor (VEGF), and elevate antiinflammatory markers interleukin-10 (IL-10), transforming growth factor-beta 1 (TGF-β1), and brain-derived neurotrophic factor (BDNF) [45]. THC activity at the CB1 receptor modulates neurotransmitter release, similar to naturally produced endocannabinoids [46]. Neuromodulation could be beneficial for contact sport athletes who are often subjected to an over-secretion of the excitatory neurotransmitters [47, 48].

The intoxicating side effects of THC complicate its incorporation as a therapeutic. However, it is possible to create a dosing ratio with other cannabinoids that minimize psychoactive effects while still providing beneficial therapeutic and health outcomes. In the case of contact sport athletes who are repeatedly subjected to inflammatory and hyperexcitatory neural conditions[48], THC could be intentionally incorporated to support and calm an overwhelmed neurotransmitter and immune system if human research supported this. Of note, the Food and Drug Administration (FDA)-approved drug dronabinol (marketed as Marinol or Syndros) has existed since 1985. Molecularly, its only active ingredient is a synthetic enantiomer of the THC molecule, identical to that of the cannabis plant [49]. Made synthetically as a pharmaceutical, THC is categorized as schedule III in the controlled substances act of the USA and considered non-narcotic with low risk of physical or mental dependence; simultaneously, the identical molecule of THC when extracted from the plant remains in schedule I at the federal level in the USA, considered a narcotic with no medicinal use. The federal scheduling of cannabis is currently under review in the USA [50].

Human studies examining cannabinoids and inflammation have shown mixed results. One study did not find any evidence that acute CBD supplementation could attenuate the inflammatory response or provide antiinflammatory effects in the context of exercise-induced muscle damage and recovery in trained female athletes [51]. In another study, CBD was found to have a modest yet notable effect on muscle damage and recovery (reduction in creatine kinase and myoglobin) within a 72-h window after 60 mg of CBD supplementation [52], whereas in a different study a dose of 150 mg CBD oil had no effect on non-invasive markers of muscle damage [53]. A small pilot study evaluated the impact of two doses of CBD oil on inflammation after an eccentric loading protocol [54]. The results suggested that CBD supplementation may attenuate the acute increase in interleukin-6 (IL-6), a marker of systemic inflammation, following intense eccentric exercise when compared with a placebo [54]. It is worth noting that inconsistencies in dosing (i.e., dose size, formulation, route of administration, cannabinoid ratio) and exercise protocols between studies can drive inconsistencies in study outcomes. Research into the use of CBD for inflammation in athletics is increasing. Larger well-designed studies are needed to fully elucidate the antiinflammatory potential of CBD in relation to exercise and sports performance.

Of note, the antiinflammatory properties of cannabinoids such as CBD may potentially interfere with desired training adaptations if consumed too close to a resistance training session done with the intention of eventual strength increases. A certain degree of localized inflammation is necessary to initiate the cellular and molecular responses that drive muscle growth and remodeling after resistance exercise. Antiinflammatory drugs are suggested to impair muscle hypertrophy through inhibition of the acute inflammatory response that activates skeletal muscle remodeling. As a putative antiinflammatory compound, CBD may similarly have negative effects on muscle repair [22]. However, staggering the dosing of antiinflammatory agents for at least 6–8 h after resistance exercise may allow for the necessary inflammatory processes to occur depending upon the pharmacokinetic characteristics of the antiinflammatory agent [22]. Whether dose staggering relative to resistance training could successfully be applied to CBD requires investigation. It is important to note that this advice is specific to the context of resistance training, keeping in mind that chronic or excessive inflammation is a key factor in skeletal muscle atrophy, the exact opposite of muscle and strength gain [20]. While some inflammation is necessary for muscle gains, too much becomes detrimental and can lead to muscle loss.

Pain Pain is a subjective feeling that is distressing, and often caused by intense or damaging stimuli. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [55]. One consequence of inflammation and overstimulated neural pathways is pain. The consequence of pain in athletes are numerous, and can be exceedingly costly, both physically and monetarily.

Pain can hinder an athlete's ability to perform at their best [56]. The reduction in speed, strength, or endurance can ultimately lead to loss of contractual bonus incentives, or contract renewal in professional sports. An athlete's body is their most valuable tool, and pain obstructs it from functioning optimally. In the case of professional sports, this could equate to the loss of millions of dollars and performance statistics; thus, athletes often strive to play through their pain [56]. Attempting to push through pain raises the risk of more serious or additional injury from unnatural movements used to compensate for discomfort. Rehabilitation procedures are also delayed by the sensation of pain, prolonging the time it takes to heal from injury. Pain can lead to mental health consequences such as depression and frustration from being sidelined, or anxiety wondering if a career is coming to an end [57].

The sensation of pain is difficult to quantify since it is a subjective experience. It is experienced differently by

different people, and can lead to different physiological and clinical outcomes, necessitating a variety of measurement tools to assess pain. Pain can be categorized as nociceptive or neuropathic, each with their own unique characteristics [58]. Nociceptive pain is caused by signals from invading immune cells, sent in response to tissue damage. These sensory signals are carried by peripheral nerves to the cortical area of the brain to be interpreted as a warning sign of damage and danger to the body. In contrast, neuropathic pain is not a warning sign, but rather is more complex and an abnormal signal caused by damage to sensory nerves, resulting in inaccurate and amplified pain messages to the brain [58]. Neuropathic pain is a signaling misfire and can occur without a clear underlying cause.

The endocannabinoid system is instrumental in the process of pain. It is called upon to suppress inflammation and nociceptive signals by secreting ligands AEA and 2AG to activate cannabinoid receptors. This activation modulates the pain signals, reducing the subjective experience of discomfort. Neural and nonneural cells both produce endocannabinoids upon injury as a first response to inflammation and pain signals [58]. Notably, CB2 receptors have been found to increase in number in a site-specific manner in response to nerve damage. This receptor concentration increase is associated with several neurodegenerative disorders such as Alzheimer's and Parkinson's disease [59].

Since the phytocannabinoid THC is primarily active at cannabinoid receptors, it has the potential to mimic antiinflammatory and pain-reducing effects of endocannabinoids. Research has shown THC activates pre-synaptic CB1 receptors, causing similar downstream effects as AEA and 2-AG [44]. This includes analgesia and the neuromodulation of dysregulated neurotransmitters, which are both relevant in the sensation of chronic pain. These mechanisms of action align with the conclusions made by the Committee on the Health Effects of Marijuana from the National Academy of Science and Engineering in their evidence review in 2017. They confirmed cannabis to be an effective treatment for chronic pain in adults after thoroughly reviewing existing research [60]. An additional systematic review included 28 placebo-controlled trials researching cannabinoids for medical use. This meta-analysis found a greater reduction in pain and numerical pain ratings with cannabinoid use in a chronic pain population [61]. Of note, both THC, CBD, and a combination of minor cannabinoids and different ratios of THC:CBD were included in this review. The ability to reduce chronic pain and dysfunctional neuromodulation by intentionally creating a cannabinoid therapy plan could benefit athletes who struggle with these conditions.

CBD is a relevant phytocannabinoid in decreasing the sensation of pain, although its mechanism of action is less well understood. There are several proposed mechanisms that suggest CBD's influence on pain may come directly from its antiinflammatory properties, such as its ability to attenuate proinflammatory cytokine and chemokine invasion. This provides a less acute but more long-lasting analgesic effect than THC alone [62]. Alternatively, CBD's effect on pain could largely come from its indirect consequences on endocannabinoidome components. CBD has high activity at the ionotropic receptor TRPV1, which can lead to eventual desensitization and reduction of downstream pain signaling [62]. CBD was found to bind to intracellular endocannabinoid transporters (fatty acid binding proteins), indirectly inhibiting AEA uptake and enhancing its availability and endogenous activity [62]. CBD inhibited various hydrolytic enzymes responsible for AEA degradation (i.e., FAAH), additionally contributing to increases in endocannabinoid serum levels and the anti-nociceptive effects that accompany them [62]. With some human clinical trials showing CBD to be safe and low risk for even mild side effects, the benefit to athletes for pain reduction is encouraging and must be explored further. Research is ongoing.

While clinical trials have shown CBD and THC to each be effective in the reduction of pain and inflammation, numerous clinical trials have been done combining the two. Mixtures of different ratios of cannabinoids (compared with a single isolated cannabinoid) have altered pharmacokinetic and pharmacodynamic characteristics leading to significant changes in use outcomes. This is often referred to as the "entourage effect." For example, when CBD is co-administered with THC, the often-undesirable psychotropic effects of THC are notably reduced [62]. In addition, the presence of CBD has been found to increase THC plasma concentrations [63]. The approved pharmaceutical drug Sativex is a 1:1 blend of plant-produced CBD and THC containing 2.5 mg CBD and 2.7 mg THC per oral mucosal spray (equating to 25 mg mL^{-1} CBD and 27 mg mL^{-1} THC) [64]. It is approved for use on multiple sclerosis spasticity and pain in many countries, including Canada and most of Europe, and has been investigated for other applications such as the reduction of pain and inflammation and quality of life improvements.

One enzyme widely recognized for its involvement in pain and inflammation is cyclooxygenase-2 (COX2), the target of nonsteroidal antiinflammatory drugs (NSAIDS) used to reduce inflammation and pain [65]. THC and CBD are COX-2 enzyme inhibitors, leading to a reduction in inflammatory prostaglandins [19]. Since they share an upstream synthesis pathway, the reduction in prostaglandin synthesis leads to an increase in AEA and 2AG synthesis, and hence their leading availability to participate in their regular antiinflammatory and pain modulating activities [19]. Using defined cannabinoid ratios of THC and CBD, clinical studies have shown reduced pain scores, increased pain thresholds, and improvements in sleep and quality of life in varying pain conditions [63]. However, not all studies on cannabinoids

and pain have shown positive results. A recent systemic review with meta-analyses of cannabinoids versus placebo for pain concluded that cannabinoids reduced chronic pain with questionable effect size, and had no effects on acute pain or cancer pain [66]. Although human studies are mixed, the high safety profile and increasing ability to purchase cannabinoids creates an opportunity for athletes to investigate cannabinoid therapeutic protocols designed to reduce pain in sport populations.

Opioid Sparing Opioids are a broad group of narcotics used for pain relief by acting on different brain centers. Specifically, they interact at opioid receptors found throughout the central nervous system (CNS). The three main types of opioid receptors, include mu (μ), delta (δ), and kappa (κ). Each are found in different regions of the CNS, playing a role in pain modulation, reward processing, and autonomic function [67]. Examples include tramadol, oxycodone, fentanyl, morphine, and hydromorphone.

Opioids are commonly prescribed to patients, including elite athletes, as a medication to combat the sensation of pain. The athlete demographic is at increased risk for future problematic use of opioids based on increased exposure to the substance to reduce pain from injury in sport or necessary surgeries. Opioids are effective at reducing acute, chronic and postoperative pain; however, they have an extremely high abuse rate following use [68]. Recently, the opioid addiction rate of patients prescribed opioids by their doctor for chronic pain was estimated as roughly 22% [68]. Potentially of more concern is that approximately 80% of current heroin users in the USA cite prescription pills as their initial exposure to opioids that led to the subsequent use disorder [69]. Additionally, opioids are an important cause for overdose and death. In 2021, the Center for Disease Control and Prevention (CDC) tallied 107,000 drug overdose deaths in the USA, with 75% of these being from an opioid [70]. Incidentally, the number of overdose deaths in 2021 was six times the number recorded in 1999 [70]. Understandably, opioid overdose was declared a national emergency in the USA in 2017 [69]. Canada mirrors the USA with their opioid crisis. The rise in fatalities and the increase in product strengths has led many provinces to declare public health emergencies, particularly the western provinces of Alberta and British Columbia [71]. In general, European countries are not facing as much of an opioid crisis, with the exception of the UK and Ireland, where use continues to rise [72]. A 2020 systematic review of opioid use in athletes calculated opioid use over the course of a National Football League (NFL) career was 52%, with high school athletes found to have lifetime opioid use rate of up to 46% [73]. Concerningly, up to one-half of high school athletes reported using non-prescription opioids at some time essentially unmonitored by a healthcare provider [73]. Risk factors associated with opioid use included sports that involve contact (i.e., hockey, football), post-retirement unemployment, and undiagnosed concussion [73]. Considering that the use of opioids while playing predicted the use of opioids in retirement [73], it is imperative to consider all therapeutic pain reduction options while players are currently on the roster to protect their future selves. Cannabinoid therapy is a growing area of interest not only for its own pain reduction properties, but also for its opioid-sparing effects.

Opioid-sparing medications are medications that when used together with opioids reduce the necessary dose of opioid required to achieve the same analgesic efficacy. Cannabinoids have been proposed to fall in this category due to their ability to reduce the amount of opioid needed when used together for pain. A systematic review and meta-analysis of preclinical studies on the opioid-sparing effects of cannabinoids found THC reduced the median effective dose (ED_{50}) of morphine 3.6 times [67, 74–79]. Similarly, the ED_{50} for codeine was reduced 9.5 times when administered with THC [67, 74, 75]. Both cannabinoid and opioid receptors are expressed in several regions of the brain involved in anti-nociception [67]. They have similar signal transduction systems in afferent pain circuits that transmit pain messages to the brain [80]. Furthermore, mu-opioid receptors and CB1 receptors are found in many of the same locations in peripheral afferent neurons [81]. Given their co-localization, cannabinoid and opioid receptors may heterodimerize and function together in some capacity, supporting the idea that activity at the CB1 receptor could indirectly affect opioid receptor activity. In addition, CB2 receptors have been shown to indirectly stimulate opioid receptors in afferent pathways [67]. Both CBD and THC cause positive allosteric modulation of the opioid receptor [19]. Additionally, multiple studies provide evidence that CBD can inhibit key P450 enzymes such as CYP3A4 and CYP2D6 that are involved in metabolizing opioids such as oxycodone and codeine. Clinically relevant interactions at P450 enzymes could potentially increase the bioavailability of these opioids by reducing their first-pass metabolism [82–84]. The value of an opioid-sparing effect to lower the opioid doses required to treat acute, chronic, and postoperative pain could translate to a reduction in opioid-related abuse and mortality in the high-risk athletic population.

Mild Traumatic Brain Injury (mTBI) or Concussion Contact sports have a high prevalence of concussion, also referred to as mild traumatic brain injury (mTBI). In addition to suffering the initial injury and resulting symptoms, repetitive concussions early in life increase the risk for future neurodegenerative disorders such as Alzheimer's or Parkinson's disease [85, 86]. Such risks bespeak a need to investigate interventions that can reduce the incidence and consequences of this type of injury. The endocannabinoid system could be an effective therapeutic target to decrease

secondary metabolic effects that follow the primary impact on the brain.

The primary physical impact involved in concussion initiates secondary metabolic effects such as enhanced glutamate release at the synapses between neurons [86, 87]. Glutamate is an excitatory neurotransmitter known to become unregulated and excitotoxic after head contact [88]. One downstream effect of glutamate binding to N-methyl-D-aspartate (NMDA) receptors is an influx of calcium ions (depolarization) and a reduction in glucose metabolism, which suppresses neuron activity [89]. This depleted energy state impairs aerobic oxidative metabolism, necessitating anaerobic glycolysis and leading to acidic lactate by-products in the brain (Fig. 3). The increased lactate levels are not only metabolic end products; lactate also serves as an important signaling molecule to modulate cellular processes such as neuronal excitability, neuronal plasticity, and neuroprotection [90]. In addition, under conditions of excessive activity, neurons may use lactate as a glucose-sparing substrate when present in high concentrations [91]. As an energy substrate, lactate is converted into pyruvate in the cytosol, which is then shuttled to the mitochondria and used as fuel or converted into glucose [91]. If sufficient fuel is not available to the neurons, increased reactive oxygen species (ROS) and local oxidative stress may result from this depleted energy state [89]. Increased oxidative stress can lead to chronic inflammation. Endocannabinoids are suggested to play a role in reducing this inflammation after traumatic head contact [92]. In a mouse experiment, for example, the level of the naturally secreted 2-AG significantly increased in the brain both temporally and locally following closed head trauma, initiating inquiries into its role in neuroprotection [92]. In addition, neuronal cell death was reduced and tissue recovery was faster in mice treated exogenously with 2-AG compared with vehicle-treated mice [92]. On the basis of mouse research showing that phytocannabinoids mimic endocannabinoids in some capacities, phytocannabinoids might have the ability to modulate the concussion pathway to reduce neural inflammation in humans and sustain its downstream effects. Human research is currently ongoing to further investigate this concept (e.g., clinicaltrials.gov NCT06204003, NCT05066308, NCT05514899).

Preclinical research has shown that THC and CBD may have neuroprotective properties. THC can provide neural protection from excitotoxicity via CB1 receptor mediated mechanisms [93]. Contrary to the influx of calcium ions (depolarization) in concussion, CB1 receptor activation by THC induces hyperpolarization, which causes Ca^{++} channels to shut and Ca^{++} influx to cease, inhibiting the release of the neurotransmitter glutamate [93]. In vitro and rodent models also suggest CBD may reduce unregulated glutamate release and block glutamate toxicity [89]. CBD is an antagonist of the orphan receptor GPR55, which results in reduced Ca^{++} release and enhanced inhibitory GABAergic neurotransmission [89]. CBD has ability to inhibit the inactivation of AEA by the FAAH enzyme [41]. The reduction of this enzyme activity leads to higher availability of circulating endogenous endocannabinoids, enhancing their activity at many of the ECS receptor sites such as CB1, CB2, TRP, and PPAR receptors [41]. An in vitro study of CBD showed reduction of cell death and inhibition of neuroinflammatory responses, such as oxidative stress and immune mediators, in addition to enhancing neuroplasticity and neurogenesis [94]. In vivo, CBD has been found to increase brain adenosine levels by slowing reuptake [94]. This increase is associated with decreased inflammation and neuroprotection after head contact. A mouse study to investigate the effects of CBD on mTBI concluded that chronic CBD administration reduced behaviors such as aggressive, depressive, and anxious dysfunctions that often occur post-concussion [95]. Another recent study on male Wistar rats concluded that orally administered pretreatment with CBD reduced the increase in glutamate concentration induced by TBI [96]. With the reduction of TBI-induced glutamate excitotoxicity, high sensorimotor function improved and mortality rate declined, suggesting that pretreatment with CBD could lessen the adverse effects of TBI in mice [96]. Research is ongoing to investigate this in humans (e.g., clinicaltrials.gov NCT06204003, NCT05066308, NCT05514899).

CBD has been proposed to reduce disruptions in cerebral blood flow that is typical of post-concussion syndrome. The mechanism of action could be through the TRPV1 receptors, which are prevalent at vagal afferent neurons and blood vessels in the brain. CBD reduced the permeability of the blood–brain barrier in a model of ischemia [39]. This permeability, or "leaky brain," is commonly referenced in concussion research. CBD also increased cerebral blood flow in the brain's memory processing regions. This is noteworthy since reduced cerebral blood flow is often a characteristic of acute concussion [97]. CBD has demonstrated selective activity at the PPARγ receptor in vivo [98]. This activity resulted in dose-dependent reduction of proinflammatory tumor necrosis factor alpha (TNF-α), inducible nitric oxide synthase (iNOS), and interleukin-1β (IL-1β) [98]. CBD inhibited tau protein hyperphosphorylation in amyloid-beta (Aβ)-stimulated neurons, which is clearly a needed area of research in a demographic such as US football players, of which 87% showed the presence of chronic traumatic encephalopathy (CTE) with tau aggregates in neurons and Aβ deposits when autopsied post mortem [98]. The increase in available endocannabinoids, reduction of glutamate hyperexcitability, reduction of calcium influx, reduction of neuroinflammation, and reduction of cell death, in addition to enhanced neuroplasticity and neurogenesis from cannabinoid therapy, could provide contact sport athletes an advantage in the scenario of concussion [99]. The need for

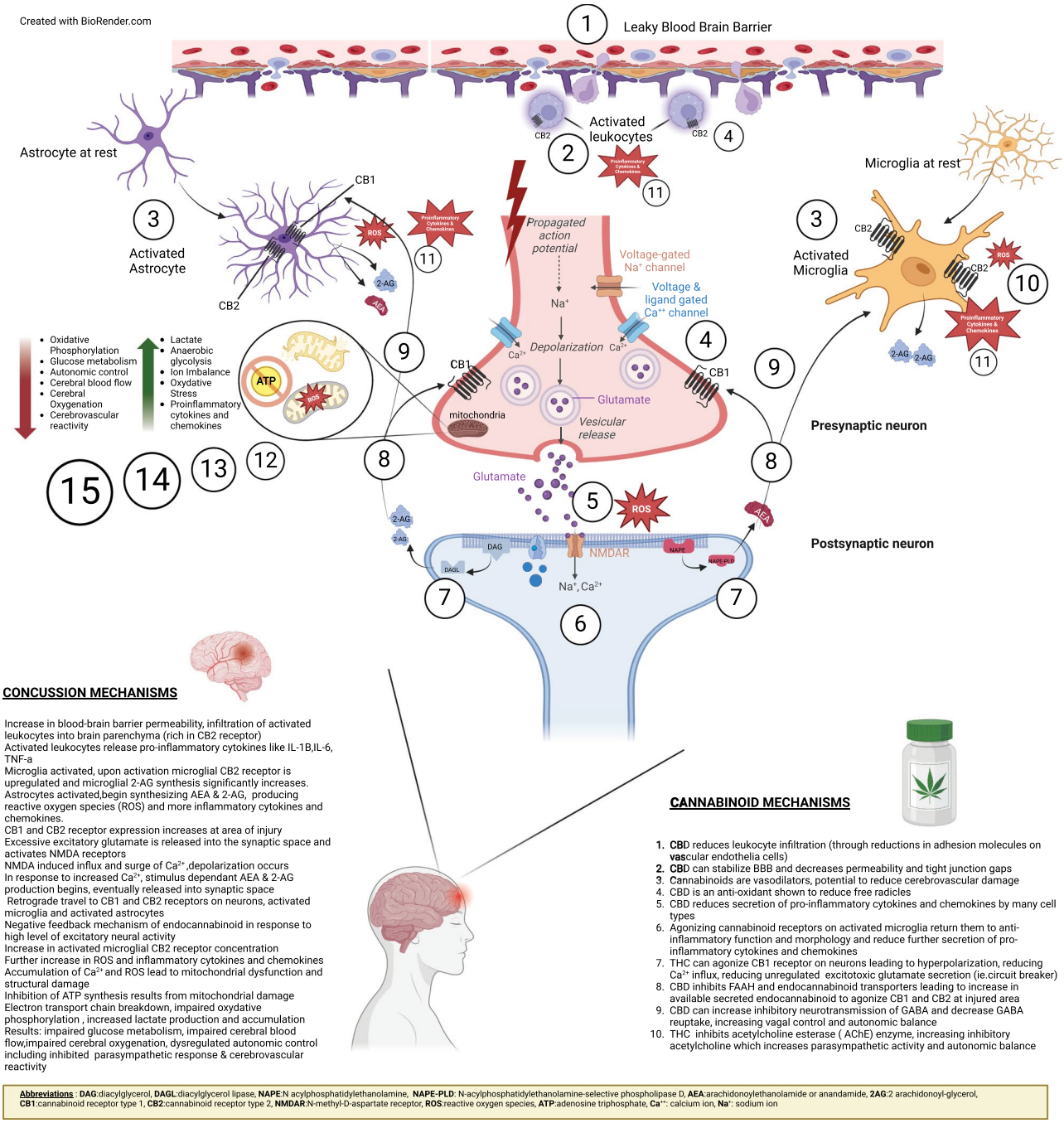


Fig. 3 Mechanisms of the endocannabinoid system and cannabinoids in concussion

research on cannabinoid therapy to reduce neuron disruption in concussion is critical.

Microglia that surround the neurons are also disrupted in concussion [100]. Microglia are the resident immune cells of the brain, activated in response to central nervous system insults. While at rest, they regulate and support neuron activity, but once they are activated (i.e., by a blow to the head or via a whiplash movement) they transition into a proinflammatory state producing toxic cytokines and reactive oxygen species [101]. CB2 receptor expression is upregulated in activated microglia as a first line of defense in nerve injury [28]. Their role is to modulate inflammation and pain. Importantly, rodent models of neurodegenerative diseases such as Alzheimer's demonstrate upregulation of CB2 in reactive microglial cells. In vitro studies with activated microglial cells demonstrate ability of both THC and CBD to decrease microglial production, release proinflammatory cytokines, and decrease the activation of

the pro-inflammatory transcription factor signal transducer and activator of transcription 1 (STAT1), involved in IFN-β signaling. However, only CBD reduced the activity of the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) pathway, which regulates expression of pro-inflammatory genes and upregulated the antiinflammatory transcription factor signal transducer and activator of transcription 3 (STAT3) [102]. Microglial activation and neuroinflammation appear to be the upstream mechanism underlying the pathogenesis of many neurodegenerative diseases and neuropathic pain [28]. This fact must be emphasized in consideration of the higher rate of future neurodegenerative disorders in contact sport athletes.

Phytocannabinoid therapy has the potential to calm down overactive microglia immune cells. Cannabinoid agonists of the CB2 receptor can return proinflammatory microglia to their normal, non-activated function and morphology [28, 103]. Phytocannabinoids are partial agonists of the CB2 receptor, and the cannabis terpene β-Caryophyllene is a selective CB2 agonist potentially providing additional avenues for the use of cannabis bioactive metabolites in concussion [104, 105]. A recent publication investigating cannabinoid use and sub-concussive head contact in the form of heading a soccer ball repeatedly supported this theory. When comparing subjects who used cannabis at least once a week for the past 6 months with those who did not use cannabis, the escalation of inflammatory biomarker S100B was significantly less for those who used cannabinoids [106]. The level of ocular motor function impairment was also less in the cannabis-using group [106]. This study suggests a potential role for cannabinoids to reduce neuroinflammation resulting from head contact in sport, which is supported by another study that found that cannabis use in humans lowered symptom burden in the third and fourth weeks after injury, although it did not improve concussion recovery time [107].

Given that the rate of dying from a neurodegenerative disorder was threefold higher in retired NFL players than in the general population, this should attract research attention to the potential therapeutic use of cannabinoids in contact sport to reduce neuroinflammation.

Mental Health Conditions Mental health disorders are characterized as behavioral, psychological, or both, i.e., regarding mood, thoughts, and behavior. Some examples that are common to athletes include (but not limited to) anxiety disorder, sleep disorder, and depression. Optimal mental health (and void of these disorders) is essential for high performance within elite-level sports. Relevant to contact sport athletes, neuroinflammatory processes are now understood to be the driving force behind multiple neuropsychiatric conditions. Consequently, reducing neuroinflammation in this population could also reduce the inflated rate of mental health pathophysiology in this demographic.

Research has demonstrated acute interactions between cannabinoid signaling and the alteration of neuropsychiatric symptoms [108]. This has been attributed to endocannabinoid system modulation of the mesolimbic dopamine system (DA), which includes the dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the brain. CB1 receptor activity controls VTA neuronal states, modulates DA release, and regulates inhibitory GABAergic signaling within the VTA [108]. Dysregulation of CB1 receptor activity in this area of the brain is associated with addiction and anxiety psychopathologies. CB1 receptors are abundantly expressed in the medial prefrontal cortex (mPFC), where they are known to control inhibitory signaling and emotional processing. The dysregulation of cannabinoid receptor signaling in this region of the brain has been associated with neuropsychiatric disorders such as major depressive disorder [108]. Additionally, the PPAR receptors of the ECS are involved in neuropsychiatric disorders. PPARs increase neuroprotection, regulate lipid and glucose metabolism, and mediate antiinflammatory effects throughout both the body and brain [109]. PPAR receptors are highly expressed in GABA neurons and are found in the VTA, NAc, and mPFC. Their activation attenuates VTA neuron activity and contributes to the regulation of DA signaling [108]. This is involved in pathologies such as anxiety and addiction; in fact, preclinical trials have shown PPAR signaling to inhibit anxiety [108].

Evidence supports the potential for CBD to help regulate DA activity. CBD can activate PPAR receptors; however, the exact mechanism responsible for the apparent neuropsychiatric therapeutic effects remains undefined [108]. Possibly, CBD helps regulate local GABAergic transmissions through PPAR receptors, helping to balance excitatory–inhibitory disturbances. Alternatively, it may participate indirectly by the inhibiting FAAH and increasing naturally secreted endocannabinoids as described above [108]. The therapeutic benefits of CBD on mental health symptoms were associated with increases in 2-AG and AEA, supporting this latter theory [108]. Several studies investigating CBD use and anxiety suggest that CBD could be anxiolytic in stress-inducing situations such as sports performance anxiety or public speaking [110]. It does not seem to have an effect in low-stress conditions. Studies on CBD and anxiety show a U-shaped dose–response, with 300 mg of CBD isolate reducing subjective anxiety significantly more than either 600 mg or 150 mg [94]. An open-label study using whole-plant, full-spectrum products for 4 weeks on patients with anxiety used a much lower daily dose of 30 mg CBD and < 1mg THC. Patients reported reduced anxiety and improvements in mood, sleep, self-control, and quality of life with few reported side effects [111]. As for the purported antidepressant qualities of CBD, evidence suggests it is an agonist at the 5HT1A serotonin receptor and the D2 dopamine receptors, invoking similar

emotional outcomes as the neurotransmitter itself [112, 113]. This has been explored in rodent studies. Although CBD is widely available over the counter and individuals can now self-treat, human clinical trials are needed to evaluate CBD's therapeutic potential in mental health conditions. Thus far, studies suggest inter-individual differences to stressful situations seem to impact the effectiveness of CBD to act as a therapeutic agent, and a one size fits all approach to CBD use and dosing is unlikely to bring about therapeutic benefit to those wishing to use cannabis to address their mental health condition.

CBD has been found to reduce the mind-altering effects of THC, in addition to the anxiogenic effects that often accompany THC use [112]. CBD is a negative allosteric modulator at the CB1 receptor, reducing the pharmacodynamic ability of THC to bind at the orthosteric pocket and activate downstream events [112]. This is a useful fact when looking to tailor therapeutic approaches and one example of why education regarding dosing is imperative for individuals seeking to implement cannabinoid therapies in an optimal way. There may be ways to structure dosing that do not lead to impairment yet still deliver the therapeutic benefits reviewed above. THC has been studied for its role in mental health conditions and is advisable to include CBD together with THC as a therapeutic agent to avoid provoking anxiety or cognitive impairment that is found to accompany THC on its own [112].

Performance Enhancement Anecdotal reports from athletes of cannabinoids helping with performance, rest, and recovery are becoming more common. Studies done to investigate these claims have shown mixed results [114–127]. As with other therapeutic areas involving cannabis use, mixed results are not surprising. Studies generally give limited consideration in any systematic way to the cannabinoid and cannabis product, dosing and route of administration, the population under investigation, and study design. Outcomes of one study may be confounded by inadequate attention to the cannabinoid dose and product, for example, and should remain context specific with an understanding that those outcomes may not be translatable to other study populations or with other cannabinoids or cannabis products. Significant differences in results can be found between studies on the basis of differences in cannabinoid types, administration routes, consumption timing, environment of study (i.e., lab versus real world), biological sex of subjects, health state of subjects, and experience with cannabis (i.e., chronic user versus non-user or occasional user) [116]. The unique population of athletics and sport performance will benefit from additional human clinical trials on cannabinoids to produce data pertinent to their distinctive physiological and psychological profiles.

Research on THC has yielded a spectrum of conflicting results. Some investigations suggest it offers no therapeutic value [119, 120], while others indicate possible positive effects [117, 127]. Conversely, certain studies have highlighted diminished physical performance associated with THC use [115, 121, 122, 127]. A clinical trial (clinicaltrials.gov identifier NCT05192239) was conducted on healthy, habitually active adults using an edible gummy containing 10 mg THC to evaluate its acute influence on various metrics of exercise performance [123]. Participants were regular users of cannabis products. This study concluded that when this product was consumed by this population, it had minimal physiological effects on exercise output and was "neither ergogenic nor ergolytic" [123]. In contrast, a different clinical trial (clinicaltrials.gov identifier NCT04693884), carried out in a habitually active adult population of regular cannabis users, found negative effects on vigorous exercise performance from inhaled administration routes of THC [124]. Conversely, negative consequences on exercise performance were not found in inhaled CBD products that were void of THC in this trial [124]. Current research offers limited evidence to suggest that chronic cannabis use significantly impacts physical performance of healthy athletes when consumed outside of training or competition periods. Studies comparing cannabis users with non-users found minimal differences in a range of key performance indicators or inflammation markers [116]. This lack of substantial evidence indicates that regular cannabis consumption during periods away from athletic activities may not meaningfully affect these performance metrics in otherwise healthy and active individuals. However, more comprehensive research is necessary to draw definitive conclusions about the long-term effects of cannabis use on athletic performance.

Studies on acute administration of cannabinoids on cardiovascular metrics have provided information for a healthy population. Such studies note changes in heart rate [128–130] and blood pressure [128, 131] after administration, but results vary on the basis of the details of the study. THC's impact on cardiovascular function presents a nuanced picture. Multiple studies have observed that as the dosage of THC increases, there is a corresponding elevation in heart rate [132–134]. This dose-related acceleration of resting heart rate is a well-documented phenomenon. In contrast, THC's influence on blood pressure is less predictable, showing diverse outcomes across different research contexts. A single dose of THC did not affect blood pressure in exercise [129], while a persistent high-dose administration of up to 210 mg of THC over 24 h for multiple weeks did alter blood pressure in exercise [135]. This highlights the complex nature of THC's interaction with the cardiovascular system and emphasizes the fact that individual factors may play a significant role in determining these effects. In addition, the physiological profile during rest and exercise are very different, and the impact of cannabis may be quite different during exercise. It remains unclear which effects from cannabinoids

that are found at rest persist during exercise, and how those effects potentially influence performance. This is important to keep in mind when evaluating cannabinoid effects on performance metrics to ensure interpretation of results reflect the reality of what is being measured.

The phytocannabinoid CBD is distinct from THC, and research examining it is equally unique. As the only cannabinoid that became unprohibited by the World Anti-Doping Agency (WADA) in 2018, the interest in CBD from athletes has increased. Thus far, studies with CBD also show mixed results [53, 136], which may relate to lack of consistency in the study population, dosing, and inconsistency in the metrics being measured. Distinct populations and study designs will have distinct results, and it is too early to draw any conclusions from existing CBD research. For example, a recent study investigated the safety, tolerability, and preliminary effects of a cannabidiol (CBD)- and cannabigerol (CBG)-based beverage powder on delayed onset muscle soreness (DOMS) in exercise-trained individuals [137]. Relative to placebo, participants receiving a formulation twice daily for 3.5 days containing 35 mg cannabidiol (CBD), 50 mg cannabigerol (CBG), 25 mg beta-caryophyllene, 3.8 g branched-chain amino acids, and 420 mg magnesium citrate showed reduced ratings of interference of DOMS on daily activities at 48 h, suggesting improved functional recovery when using the formulation [137]. These outcomes cannot be translated directly to other study populations, nor can the effects be directly attributed to CBD alone given the known entourage effect associated with cannabis use. This point is highlighted with another recent study involving short-term oral CBD supplementation (60 mg oil) on muscle recovery and performance after intensive training protocol in trained individuals [138]. CBD oil supplementation was associated with reduced myoglobin levels compared with placebo, suggesting reduced muscle damage, but this was only found in the more advanced athletes. The subjects' training level proved to be an important factor, with advanced athletes responding differently to both training stimulus and CBD supplementation. CBD did not improve objective markers of muscle recovery such as creatine kinase when compared with placebo, nor did it significantly impact performance measures such as maximal strength, power output, or endurance compared in either training level group. While this study showed CBD oil had a potential benefit for reducing muscle damage markers in advanced athletes, clear effects in lesser trained athletes for muscle recovery or performance were not observed. When considering existing human research and human research yet to come on the effects of cannabinoids in athletics, it is imperative that the reader recognize the relevance and power of the details in the study. Often, the results from one study cannot be applied to a dissimilar population, a different cannabinoid formulation, a different administration route, or a different exercise state. The context in which study results were found absolutely must be considered when interpreting how they apply to populations different than the exact context in which they were produced. Clearly, the athletic population will benefit from more cannabinoid research specific to their demographic.

6 Available Cannabinoid Products and Differences in Administration Routes

As a profitable industry, the number of cannabis product choices is growing rapidly, with new items coming frequently to market. The distinction between medical use and recreational use often comes down to intention, healthcare provider interactions and recommendations, and price of product. The growing availability and access to recreational products has directly impacted the medical cannabis system [139]. Patients routinely question the value of being a registered user when they can access products and self-treat without doing so, often at a lower overall cost [140]. Although not recommended, athletes can do the same, which is why educating this demographic on the details of use is critical. Cannabis can be consumed through various administration routes, each offering distinct effects and absorption rates [141, 142]. Different routes of administration change the onset, magnitude, and duration of pharmacodynamic effects [142]. Understanding the differences and the details is critical for making a completely informed decision.

Inhalation is a method that involves smoking or vaporizing dried cannabis flower. It is very popular for its rapid delivery and onset of effects. Smoking and vaporization provide rapid onset because cannabinoids are absorbed well by the lungs, and this administration route avoids first-pass metabolism by the liver, which functions to reduce the availability of the cannabinoids from the cannabis product [143]. Vaporization is an inhalation method that heats the cannabis flower or cannabinoid product at a lower temperature without combustion, reducing potentially harmful by-products [144]. This reduction in temperature also influences the resulting terpene profile, which has been suggested to lead to differences in pharmacodynamic interactions. With inhalation, THC is detected in the blood plasma immediately, with peak concentrations achieved in around 10 min, and reducing by 80% in approximately 30 min post-inhalation [143]. Bioavailability of THC is reported as 2–56% with large variability due to smoking technique dynamics such as number and duration of puffs, hold time, and inhalation volume [143]. CBD bioavailability was reported as 11–45% when inhaled [143]. Recently, an increase of concentrated THC inhalable products such as oils, waxes, shatter, and vape pens have appeared on the market. These are extremely potent forms of cannabinoids that also require heat to administer. Caution must be exercised by the user as these products

are in high concentrate, often over 70% THC, and thus a very small volume can deliver a very large cannabinoid dose with a potential for overdosing [145]. Heating cannabinoids with a flame or alternate heating source decarboxylates the naturally occurring acidic form, Δ^9-THCA, cannabinoid to the cognitively impairing cannabinoid, Δ^9-THC. Removing the acidic group is necessary for the psychoactive effects of THC and potentially some therapeutic effects as well. As an acidic form, THCA does not have intoxicating effects and may have therapeutic value of its own [146]. The same is true for CBD where the acidic form, CBDA, needs heating to obtain the CBD molecule. Traditionally, heating comes from the flame applied to the product in a pipe or paper rolled product. If the acidic forms are the desired therapeutic molecule, heat and light must be avoided and alternate administration routes become necessary. Recent research specific to exercise demonstrated that THC altered physiological output when inhaled in either smoke or aerosol form; however, inhaled CBD did not have the same negative consequences [124]. Considering that the athlete demographic requires optimal lung function to perform their best in competition, the pulmonary and vascular consequences of any inhaled route should be carefully considered and avoided. Habitual smoking of commercial cannabis can alter cardiac mechanics and arterial stiffness in young healthy cannabis smokers [147], thus other administration routes should be prioritized.

Another popular cannabis delivery route is oral ingestion, commonly available commercially as edible gummies or baked goods. When compared with inhalation, this method results in a slower onset of effects due to slower absorption and significant loss of cannabinoids with first-pass metabolism, but often leads to longer-lasting experiences [142]. The delayed onset and prolongation of effect associated with oral administration may or may not be ideal depending on the therapeutic need. New "fast-acting" edible and drinkable commercial products have recently become available. Purportedly, they are engineered for a faster time to maximum cannabinoid concentration (Tmax) when compared with non-fast-acting oral products [9].Contemporary cannabinoid product formulations have manipulated characteristics such as water solubility, self-emulsification capabilities, encapsulation, and delivery system ingredients in the development of these products in attempts to ensure faster onset of effect and increased bioavailability [9, 148].

Generally, cannabinoid oral bioavailability is low. The literature reports a bioavailability of CBD between 13 and 19% when orally administered [143], with peak plasma concentration 1–3 h after ingestion, depending on the formulation [148]. Oral THC bioavailability is 4–20%, with plasma concentration peaking 4–6 h after ingestion in a non- "fast-acting" commercial product [143]. New fast-acting THC commercial products can now achieve peak plasma concentration in 30–60 min [9]. Peak THC concentrations are lower and slower with any type of oral delivery compared with smoking; however, both psychotropic 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and non-psychotropic 11-nor-9-carboxy-THC or COOH-THC metabolites are higher due to hepatic first-pass metabolism that occurs with oral delivery but not with inhalation [143], and 11-OH-THC metabolite is psychotropic and contributes to the intoxicating effects of oral cannabis products. Anecdotal claims of the metabolite 11-OH-THC being more psychotropic than smoked Δ^9-THC are common and need to be emphasized for harm reduction purposes. Since the effects of oral administration tend to last longer than when cannabis is smoked [149], it is imperative to allow ample time for absorption with oral administration (i.e., 90 min) before evaluating whether an additional dose should be consumed. If enough time is not given and additional product is consumed, the result could be an excessive amount of 11-OH-THC and an uncomfortable experience. When deciding on which oral products to ingest, consumers must be aware of both timing and cannabinoid content, which can each vastly change the therapeutic outcome and experience. Of note, research suggests bioavailability of cannabinoids increases roughly 3–fivefold when consumed with a fatty meal [150, 151]. This is attributed to the evoked role of lipases to cleave fatty acids and stimulate micellarization of fat-soluble compounds such as cannabinoids. These micelles have enhanced uptake by epithelial cells in the gut.

Oromucosal delivery is a popular delivery route for cannabinoids and is the most common administration route for commercially available CBD solutions. Liquid cannabis products are held under the tongue sublingually (or buccal) for several minutes to absorb cannabinoids, as mucus membranes facilitate absorption. Oromucosal delivery results in cannabinoid absorption directly into the blood stream and avoids first-pass metabolism. What is absorbed should become available quickly; however, a recent research project found no significant difference between sublingual cannabinoid administration and oral capsule ingestion when plasma concentration characteristics were compared [152]. Hundreds of commercially available CBD solutions are available on the market today, including alcohol-based tinctures and oil-based mixtures. Several approved medications use this delivery method as well. Sativex is a prescription oromucosal cannabis medication that has Health Canada approval for use for multiple sclerosis (MS) spasticity and pain in Canada and many European countries. It contains 1:1 plant derived THC:CBD ratio (2.7 mg THC:2.5mg CBD per spray) available as a liquid spray. The presence of CBD affects the pharmacokinetics of THC and can be strategically used to offset undesirable cognitive effects as has been done in this and many available therapeutic products [143]. When seeking to self-treat with cannabinoids, oral mucosal delivery has the advantage of measurable and repeatable dosing.

Additionally, it is possible that less quantity of CBD and/or THC is needed compared with oral administration; however, this remains to be clinically tested in humans. These features make oromucosal delivery a popular choice for individuals trying to discover their own optimal cannabinoid ratio and dose.

Of specific interest to the athletic population, studies have investigated the effects of body composition on cannabinoid metabolism and pharmacology [9, 148]. Physiological differences between the athletic body type and sedentary, non-athletic body type may affect the pharmacokinetics of oral cannabinoid products. Since cannabinoids are lipophilic molecules soluble in fats, they can accumulate in adipose tissue [148], which is relevant to athletes based on their body composition. Additionally, increased lean mass is associated with increased total blood volume, which could affect concentrations of circulating cannabinoids potentially diluting it in larger circulating volume of blood compared with individuals with less lean mass [148]. In a CBD study, only fat-free mass was a predictor of pharmacokinetic parameters, with a larger fat-free mass associated with faster time to maximum plasma concentration (Tmax) [148]. This was counterintuitive but rationalized by authors that perhaps since skeletal muscle is metabolically active and well perfused, it could promote greater distribution into the muscle. Similar results were not found in an investigation into the effects of body composition on THC pharmacokinetics [9]. No body composition characteristics were consistently related to pharmacokinetics of the products being studied. Even though THC is lipophilic and could in theory be absorbed by adipose tissue, this was not found to influence the short-term pharmacokinetics of the THC products in their study [9]. More research is clearly needed into the effects of physiological differences between the trained athlete and sedentary non-athletes on the pharmacokinetics of cannabinoid products. Physiological differences, in addition to formulation characteristics are well known to affect time to maximum plasma concentration (Tmax) and persistence of a compound in the body.

Topical administration of cannabinoid salves, balms, and lotions is growing in popularity for people seeking antiinflammation, relief from neuropathy, and muscle spasms. The number of available topical products has steadily increased in the marketplace. CB1 and CB2 receptors are present in keratinocytes, hair follicle cells, sweat glands, sensory neurons, immune cells, mast cells, and fibroblasts [153]. This delivery route targets the cannabinoid receptors that exist on the lipophilic outer layer of the skin known as the stratum corneum. Deeper transdermal penetration is difficult since the skin is a selective protective barrier. Intercellular channels and cytoplasm are hydrophilic, repelling lipophilic substances such as cannabinoids. For people concerned with keeping phytocannabinoids out of the blood circulation, this feature can be appealing, but very little research has been done to confirm that this is true [154]. No guarantees can be made that a drug test would not show the presence of phytocannabinoids that were applied topically. Research is ongoing to confirm whether meaningful systemic levels of cannabinoids result from topical administration.

Suppository cannabinoid products are the latest administration route gaining traction in the commercial marketplace. Given that the rate and extent of oral cannabinoid absorption is low, and that inhalation is associated with potentially negative pulmonary and cognitive effects, suppository delivery is a novel method that may avoid these issues and provide therapeutic advantages. Studies have shown the bioavailability of oral delivery to be only 45–53% that of rectal delivery due to lower absorption and higher first-pass metabolism [155]. Reported patient effectiveness for oral delivery was only 25–50% that of suppository delivery in metrics measuring spasticity, pain, and mobility [155]. In a study that compared orally administered dronabinol (pharmaceutical grade synthetic THC capsules) with a rectally delivered prodrug Δ9-tetrahydrocannabinol-hemisuccinate (THC-HS) that hydrolyzes to THC upon absorption, the overall exposure to Δ9-THC was a factor of 2.4 higher via suppository route, even though maximum THC concentrations were slightly less [156]. This is likely due to slower absorption and reduced metabolism that would both enhance systemic bioavailability and increase duration of therapeutic plasma concentrations. Reducing first-pass metabolism also reduces the presence of psychotropic 11-OH-THC, which was documented in a pharmacokinetic study of suppositories in healthy volunteers. This is beneficial for strategies looking to provide THC for its therapeutic benefits but avoid intoxication. Vaginal suppositories are also gaining popularity for menstruation pathologies and endometriosis. The endocannabinoid system has recently been identified as highly involved in menstrual and endometriosis pain mechanisms [157], and the suppository administration route can more directly target affected areas while providing the therapeutic advantages mentioned above. For example, an increase in TRPV1 receptor expression is related to chronic pelvic pain in endometriosis [158] and CBD can stimulate and desensitize TRPV1. THC also may reduce chronic pelvic pain and shrink uterine growths [159]. Administering these cannabinoids more directly to the affected area via suppository is gaining popularity, and future research in this area will undoubtedly benefit female athletes during exercise training and competition.

7 Engaging in Cannabinoid Therapeutics

If an athlete or patient wants to engage in cannabinoid therapeutics, it is advisable to work collaboratively with a healthcare provider educated in cannabis therapeutics.

Seeking guidance from a knowledgeable clinician will ensure safety and increase the chances of good therapeutic outcomes. Although not required to obtain cannabis products, an ongoing relationship with a trained advisor is valuable for product and dosing suggestions. All administration routes described above are available at dispensaries without prescription in Canada, many states in the USA, and a growing number of countries around the world. Product selection requires attention to the concentration and relative ratio of cannabinoids and terpenes in the product. It is advisable to ask for the Certificate of Analysis (CoA) showing a detailed breakdown of cannabinoid and terpene profile, in addition to limit tests for pesticides, heavy metals, and other concerning toxins. Recent studies have investigated the accuracy of product labelling from retailers in both the legal and the unregulated market and found discrepancies and mislabeling issues in the cannabis product market [160–162]. These included products containing THC when labeled as THC-free and lack of CBD in products marketed as containing CBD, highlighting the importance of obtaining products from a strictly regulated and audited source. Finally, dosing should be done in consultation with a trained healthcare professional to ensure safety of use of a cannabinoid therapeutic product. High-dose CBD, for instance, can be associated with elevated serum liver enzymes [163]. Routine monitoring of serum liver tests can be done with a healthcare provider to ensure levels remain with in a normal range, as well as be advised on any potential drug–drug interactions based on drug metabolism. Furthermore, users who participated in the medically authorized stream were more likely to know the amount and type of cannabinoid they were taking, were less likely to report side effects, were more likely to use regulated sources to obtain product, and were more likely to seek information from healthcare professionals [139] Research into health outcomes suggests that using a personal journal or a tracking app to record what product and amount(s) are consumed is helpful [164], including the time of day of consumption and what food or other substances are included while recording feedback to the experience. With an endless number of available products on the market, and other variables that could affect consumer outcomes, keeping good records of what and how much was used is a valuable habit [164]. The most necessary element to any cannabinoid therapy approach is accurate information and quality education from a healthcare professional. If an athlete is looking to incorporate cannabinoid therapy into a wellness routine, high-quality information and a well-designed plan is essential. It is useful to continually re-evaluate the relationship with anything that has abuse potential, including cannabis products. This will reduce the chance for bad habits and misuse to ensue.

8 Cannabis Use Disorder

Cannabis use can be associated with some negative health effects. Of note is cannabis use disorder (CUD), which has been associated with the THC content of cannabis products. CUD is a problematic pattern of cannabis use that athletes and medical training staff need to be cognizant of, especially with the increase in available high THC commercial products. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines CUD as the continued use of cannabis, despite clinically significant impairment or distress [165]. For cannabis use to qualify as disordered, at least two of the criteria in the following table must be experienced within a 12-month period (see Table 1).

The prevalence of CUD in a population varies according to geographic location and intent of use. Among past-year weekly non-dependent cannabis users, 9.7% progressed to cannabis dependence over a 3-year follow-up period[166]. The prevalence of CUD in a sample of primary care patients located in a cannabis legal state, using cannabis regularly for either medical or non-medical purposes, was roughly 21%, with 6% of these being classified as moderate to severe. [167]. Interestingly, within this moderate-to-severe CUD group, the number of individuals with CUD who used cannabis only for medical purposes was significantly less than the non-medical group, at 1.3% versus 7.2%, respectively [167]. This discrepancy emphasizes the importance of healthcare provider guidance and education, as well as predefining the intention and dosing of cannabis use with the patient. CUD has been associated with several adverse health effects, including impaired cognitive function, respiratory issues, and increased risk of mental health disorders such as anxiety and depression [168]. With recent studies estimating that 23–26% of athletes consume THC, CBD, or both [115, 169], athlete education assistance with dosing regimens and use pattern monitoring and awareness of CUD prevention and assessment strategies is imperative.

9 Barriers to Cannabinoid Therapy

Generations of stigma and misinformation about the cannabis plant remain important barriers to investigation and use of cannabinoids as a therapeutic option in sports and athletics. Although many amateur and professional sports leagues are adjusting their policies to align more closely with recent legal adjustments to cannabinoid access, many outdated regulations remain in place. With federal legalization having occurred in Canada in October 2018, Canadian universities removed the ban on cannabis products in University Sports (USports) athletics in August of 2020, but only for sports played within Canada and under their Canadian Collegiate

Table 1 DSM- 5 criteria for Cannabis Use Disorder: at least two of the listed criteria must be experienced in a 12-month period [165]

Cannabis taken in larger amounts or used over a longer period than intended
Persistent desire or unsuccessful efforts to cut down or control cannabis use
Excessive time spent in activities to obtain, use, or recover from the effects of cannabis
Craving or a strong desire to use cannabis
Recurrent cannabis use resulting in failure to fulfill major obligations at work, school, or home
Continued cannabis use despite persistent social or interpersonal problems caused or exacerbated by its effects
Important social, occupational or recreational activities given up or reduced because of cannabis use
Continued cannabis use despite physical harm
Continued cannabis use despite knowledge of persistent physical or psychological problems caused or exacerbated by cannabis
Tolerance, defined by a need for increased amounts to achieve intoxication or diminished effect with continued use of the same amount
Withdrawal symptoms when not using cannabis

Athletic Association (CCAA) jurisdiction. Anyone competing in non-CCAA events, such as International University Sports Federation or World Championships, must comply with the World Anti-Doping Agency (WADA)'s prohibited list, which still includes THC (but not CBD) [170]. In June 2023, a National Collegiate Athletics Association (NCAA) panel in the USA recommended the removal of cannabis products from the banned substances list, as they questioned the validity of the claim that they are performance enhancing [171]. In June 2024, cannabinoids were officially removed from the NCAA Division 1 banned substances list for post-season competition [172]. While each individual school will still have the authority to implement their own drug policies during the regular season, league policies and penalties will take effect in the post-season. The league had increased THC thresholds from 35 nanograms per milliliter to 150 nanograms per milliliter to constitute a positive test, in alignment with WADA rules for international competition; however, the disconnect and rationality of this rule in the current legal landscape of recreational product use in the USA is problematic when compared with the lack of regulation of other recreational products such as alcohol, caffeine, or nicotine. In a statement regarding the removal of cannabis products from the prohibited list, Josh Whitman, chair of the NCAA Division I Council, stated, "The NCAA drug testing program is intended to focus on integrity of competition, and cannabis products do not provide a competitive advantage" and that "the council's focus is on policies centered on student-athlete health and well-being rather than punishment for cannabis use" [172]. The same should be considered by professional leagues when examining the practicality of cannabis regulations in the context of a lack of regulation of more addictive substances such as caffeine, nicotine, alcohol, or opioids commonly prescribed for pain.

To remain internationally eligible, athletes are subjected to strict compliance with the WADA prohibited substance list. They must ensure that any product they take does not inadvertently contain other banned substances. One common source of confusion and also product specifics is that Δ9 tetrahydrocannabinol (THC) from the cannabis plant is considered a banned substance by the World Anti-Doping Agency, but cannabidiol (CBD) from the cannabis plant is not [173]. The National Sanitation Foundation (NSF) is an independent, non-government third party certification organization that created the Certified for Sport® program to ensure label accuracy, safe levels of contaminants, and no prohibited substances or masking agents [174]. This certification is required by many professional sports leagues and college athletics to provide or recommend a supplement product. Since permitted cannabinoid therapy options can include a THC-free oral substance, for example a CBD recovery drink, care must be taken to ensure there is not THC or any other banned substance included by accident. Although useful for athletes and teams to have an easy certification marker, product makers encounter very high costs associated with acquisition of NSF certification. Currently, very few cannabinoid products are available that target athletics specifically and commercial entities that are willing to incur this additional cost. The lack of available cannabinoid products that have NSF Certified for Sport® certification is a barrier specific to athletes looking to incorporate cannabinoid products therapeutically while remaining compliant with regulations that bound their professional activities.

A glaring lack of education and quality information for both athletes and medical professionals responsible for their care is another barrier to successful cannabinoid therapy in athletes. A recent survey of Association of American Medical College (AAMC) curriculums reported that only 9% of medical schools included any teachings on therapeutic uses of cannabis [175]. In Canada, 76.3% of nurse practitioners feel unconfident in their knowledge level of cannabinoid therapy, especially in the topics of dosing and protocol development, and cited the need for more education on cannabinoid therapy [7]. Similarly, only 14% of surveyed

pharmacists received any formal training on cannabinoid therapy [176]. In Canada, 92% of practitioners have been asked by patients for information about cannabinoid therapy [177] but lack of education, low knowledge levels, and low confidence in advising about therapeutic cannabinoids were cited as reasons why healthcare practitioners were not able to help when asked for advice [178]. The lack of adequate medical school curriculum and physician training was echoed in Israel and several European and Asian countries [179], and the lack of healthcare provider education is largely based on the limited availability of evidence-based information. Regulatory agencies place important restrictions on human clinical trial research with cannabinoids. Meeting extremely restrictive research policies slows the pace at which work can be done, and funding sources are sparce since research is not required to put a cannabis product on the shelf. In essence, commercial cannabinoid products are currently being sold in the regulated market without the requisite human safety and efficacy studies.

The lack of advocacy for this demographic is a barrier to the potential beneficial therapeutic use of cannabinoids. Cannabis therapy is a complicated topic that requires an understanding of local laws, policy, biology, and both harms and benefits to be properly represented. The athletic population looking to use cannabinoids therapeutically is a distinct population from either the medical or recreational populations, each of whom have advocates funded by interested parties to speak on their behalf. The athletic population has high exposure to pain medications, mental health stresses, and addictive substances, so advocacy to find realistic and less harmful therapeutic solutions is warranted. An increase in advocacy for this population and how cannabinoid therapy could be meaningfully approached is desperately needed. Many retired athletes have found benefit in cannabinoid therapy and publicly share their anecdotal experiences; however, a complete understanding of endocannabinoid physiology and published research data are often beyond the scope of their knowledge, yet essential to engage league policymakers in any meaningful way.

Suitable product availability has recently become a barrier to the therapeutic application of cannabinoids. As the high THC recreational market grows, medical product shelf space continues to decrease, being replaced by high-potency products [180]. As a function of supply and demand, THC products of 20% or higher drive profits for recreational dispensaries and thus capture most of their attention [180]. Therapeutic products that contain mostly CBD or ratios of non-THC phytocannabinoids do not evoke intoxication and are thus of little interest recreationally. These products bring in less revenue for dispensary owners, and thus are not featured as prominently, if at all. In Canada, being a licensed producer of medical cannabis requires additional paperwork and regulations compared with growing the same product for the recreational market. This is contributing to a reduction of growers interested in growing therapeutically suitable plants [140]. The cost of this additional regulatory work is passed on to the end user, as medical cannabis products are more expensive in Canada. Unfortunately, the lack of appropriate products could lead therapeutic consumers back to the unregulated market, which is counterproductive to maintaining safety for non-recreational use. The USA has a very complex burden of cannabis regulation, varying from state to state, but each in disconnect with the federal government scheduling of a category 1 narcotic. In August of 2023, the US Department of Health and Human Services (HHS) made a recommendation to the Drug Enforcement Administration (DEA) to move cannabis from schedule 1 to schedule 3, which could relieve some hardships of the regulated market, but many will remain in place, which contribute to the lack of therapeutic products.

A major barrier to cannabinoid therapy is the cost and lack of insurance coverage as a medicine. When used effectively for medical reasons to treat ailments such as pain, seizures, or mental health issues, cannabinoids warrant consideration to be included in prescription insurance plan coverage in a manner similar to other medications. Additional measures such as healthcare provider involvement would need to be implemented to follow a pharmaceutical model. Cost and lack of insurance coverage are removing the patient from the decision on which therapeutic medication works best for them. In Canada, compassionate pricing exists for medical conditions; however, the resulting cost is still high. Health spending account balance (HSA) can be applied toward cannabis therapies and some Canadian extended insurance plans are starting to include cannabinoid therapeutics in their offered packages [181]. The USA has yet to consider insurance coverage, with cannabis continuing to remain federally in the schedule 1 category, technically classified as having no medicinal value. Incidentally, this same US federal government currently holds a patent (US 9,895,342 B2) on using cannabinoids for neuroinflammation and neuropathic pain, in addition to a 2003 patent (US 6,630,507 B1) for cannabinoids as antioxidants and neuroprotectants [182].

10 Perspectives

Misinformation, stigma, and barriers to research continue to perpetuate the confusion of the public regarding the potential therapeutic use of cannabinoids. The very profitable recreational use industry that dominates political and legal attention further complicates public understanding and validation of cannabinoid therapies. Nonetheless, patients,

athletes, and the general population continue to make a growing number of inquiries and requests for legitimate cannabinoid therapy. A more comprehensive understanding of cannabinoid therapeutics will positively impact the policies that direct its use. In addition, barriers to performing quality research on humans with cannabinoids need to be addressed. Policymakers must encourage evidence-based research to better serve their citizens and keep them safe. However, this will require an untangling of a labyrinth of research regulations that make it nearly impossible to research real-world products in a setting other than that which is funded by a commercial product developer.

11 Conclusions

Education is a proven harm reduction strategy. While efforts are made to provide information to the public on potential harms of cannabinoid products, equal efforts should be made to research and understand their potential benefits. A focus primarily on negative messaging does not align with the anecdotal positive experiences of a growing number of people using cannabis products and contributes to a lack of trust in health policymakers. Educating healthcare providers will also benefit patients and athletes who are requesting their assistance with cannabinoid therapy. As with any other medication or condition, healthcare providers should understand the mechanisms of action and the physiology behind use outcomes. Curriculum should be designed and delivered to any provider who anticipates working with individuals seeking cannabinoid therapy advice. Due to prohibition, we currently have a generation of healthcare providers with minimal understanding of a substance that is increasingly available for both therapeutic and recreational purposes. This knowledge gap needs to be addressed. Restrictive policies and over-regulation have hampered an opportunity for Canada and the USA to be global leaders in cannabinoid research.

Glossary

11-OH-THC	11-Hydroxy-Δ9-tetrahydrocannabinol.
2-AG	2 arachidonoyl-glycerol.
2-MAG	2-monoacyl-glycerol.
5HT1A	5-hydroxytryptamine receptor 1A.
AAMC	Association of American Medical Colleges.
Aβ	Amyloid beta proteins.
AEA	Arachidonoylethanolamide or anandamide
BDNF	Brain derived neurotrophic factor.
Ca^{++}	Calcium ion.
CB1	Cannabinoid receptor type 1.
CB2	Cannabinoid receptor type 2.
CBD	Cannabidiol.
CBDA	Cannabidiolic acid.
CCAA	Canadian Collegiate Athletic Association.
CDC	Center for Disease Control and Prevention.
CNS	Central nervous system.
COOH-THC	11-nor-9-carboxy-Δ9-tetrahydrocannabinol
COX-2	Cyclooxygenase-2.
CTE	Chronic traumatic encephalopathy.
DA	Dopamine.
DEA	Drug Enforcement Administration.
ECS	Endocannabinoid system.
ED_{50}	Effective dose 50%.
FAAH	Fatty acid amide hydrolase.
FDA	Food and drug administration.
GABA	G-protein coupled receptors.
HHS	US Department of Health and Human Services.
HSA	Health spending account.
IL-10	Interleukin-10.
IL-1β	Interleukin-1β.
IL-2	Interleukin-6.
iNO	Inducible nitric oxide synthase.
MAGL	Monoacylglycerol lipase.
MLB	Major League Baseball.
MMP-9	Matrix Metalloproteinase-9.
mPFC	Medial prefrontal cortex.
MS	Multiple sclerosis.
mTBI	Mild traumatic brain injury.
NAc	Nucleus accumbens.
NAE	N-acylethanolamine.
NBA	National Basketball League.
NCAA	National Collegiate Athletics Association.
NF-kB	Nuclear factor-kappaB.
NFL	National Football League.
NMDA	*N*-methyl-D-aspartate.
NSAIDS	Nonsteroidal anti-inflammatory drugs..
NSF	National Sanitation Foundation.
PMN	Polymorphonuclear neutrophils.
PPARs	Peroxisome proliferator-activated receptors.
ROS	Reactive oxygen species.
S100B	S100 calcium-binding protein B.
TGF-β1	Transforming Growth Factor Beta-1.
THC	Δ9-tetrahydrocannabinol.
THC-HS	Tetrahydrocannabinol-hemisuccinate.
THCA	Tetrahydrocannabinolic acid.
TNF-α	Tumor necrosis factor alpha.
TRPVs	Transient receptor potential ion channels.
VEGF	Vascular endothelial growth factor.
VTA	Ventral tegmental area.
WADA	World Anti-Doping Agency.

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