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Abstract

The Endocannabinoid System is a physiological system in the body that includes several receptors and ligands. Due to its relatively recent discovery, there is a need for healthcare professionals to be formally educated on the function of this system in the body. The endocannabinoid system is seen as having an increased research interest since the early 1990s given its current status of uncertainty amongst many. The goal of this scoping review is to provide a synoptic analysis of how the Endocannabinoid System functions and integrates within and between different systematic relationships in the body.

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The Endocannabinoid System Signaling, a Precursor to Homeostasis: A Scoping Review

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ABSTRACT

Purpose/Background: The Endocannabinoid System (ECS) is a physiological system in the body that includes several receptors and ligands. Due to its relatively recent discovery, there is a need for healthcare professionals to be formally educated on the function of this system in the body. The endocannabinoid system is seen as having an increased research interest since the early 1990s given its current status of uncertainty amongst many. The goal of this scoping review is to provide a synoptic analysis of how the ECS functions and integrates within and between different systematic relationships in the body. **Methods:** A full article review was conducted on one database website (PubMed) with results from 2012 – 2022. Articles included are limited to those directly explaining the ECS and its functions unrelated to the direct impact of disease or condition. **Results:** 1,031 published articles were identified from 2012 to September 2022. The reviews varied in terms of purpose and pathology. Nineteen percent (19.2%) of articles were removed because neurological pathologies were the topic of interest. This does not apply to this scoping review as articles were excluded when discussing pathologies. The second largest category of removal was scored at 18.9% which did not include ECS system. Remaining topic removals included: drugs/alcohol, mental illnesses, pain, disease, relationship to immune system/illnesses, cancer, and other systems within the body. In total, 6 articles were selected for the final scoping review removing all external factors that would prevent recognition of a homeostatic analysis of signaling and synaptic function. **Conclusion:** The process of homeostasis is not limited to one area or system. The body's ability to maintain homeostasis is connected deeply to the ECS and other systems in the body. Understanding the signaling process of the receptors and enzymes in the ECS, directly align with the other systems involved in homeostasis. Learning the operations of the ECS will further explain how neurotransmitters or other signals in the body are transferred across membranes.

Keywords: scoping review, endocannabinoid system, signaling

INTRODUCTION

Cannabis Sativa is a plant that is currently regulated within the United States, whereas previously it was used for centuries for medicinal purposes. This plant is currently recognized as a schedule I drug which is defined as having “no current accepted medical use” in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.¹ Due to this level of regulation, there is limited research being conducted about the plant as it relates to humans. However, with the Endocannabinoid System, or ECS, being discovered in 1988, more research is being conducted with specific isolates as well as cannabinoid combinations from the plant or related to the system that regulates it.² The primary function of this scoping review is to explore the research available on the ECS that is currently available specifically with respect to how signaling of the system impacts homeostasis of the body.

With recent discovery in the 1980s, the ECS has been shown as a vital system whose responsibility is to help the body maintain a homeostatic status regardless of the stressor received.^{3,4} Cannabis related topics are emerging with positive patient outcomes becoming more typical albeit mostly from self-reported outcomes and individual case studies. One must first understand the ECS in order to best treat his or her patients. Specifically, healthcare providers, can positively treat their patient population through understanding the ECS. Therefore, the following question framed this scoping review was asked: *How does the synaptic function of the ECS, maintain homeostasis, in the absence of disease?*

Endogenous cannabinoids, or endocannabinoids, are molecules self-produced within the human body.^{5,6,7} Exogenous cannabinoids are plant-based and have gained widespread popularity through supplementation.^{5,6,7} The most commonly studied endocannabinoids to date are 2-arachidonoylglycerol, more commonly referred to as 2-AG and N-arachidonylethanolamide, or anandamide, most specifically abbreviated as AEA. Both of these are defined as lipid derived, meaning they are not water soluble.^{8,9}

Two commonly reported receptors, that receive signals from the ECS are referred to as, cannabinoid receptor 1 or CB1, and cannabinoid receptor 2 or CB2.^{8,10} CB1 is more predominant in the brain, skeletal muscle, and central nervous system.^{6,11} CB2 is found more readily in peripheral and immune cells or PNS.^{12,10} CB2 receptors are classified as class-A G-protein coupled receptors, or GPCRs.^{8,11} These four major components of the ECS are best known by the abbreviations as, CB1 and CB2, 2-AG, and AEA.⁴ The purpose of these neurotransmitters, receptors and endocannabinoids is to directly affect the modulations in order to maintain homeostasis.¹³

METHODS

Research Question

The objective of this scoping review is to gain an understanding of how the system regulates homeostasis without the impact of disease or chronic condition. More specifically, *How does the ECS maintain homeostasis in the absence of disease through signaling?*

It is common for an individual to be prescribed a medication to regulate symptomatic pathology in the body. Some healthcare professionals can prescribe medications for a patient's disease, condition or injury. At this time, *Cannabis Sativa* and its isolates are not highly recommended by healthcare professionals due to limited education and acceptance as a treatment option from healthcare practitioners. Discussions for marijuana as a treatment intervention can occur in any location; however, in states where it is medically or recreationally legal, there are regulations to obtain this as a treatment option. It is common for a healthcare professional that sees his patient daily; i.e., physical therapist, athletic trainer, nurse, to be asked by his patient about cannabis. This scoping review was designed to gather specifics about the ECS to be understood by any healthcare provider as it relates to the function of receptive binding to achieve homeostasis.

Data Source and Search strategies

Pubmed was the only database used for article search review. A time frame of the last 20 years, 2002-2022, was used. All variety of scholarly peer reviewed articles were included for review regardless of type of article; literature review, case study, research articles, etc. The search strategies typed into the database included “cannabis, endocannabinoid system, homeostasis” and “signaling.” Independently, “homeostasis” was not of value in the search database as articles. It often yielded issues of disease, or did not includes the ECS. The most successful search criteria included “endocannabinoid system” and “signaling.”

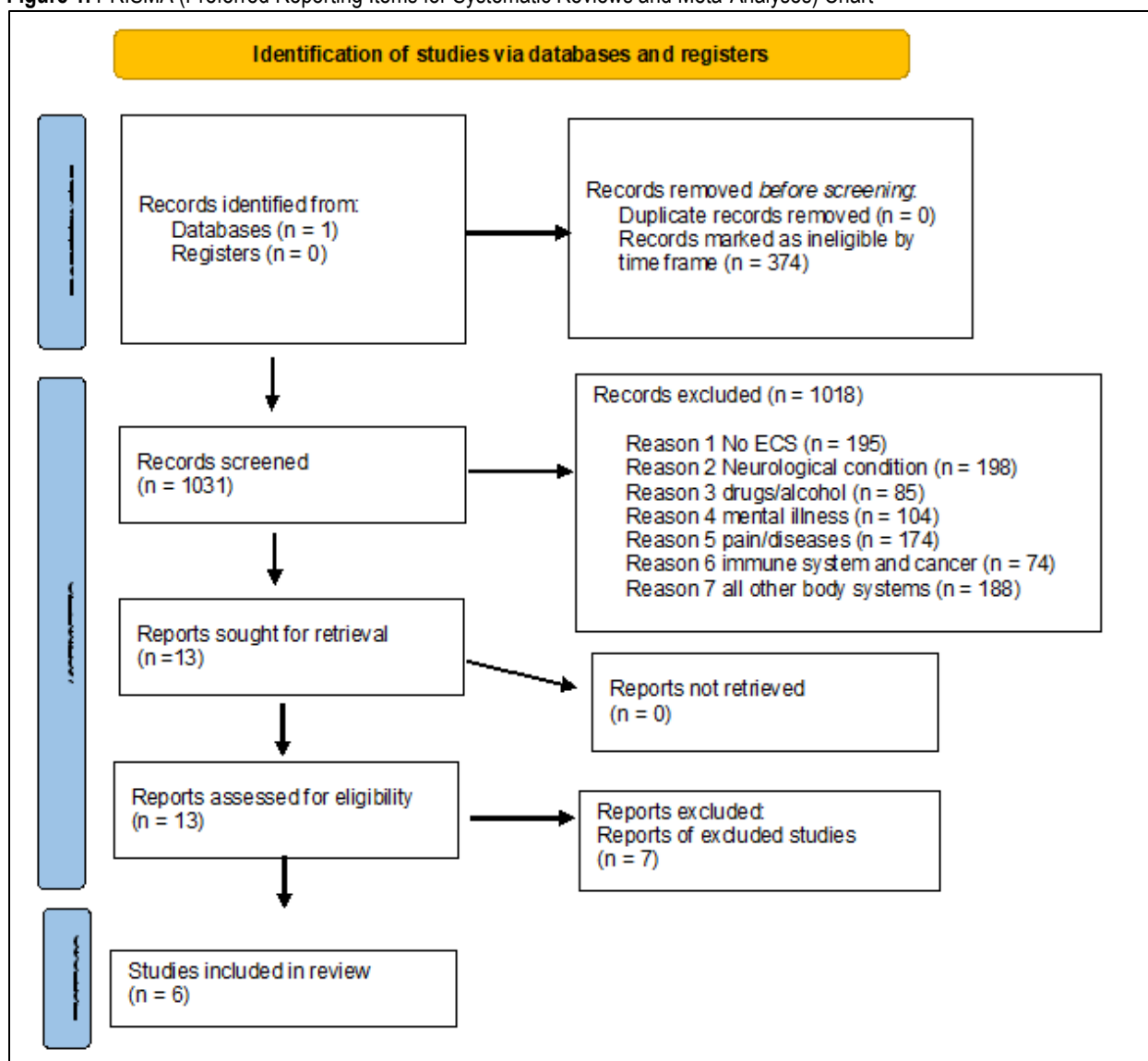
Citation Management

All citations were found on Pubmed website database with no duplicate citations recorded from this scoping review. Citations were then reviewed for subsequent title, abstract relevance screening and data characterization of full manuscripts. All citations included for full text review were downloaded and saved onto the computer's desktop for continued digital reference.

Eligibility Criteria/ Title and Abstract Screening

From the initial keyword and phrases search, 1,405 articles were included that matched to the keywords “endocannabinoid system” and “signaling.” Since no quantitative data was assessed at this time, publication date and article title review were the two initial points of analysis. 374 articles were removed as they were published outside of the 10-year time frame from 2012 to 2022. This left 1,031 articles for title review. If the title included regulatory functions of the ECS without discussion of pathology, drugs, or reproductive system, the abstract was evaluated. A total of 1,018 articles were removed from those title limitations (See Figure 1). The final thirteen eligible articles were screened for abstract and full article content comparison. Of those 13, six total articles were included based on the explanation of the ECS normal function without pathology.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Chart



Data Characterization

All citations deemed relevant after title and abstract screening were procured for subsequent review of the full text manuscript. Articles procured from Pubmed were searched as free full text articles only. If there was no access to free full text they were removed and not included in the count within this review. This major limitation is explained further in the section of Reported Challenges and Limitations. The majority of articles more clearly described the input of pathology relative to the ECS.

Data Summary and Synthesis

No numerical data was collected nor analyzed for the purpose of this scoping review. Only qualitative analysis of the ECS. An accurate search criteria vocabulary successfully deposited 1,031 articles for title review. If the title included regulatory functions of the ECS without discussion of pathology, drugs, or reproductive system, it was selected. Six total articles were viable; article details can be seen in Table 1. Each selected, provided substantial insight details of the ECS in homeostasis, more specifically to the signaling process across the membrane in the synapses. There was no specific bias present when selecting articles.

Table 1. Reporting Results of Included Scoping Review

Article's First Author, Year	ECS Overview	Receptors (CB1, CB2)	Endogenous (2-AG, AEA)	Exogenous (CBD, THC, etc)	Signaling system
Castillo, 2012	Included**	Limited description*	Limited description*	Limited description*	Included**
Zou, 2018	Included**	Included**	Included**	Limited description*	Included**
Hilliard, 2015	Limited description*	Included**	Included**	Limited description*	Included**
Janero, 2014	Limited description*	Limited description*	Included**	Limited description*	Included**
Battista, 2012	Included**	Limited description*	Limited description*	Limited description*	Included**
Kano, 2014	Limited description*	Included**	Limited description*	Limited description*	Included**

Articles defined as having *limited description** means the segment was included in the article but not the primary focus or intent of the author. Whereas, *included***, had a thorough description in the article. The fifth column declared the inclusion of exogenous cannabinoids. None of the articles went into great detail of this category and were removed from this scoping review based on other exclusionary criteria, see Figure 1. PRISMA chart, or Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹⁴

RESULTS

Search and Selection Results

Search criteria that was most abundant included “endocannabinoid system” and “signaling.” The majority of articles discussed the ECS when a disease is present, manipulation of the ECS, or ECS in combination with additional drugs. Selected articles of primary search found a few authors contributed repetitively to the topic of the ECS. These authors were cited in the bibliography of manuscripts they did not publish themselves. It should be noted no articles were selected after the year 2018. Relevant information for the scoping review was found in earlier articles due to the descriptive nature of the components. Later produced articles go into greater detail about pathology or other exclusionary criteria for the purpose of this scoping review. Final search criteria results are listed below per number count per year (See Table 2).

Table 2. Final Search Criteria Demographics

Year	Count of articles published from search criteria “ECS” and “signaling” (N=)	Final count of articles from search used in scoping review (n=)	Final percentage in scoping review within calendar year (%)
2012	N=120	n = 2	1.67%
2013	N=86	n = 0	0%
2014	N=78	n = 2	2.56%
2015	N=89	n = 1	1.12%
2016	N=105	n = 0	0%
2017	N=99	n = 0	0%
2018	N=106	n = 1	0.94%
2019	N=100	n = 0	0%
2020	N=142	n = 0	0%
2021	N=167	n = 0	0%
2022	N=75	n = 0	0%

N= number of articles published with specific search criteria in one year of the 1,405 positive keyword search

n = number of articles used from that year of the final six included in scoping review

General Characteristics of Included Manuscripts

The focus was to review the ECS in a homeostatic status without the inclusion of bodily, or environmental pathologies. As a result, 13 articles were included for full article analysis. Of those, six were selected to provide the functions of the ECS to maintain homeostasis. A systematic review was conducted and outlined below via the PRISMA flow chart (Figure 1).¹⁴

Castillo et. al states the ECS is comprised of two G-protein-coupled receptors (GPCRs), known as the cannabinoid type-1 and type-2 receptors CB1 and CB2.⁵ Endogenous ligands are known as anandamide, AEA and 2-arachidonoylglycerol, or 2-AG.⁵ Synthetic and degradative enzymes, along with transporters, regulate the endocannabinoid levels and actions found at all receptor cites, further proving the essential relationships within the body to regulate the ECS.⁵ Those enzymes and transporters are the single most relevant component which regulate neurological functions and behaviors via retrograde or nonretrograde signaling.⁵ Zou and Kumar, focus primarily on the receptors and ligands that are processed in the ECS at the CNS level.⁶ The CB1 receptor was the most widely expressed receptor found in the GPCR in the brain.⁶

The most thorough and detailed review included was written by C. Hilliard, included the definition and connection of the receptors, ligands and signaling cohesively.¹³ The most in-depth descriptions of the types of signaling process included synthesis and degradation of endocannabinoids were specifically outlined.¹³ The article written by Janero and Mayriannis was included because most information was about endogenous cannabinoids.⁸ The most frequently studied endocannabinoids, 2-arachidonoylglycerol, 2-AG and N-arachidonylethanolamide, anandamide or AEA, are lipid mediators.⁸ They originate from membrane phospholipids by distinct enzymatic pathways and possess specific functional and pharmacological properties.⁸ The presence of the ECS has a role in several physiological processes, including appetite, cancer, cardiovascular diseases, fertility, immune functions, memory, neuroprotection, and pain modulation.¹⁰ Although Battista's article included those accessory facts, a primary review of the system was included and selected for that purpose.

The final article was selected for its inclusion of detail on the synaptic relationships of enzymes of the ECS. Recent studies showed how endocannabinoids were released from neurons and induce short-term and long-term forms of synaptic plasticity.¹² Kano goes into further detail about short-term and long-term synaptic depression of the mediators of the ECS.¹² The methodological characteristics of the selected articles were broken down into *table 3* with a brief description seen below.

Table 3. General Characteristics of Included Papers

Title	Date	Author	Relevant findings and conclusions.	Journal
Endocannabinoid signaling and synaptic function	2012	Pablo E. Castillo, et. al	Endocannabinoids are fundamental modulators of synaptic function	Neuron
Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System	2018	Zou & Kumar	Cannabinoids modulate signal transduction pathways	International Journal of Molecular Sciences
The Endocannabinoid Signaling System in the CNS: A Primer	2015	Cecilia J. Hillard	The ECS modulates the functions of the major excitatory and inhibitory neurotransmitters	International Review of Neurobiology
Terpenes and Lipids of the Endocannabinoid and Transient-Receptor-Potential-Channel Biosignaling Systems	2014	David R. Janero and Alexandros Makriyannis	Both CB1 and CB2 are class A G-protein coupled receptors. CB1 Found in the CNS and CB2 in the periphery	ACS Chemical Neuroscience
The Endocannabinoid System: an Overview	2012	Battista et al	This complex system of receptors, ligands, and enzymes is integrated in helping to regulate fundamental processes in the CNS and PNS	Frontiers in Behavioral Neuroscience

Control of synaptic function by endocannabinoid-mediated retrograde signaling.	2014	Kano	It has also been demonstrated that the endocannabinoid system itself is plastic, regulated by experimental or environmental conditions	Proceedings of the Japan Academy
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Reported Challenges and Limitations

An issue of the search criteria was removing any articles with fees attached to their access. Only free full text articles were used which can be viewed as incomplete due to the potential for qualified articles not included due to cost associated with the article. This was an attempt to populate the articles most likely searched and read with ease by a healthcare professional in a brief search to provide information to a patient. Additionally, a challenge that was presented came about because of the regulation on cannabis. Many articles depended on the ECS relationship to *cannabis sativa* behind the sources of why articles have been identified in the exclusionary criteria.

DISCUSSION

Understanding the ECS can provide healthcare professionals with essential knowledge of another system in the body that regulates and contributes neurotransmitter signaling at the CNS level and homeostasis. The ECS allows for optimal functioning of essential transactions at the cellular level. These processes allow the body to stay in a regulated status of homeostasis. It is just as important as the other major systems in the body as it plays a role in a wide variety of neuronal and immunological processes including: memory, neurogenesis, appetite, metabolism, stress/anxiety, analgesia, thermoregulation sleep and immune cell function.^{15,16} Further proving the essential nature of the ECS to maintain homeostasis: C. Hilliard concludes there is strong evidence that dysregulation of the ECS contributes to many human maladies, including pain, psychiatric disorders, neurodegenerative diseases, and inflammation.¹³ Functions of the system are regulated via retrograde signaling, the activity of the post-synaptic neuron leads to production and release of ECBs.¹⁷ Those endocannabinoids in the body then diffuse in a retrograde manner across the synapse, and subsequently activate CB1 receptors present at the pre-synaptic terminal to inhibit neurotransmitter release.¹⁷ This can be seen in *Image 1*. The directional nature of the signaling is what permits optional signal transduction for the ECS to operate.

Overview of Included Manuscripts

Castillo et al. focuses on synapse function as a very important piece of the ECS. The authors noted emerging levels of complexity clearly indicate that much more work lies ahead in our pursuit to fully understand ECB signaling at the synapse function.⁵ Zou and Kumar detailed the central nervous system, or CNS as one of the most single important pieces to the ECS. Most receptors and retrograde signaling happens at the synapses within the CNS.⁶ Defined in the article, there are many locations for the ECS to be present within the body, however the key components and relationships occur within the CNS.⁶ Hilliard clarifies roles of the endocannabinoids, 2AG and AEA; how they are synthesized and catabolized.¹³ Along with review of the receptors of CB1 and CB2 and their function at the synapse.¹³ Janero and Makriyannis article reviews the essential components of the ECS such as, endogenous ligands and terpenes, along with a couple pathological references that are often a comparison or baseline when analyzing the ECS.⁸ The article also focuses on ligands belonging to the terpene or lipid chemical classes that interact with both systems.⁸

With fundamental information that is essential to understanding the ECS, an essential overview of information is included in this review published by Battista et. al. Definitions for key components and their function, relationship to each essential molecule, along with some physiological considerations.¹⁰ The complex system of receptors, ligands, and enzymes is integrated in helping to regulate fundamental processes at level of central nervous and peripheral systems.¹⁰ Additional molecules responsible for retrograde signaling of the ECS, are included along with long term and short-term depression from signaling response activity in the area.¹² Most importantly the definition of retrograde signaling and what that means for the ECS.¹² Due to the relationship with pathologies or conditions, behavioral studies with pharmacological and genetic manipulation of retrograde endocannabinoid signaling have demonstrated that it is involved in "various aspects of neural functions, including learning and memory, mood and anxiety, drug addiction, feeding behavior, motor learning and analgesic".¹² In this review these issues are not addressed but there is an abundance of information available for review to see the changes and difference within the ECS including pathologies.

Recommendations

Healthcare professionals understand homeostasis as a way the body regulates systems. The connection between homeostasis and the ECS at this time cannot be denied yet the full explanation remains to be known. Any person that serves patients or clients can benefit from this article's review to gain an understanding of the ECS. Vital factors of the ECS are the functions of the synapse relationship [*Image 1*]. Beyond the receptors and endogenous ligands, there is a need for further development of the specifics of that relationship in addition to this process. With the endogenous cannabinoid which bind to the main receptors in the ECS much

more data is needed to confirm certain processes.¹⁸ It is recommended that continued research efforts are made in the synaptic functional process along with ligands that are involved. Moving forward, extensive research is currently focused on the identification of potential missing cannabinoid receptors.¹⁹

Weaknesses of This Scoping Review

As previously mentioned, the articles unselected due to fees associated can be removing articles in the final selection for this scoping review. However, the variety of focus on each selected article provides a different point of view to be analyzed when learning about the ECS. It was rare to have articles with overlapping key points in the final six utilized for the scoping review.

CONCLUSION

To get a better understanding of the ECS and how it operates it is essential to understand how it helps regulate homeostasis and what other systems in the body it is involved in. The ECS controls many basic biological processes, and exerts its activity in the nervous system and in peripheral tissues, with direct involvement in synaptic plasticity and neuroprotection, pain control, mood and behavior, learning and memory, stress response, reproduction, fertility and pregnancy, food intake and energy balance, immune response, cancer progression, and much more.²⁰ The ECS functions via retrograde signaling, the activity of the post-synaptic neuron leads to production and release of ECBs that diffuse in a retrograde manner across the synapse, and subsequently activate CB1 receptors present at the pre-synaptic terminal to inhibit neurotransmitter release.¹⁷

The processes outlined from the articles used in the scoping review provide evidence that endocannabinoids are utilized in retrograde signaling to enhance neurotransmitter function within the CNS. This scoping review provided descriptive conclusions about how the ECS is involved in signaling that encourages messages be sent throughout the body enlightening the reader to understand its function of homeostasis happens in signaling transcriptions. Among many other functions they help regulate by optimizing signal transduction, the CB1 receptors of the ECS are more likely to be found in the CNS and CB2 in the periphery. With proper education, healthcare professionals could understand the deep involvement of ECS in neuroinflammation points out the possible use of cannabinoids-based treatments to modulate ECS, as alternatives to more conventional pharmacological therapies could directly positively impact their patient's needs.¹³

Abbreviations

2-AG - 2-Arachidonoylglycerol
 AEA - N-Arachidonylethanolamide (or Anandamide)
 CB1/CB1Rs - Type 1 Cannabinoid Receptors
 CB2/CB2Rs - Type 2 Cannabinoid Receptors
 CNS – Central Nervous System
 ECS – Endocannabinoid System
 GPCR – G-protein-coupled receptors
 NCAA – National Collegiate Athletic Association
 PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 PNS – Peripheral Nervous System
 THC – Tetrahydrocannabinol or Δ^9 -tetrahydrocannabinol

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