The Endocannabinoidome: A Pivotal Physiological Regulator and Therapeutic Target - Implications for Medical Education and Personalized Medicine

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Abstract

The endocannabinoid system (ECS) serves as a sophisticated bio-regulatory network orchestrating a multitude of physiological processes to maintain systemic homeostasis. However, recent research has unveiled an expanded conceptualization known as the endocannabinoidome (eCBome), reflecting the intricate complexity and dynamic nature of this system. The eCBome encompasses a broader array of lipid mediators, enzymes, molecular targets, and signaling pathways beyond the classical ECS components, including endocannabinoid receptor heterodimers and their bidirectional signaling cross-talk with other receptor systems. This expanded perspective has far-reaching implications for human health and disease, unveiling new therapeutic avenues across various pathological conditions. This comprehensive article provides an in-depth analysis of the eCBome, exploring its multifaceted physiological functions spanning neuromodulation, pain management, neuroplasticity, immune regulation, metabolic homeostasis, cardiovascular regulation, and specialized systems like reproduction and musculoskeletal function. It highlights leveraging the eCBome for developing targeted interventions like cannabis-based medicinal products (CBMPs). The article addresses integrating eCBome knowledge into medical curricula, establishing guidelines for authorizing and monitoring CBMPs, and addressing stigma. Moreover, it explores the potential of complementing CBMPs with lifestyle interventions like diet, exercise, and mind-body practices to synergistically modulate the eCBome. Future directions include longitudinal studies, exploring endogenous eCBome mediators for therapeutic applications, novel drug development, interdisciplinary collaborations, and computational approaches to fully understand the complex interactions between its various components, receptors, and signaling pathways. Elucidating these intricate mechanisms is crucial for developing targeted and personalized therapeutic interventions with optimal efficacy and minimal side effects.

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I. Introduction

The endocannabinoid system (ECS) is a crucial biological network that maintains homeostasis within the human body, comprising the cannabinoid receptors CB1 and CB2, and their endogenous lipid-derived ligands like anandamide (AEA) and 2-arachidonoylglycerol (2-AG) [1,2,3]. The ECS regulates diverse physiological processes such as pain, mood, appetite, energy metabolism, immunity, and neuronal plasticity [1,2].

The endocannabinoidome (eCBome) represents an expanded conceptualization, encompassing a broader array of lipid mediators, receptors, and enzymes that interact with and modulate the ECS [4]. Beyond AEA and 2-AG, the eCBome includes N-acylethanolamines (e.g., oleoylethanolamide (OEA), palmitoylethanolamide (PEA)), 2-acylglycerols, fatty acid amides, and bioactive lipids like resolvin D2 [4,5]. These diverse components interact with various receptors, including cannabinoid, transient receptor potential (TRP), peroxisome proliferator-activated (PPAR), and G protein-coupled receptors (GPCRs), contributing to the eCBome's multifaceted effects [6,7,8].

In addition, the eCBome encompasses an expanded range of enzymes involved in lipid mediator biosynthesis and metabolism, such as cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 enzymes [4,9]. This broader enzymatic regulation implies a more complex modulation of lipid-based signaling pathways within the eCBome.

Recent studies have shed light on the role of receptor heterodimers in the eCBome's signaling complexity, adding additional layers of regulation to the system's multifaceted effects [10,11].

Interestingly, phytocannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD) also interact with various eCBome targets, potentially mimicking or modulating endocannabinoid effects on processes like pain, appetite, inflammation, and immunity [12,13,14].

The eCBome's significance lies in its potential to provide a comprehensive understanding of the intricate regulatory mechanisms governing various physiological processes and their implications for human health and disease. By studying the complex interplay between endogenous lipid mediators, their receptors, and diverse signaling pathways, researchers aim to develop novel therapeutic interventions for a wide range of conditions [4].

Molecule	Target Receptors	Biological Functions	Mechanisms of Action	References
OEA	PPAR-α, TRPV1, GPR119,	Appetite regulation, lipid metabolism, anti-inflammatory effects, analgesia, wakefulness	Activation of PPAR-α and GPR119 leading to decreased food intake and improved lipid profile, anti-inflammatory via PPAR-α	[23], [25], [27], [66], [67]
PEA	CB2, PPAR-α, TRPV1, GPR119, GPR55	Anti-inflammatory, analgesic, neuroprotective effects, wakefulness	Anti-inflammatory via PPAR-α activation, analgesic via TRPV1 desensitization, anti-nociception via CB2-mediated activation of endogenous noradrenergic system, neuroprotective antioxidant effects	[24], [67], [68], [69], [131]
LEA	PPAR-α, GPR119	Modulation of pain, inflammation, appetite	Activation of PPAR-α and GPR119, modulation of inflammatory and nociceptive pathways	[70]
DHEA	GPR110 and partial agonist of CB1 and CB2	Neurogenesis, synaptogenesis, anti-inflammatory effects	Activation of GPR110, partial agonism at CB1/CB2 receptors, anti-inflammatory and neuroprotective effects	[71], [72]
AEA	CB1, CB2, TRPV1, PPAR-α, CaV	Neuromodulation, pain modulation, appetite, mood, memory, thermoregulation, sleep	Retrograde signaling at synapses, modulation of neurotransmitter release, anti-inflammatory via PPAR-α and TRPV1 activation, immune cell modulation via CB2	[6], [7], [67]
2-AG	**CB1, CB2**, PPAR-γ, CaV	Neuromodulation, energy balance, immune function, pain modulation	Retrograde messenger, presynaptic inhibition of neurotransmitter release, anti-inflammatory via PPAR-γ activation, modulation of immune cells via CB2	[22], [73]
2-OG	GPR119	Regulation of glucose-dependent insulinotropic peptide	Activation of GPR119 on pancreatic islet cells, modulation of insulin secretion	[74]
2-PG	CB1	Functional CB1 receptor antagonist, modulation of endocannabinoid pharmacokinetics	Competitive antagonism at CB1 receptors, modulation of endocannabinoid metabolism and signaling	[75], [76]
2-LG	CB1	Partial agonist at CB1, suppression of endocannabinoid activity	Partial agonism at CB1 receptors, modulation of endocannabinoid signaling and effects	[77]
NAGly	GPR18, CaV	Suppresses tonic inflammatory pain	Activation of GPR18, modulation of inflammatory pain pathways	[78]
ODA	CB1, PPARα, CaV	Sleep induction, neuroprotection, neurogenesis	Oleamide (ODA) is a full gonist at CB1, activation of PPARα	[127], [128]
RsD2	GPR18, CaV	Resolution of inflammation, anti-inflammatory, neuroprotective	Activation of GPR18, modulation of inflammatory pathways and resolution of inflammation.	[129]
NADA	CB1, CB2, TRPV1, FAAH, CaV	Neuroprotection, pain modulation	Activation of CB1, CB2, TRPV1; inhibition of FAAH	[130]
SCFAs	GPR41, GPR43	Modulation of gut microbiome composition, influence eCBome mediator levels	Short Chain Fatty Acids (SCFAs) like butyrate, propionate, iso-propionate and acetate, modulate gut microbiome composition, in turn modulating eCBome mediator levels.	[31]
THC	CB1, CB2, GPR55, TRPV1, PPAR-γ, GPR18, opioid receptors, others	Pain relief, anti-nausea, appetite stimulation, psychoactive effects, modulation of immune responses, anti-inflammatory effects	Partial agonism at CB1 and CB2 receptors, activation of GPR55, TRPV1, PPAR-γ, GPR18 and others, modulation of various signaling pathways	[12], [13]
CBD	5-HT1A, GPR55, TRPV1, PPAR-α, PPAR-γ, CB1 (negative allosteric modulator), opioid receptors, others	Anti-inflammatory, anxiolytic, anticonvulsant, neuroprotective effects, modulation of immune responses, potential antiviral effects, analgesic effects	Negative allosteric modulation of CB1, activation of 5-HT1A, GPR55, TRPV1, PPAR-γ and others, modulation of various signaling pathways	[13], [14]
CBC	TRPV1, TRPA1	Anti-inflammatory, potential neuroprotectant	Activation of TRPV1 and TRPA1, modulation of inflammatory pathways	[79]
CBG	CB1, CB2, α2-adrenoceptors, PPAR-γ, 5HT1a	Analgesic, anti-inflammatory, neuroprotective	Partial agonism at CB1 and CB2 receptors, modulation of inflammatory and neuroprotective pathways, α2-adrenergic effects, antagonism at 5HT1a receptor	[80], [81]
CBN	CB1, CB2, TRPA1, PPAR-γ	Sedative, anti-inflammatory, analgesic, neuroprotective	Partial agonism at CB1 and CB2 receptors, activation of TRPV1 and PPAR-γ, modulation of inflammatory and neuroprotective pathways	[82], [83]
THCV	CB1 (antagonist), CB2 (agonist), TRPV1	Appetite suppression, glycemic control, neuroprotective	Antagonism at CB1 receptors, agonism at CB2 receptors, activation of TRPV1, modulation of metabolic processes	[84], [85]
BCP	CB2	Anti-inflammatory, analgesic, gastroprotective	Selective agonism at CB2 receptors, modulation of inflammatory pathways	[132]

Table 1 *eCBome-interacting molecules: Their targets, biological functions, mechanisms of action and supporting references.*

II. The eCBome: An Evolving and Fluid Conceptualization

As research into the endocannabinoid system (ECS) progressed, it became evident that this regulatory network exhibits far greater complexity than initially recognized, leading to an expanded conceptualization known as the endocannabinoidome (eCBome) [4].

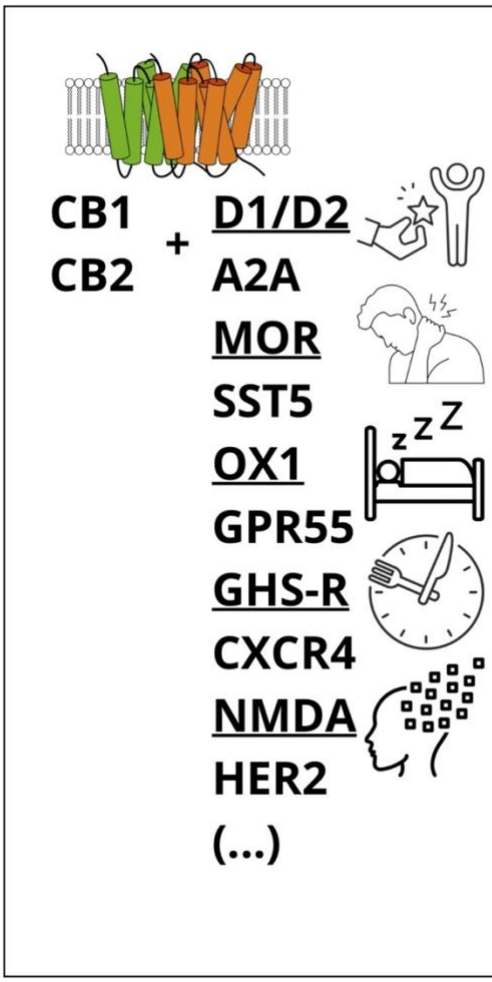
Aspect	Endocannabinoid System (ECS)	Expanded Endocannabinoidome (eCBome)	Comment
Ligands	Anandamide (AEA), 2-Arachidonoylglycerol (2-AG)	Includes AEA and 2-AG, plus N-arachidonoyl dopamine (NADA), virodhamine (OAE), oleoylethanolamine (OEA), palmitoylethanolamide (PEA), bioactive PUFA metabolites (prostaglandins, thromboxanes, resolvins)	The ECS primarily involves endogenous ligands derived from the dietary omega-6 PUFA arachidonoic acid that are naturally produced by the body and are critical for maintaining homeostasis. The eCBome includes these and additional lipid-based dietary ligands, some of which are derived from omega-3 PUFAs, reflecting a more extensive interaction with diet and lifestyle.
Receptors	Cannabinoid receptors CB1 (nervous system) and CB2 (immune system)	CB1 and CB2, plus G protein-coupled receptors like GPR55 , GPR18, GPR119, GPCR receptor heterodimers, ion channels such as TRPV1, and nuclear receptors like PPARs	The ECS's receptors are highly specific to endocannabinoids, while the eCBome's receptors show a broader specificity, allowing for more diverse physiological effects and potential therapeutic targets.
Enzymatic Metabolism	Diacylglycerol lipase (DAGL), N-acylphosphatidyl-ethanolamine phospholipase D (NAPE-PLD) Fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL)	Same as ECS plus additional metabolic enzymes like COX, LOX, CYP450, and others	ECS enzymes are specialized for the synthesis and degradation of its specific ligands. The eCBome's repertoire of enzymes have a wider range of substrates, indicating a more complex regulation of ligand levels and actions.
Mechanisms of Action	Receptor activation/inhibition, neurotransmitter modulation	Same as ECS, with many additional drug targets and mechanisms including allosteric modulation, enzyme inhibition, receptor heterodimer activation, and more	The ECS has a more defined mechanism of action, primarily through retrograde receptor activation/inhibition. The eCBome introduces additional mechanisms, suggesting a more intricate modulation of physiological processes.
Affected Signaling Pathways	G protein signaling, ion channel modulation, gene transcription regulation	All ECS pathways, plus broader interactions with other signaling systems, including GPCR heterodimers, extracellular ATP, microbiome composition, and more	The ECS affects a set of core signaling pathways, while the eCBome affects these and more, demonstrating a greater interconnectedness with other physiological systems.
Physiological Functions	Pain perception, mood regulation, appetite control, immune response, memory	All ECS functions, plus extended roles in inflammation, metabolism, neuroprotection, gut-brain axis, cardiovascular health, and more	The ECS is crucial for basic homeostatic functions, while the eCBome expands these roles, influencing a wider array of physiological functions and disease states.
Therapeutic Potential & Complexity Complexity and physiological relevance	Targeting ECS for conditions like chronic pain, anxiety, epilepsy, and autoimmune diseases	Broader therapeutic applications due to additional targets, potential for treating metabolic disorders, neurodegenerative diseases, and other conditions not fully addressed by ECS-targeted therapies	The ECS offers therapeutic targets for a range of conditions, focusing on its natural ligands and receptors. However, the eCBome's expanded network provides a more extensive and physiologically relevant range of therapeutic targets, including those influenced by diet and lifestyle, allowing for a more comprehensive and detailed understanding of the mechanisms of action of medical cannabis. The eCBome represents a more physiologically encompassing network compared to the traditional ECS, reflecting a system that is not only more complex but also more attuned to the body's physiological needs, with the ability to interact with a broader range of biological processes and increased potential to be influenced by dietary and environmental factors.

Table 2 *Comparison of the Endocannabinoid System (ECS) and the Expanded Endocannabinoidome (eCBome) across various aspects, including ligands, receptors, enzymatic metabolism, mechanisms of action, affected signaling pathways, physiological functions, and therapeutic potential and complexity.*

Figure 1 and Table 2 illustrate the expanded repertoire of lipid mediators, enzymes, and molecular targets that comprise the eCBome, extending beyond the traditional ECS components. This includes diverse lipid mediators like oleamide (ODA), N-acylethanolamines (e.g., PEA, OEA, LEA, DHEA, AEA), and 2-monoacylglycerols (e.g., 2-AG, 2-OG, 2-PG, 2-LG) [4,16]. These interact with an expanded repertoire of biosynthetic and metabolic enzymes, such as COX, LOX, and CYP450 enzymes [9].

Moreover, the eCBome targets a wide range of molecular sites beyond CB1 and CB2, including TRPV1 channels, PPARs, GPCRs like GPR55, GPR119, GPR110, and voltage-gated calcium channels [4,5].

Notably, the eCBome exhibits an additional layer of complexity through receptor heterodimers formed between cannabinoid receptors and other GPCRs, such as CB1-D1/D2, CB1-μ-Opioid, and CB2-GPR55 [10,11]. These heterodimers enable bidirectional modulation, where endocannabinoids influence additional GPCR targets, and vice versa, regulating diverse processes like motor function, pain perception, and cancer cell migration [16,17,18]. As presented in Table 3, recent research highlights the clinical relevance of ECS-GPCR heterooligomerization, with CB1-GPR55 and CB2-GPR55 heterodimers upregulated in multiple sclerosis patients' prefrontal cortex [19].



CB1 + GPCR heterooligomer	Additional Endogenous Heterodimer Ligands	Physiological Relevance	References
CB2	-	Modulation of immune function, inflammation, pain perception.	[10], [11]
D1/D2	Dopamine	Regulation of motor function, reward processing, cognition.	[86], [87]
μ-Opioid	Endorphins, Enkephalins	Pain perception, reward, respiratory depression.	[88], [89]
A2A	Adenosine	Modulation of locomotor activity, anxiety, neurodegeneration.	[90], [91]
NMDA	Glutamate	Modulation of glutamate signaling, potential neuroprotection in Alzheimer's disease.	[92], 93]
SST5	Somatostatin	Regulation of hormone secretion, neurotransmission, cell proliferation.	[94]
OX1	Orexins	Regulation of sleep/wakefulness, energy homeostasis.	[95], [96]
GPR55	NAGly, Lysophosphatidylinositol (LPI)	Modulation of bone physiology, neuropathic pain, cancer. Implicated in multiple sclerosis.	[97], [98], [19]
GHS-R	Ghrelin	Interactions between ghrelinergic and cannabinoidergic systems in CNS, impacting reward circuit plasticity.	[99]
CB2 + GPCR heterooligomer	**Endogenous Heterodimer Ligand**	**Physiological Relevance**	**References**
CB1	-	Modulation of immune function, inflammation, pain perception.	[10], [11]
GPR55	NAGly, Lysophosphatidylinositol (LPI)	Modulation of cancer cell migration, metastasis. Implicated in multiple sclerosis.	[16], [59]
CXCR4	SDF-1	Regulation of cancer cell migration, metastasis.	[17], [65]
NMDA	Glutamate	Modulation of glutamate signaling, potential neuroprotection in Alzheimer's disease.	[92]
HER2	N.A.	Modulation of tumor progression.	[18], [53]

Table 3 *Endocannabinoid Receptor Heterodimers and Their Physiological Relevance*

This figure illustrates various heterodimeric complexes formed between the endocannabinoid system (ECS) G protein-coupled receptors (GPCRs) and other receptor types, such as CB1-D1/D2, CB1-μ-Opioid, CB2-GPR55, CB2-CXCR4, and NMDA-CB1. The table provides details on the endogenous ligands that can modulate these heterodimers, their physiological relevance in processes like motor function, pain perception, cancer cell migration, and tumor progression, as well as relevant references supporting these interactions.

The eCBome's regulatory scope is further amplified by this intricate web of interactions, with implications for processes such as inflammation, metabolism, and neuroprotection, as highlighted by Di Marzo & Piscitelli [4] and Pacher et al. [2]. The eCBome concept represents a paradigm shift, acknowledging the complex interplay between endogenous bioactive lipids, their receptors, and signaling pathways beyond CB1 and CB2 [20,21]. This expanded perspective unveils new therapeutic avenues by modulating eCBome components and heterodimer formations [21,7].

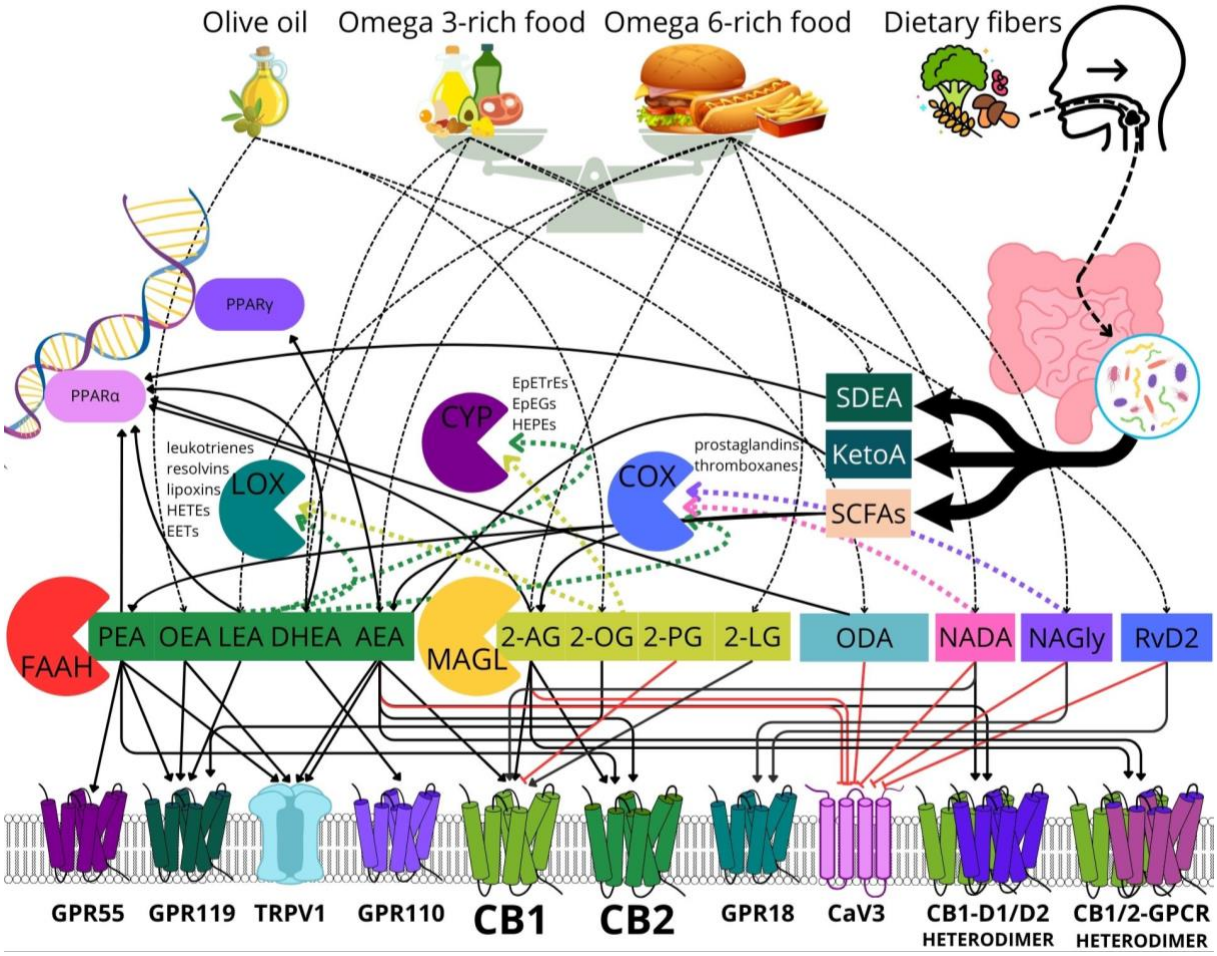


Figure 1 *Interplay between Dietary Components, the Endocannabinoidome (eCBome), and the Gut Microbiome*

Top Section: The top section depicts different dietary sources, including olive oil, omega-3-rich foods, omega-6-rich foods, and dietary fibers, precursors of many endocannabinoid-like molecules. The digestion of dietary fibers by our microbiome into short-chain fatty acids (SCFAs) that modulate endocannabinoid levels is also depicted.

Middle Section: The middle section is the most complex part of the image. It shows various lipid mediators and their interactions with different receptors and enzymes. The lipid mediators displayed include ODA (oleamide), PEA, OEA, LEA, DHEA, AEA (anandamide), 2-AG, 2-OG, 2-PG, 2-LG, NADA, NAGly, RvD2 (resolvin D2), SDEA and KetoA. Additionally, the middle section illustrates the involvement of various enzymes, such as cyclooxygenases (COX), lipoxygenases (LOX), cytochrome P450 enzymes (CYP), FAAH, and MAGL. Metabolism of eCBome mediators by COX, LOX and CYP generates 'secondary eCBome mediators, including prostaglandins, thromboxanes, leukotrienes, lipoxins and resolvins.

Bottom Section: The bottom section depicts several receptors and molecular targets that interact with the eCBome mediators shown in the middle section. These include GPR55, GPR119, TRPV1, GPR110, CB1, CB2, GPR18, and CaVs (voltage-gated calcium channels).

Top Left Section: The top left section of the image shows two related nuclear receptors, peroxisome proliferator-activated receptors alpha and gamma (PPAR-alpha and PPAR-gamma), which are activated by many eCBome mediators.

III. Physiological functions of the eCBome

The eCBome exerts a multifaceted influence on various physiological processes and homeostatic mechanisms, as highlighted in Table 4.

Function/Area	Homeostatic Mechanism	eCBome Involvement	Implications	References
Neuromodulation	Harmonizes neurotransmission and cellular signaling	CB1 activation regulates synaptic plasticity, impacts conditions like schizophrenia. CB2 modulates microglial function and neuroinflammation.	Potential in neurological treatment and research, targeting synaptic plasticity and neuroinflammation	[3], [100], [101]
Pain Management	Modulates pain across acute and chronic conditions	CB1 and TRPV1 activation influence nociceptive neurons, interacts with immune cells. OEA/PEA modulate inflammatory pain via PPARs.	Could lead to novel pain therapies targeting neuronal, inflammatory, and neuropathic pain	[102], [103]
Neuroplasticity	Modulates brain's ability to adapt and reorganize neural connections	Active interplay with lifestyle factors like diet/exercise, impacts cortical excitation/inhibition balance via CB1 signaling	Influences cognitive function and recovery from brain injuries by modulating synaptic plasticity	[103], [26]
Thermoregulation	Regulates body temperature, modulates blood flow and metabolic rate	CB1 receptors in hypothalamus, interaction with thermal signals. Endocannabinoids modulate thermogenesis.	Vital in managing body's response to temperature changes and metabolic homeostasis	[101], [104], [105]
Circadian Rhythms	Influences sleep-wake cycle timing and quality	The eCBome molecule AA-5-HT modulates circadian rhythms and sleep architecture. Endocannabinoids play an emerging role in sleep modulation.	Important for sleep quality, circadian disruptions linked to metabolic disorders	[106], [29], [67]
Immune System	Anti-inflammatory effects, regulates immune cell function	CB2 activation modulates innate and adaptive immunity. PEA/OEA exhibit anti-inflammatory effects via PPARs/TRPV1.	Potential in treating autoimmune and inflammatory diseases by modulating immune responses	[8], [30]
Oxidative Stress	Regulates oxidative stress and intracellular redox state	Endocannabinoids like AEA possess antioxidant properties. CB2 activation protects against ROS and improves mitochondrial function in preclinical models.	CB2 activation could be beneficial in neurodegenerative and inflammatory conditions involving oxidative stress	[30], [107]
Endocrine System	Regulates hormonal balance and stress response	CB1 in endocrine organs, influences hormone secretion. Interacts with peripheral nerve endings.	Impacts a range of physiological functions from metabolism to reproductive health	[108], [109]
Lipid Metabolism	Regulates energy homeostasis, influences lipid and glucose metabolism	CB1 actions in liver, adipose tissue, muscle, and pancreas. OEA/PEA modulate lipid metabolism via PPARs.	Integral in managing metabolic disorders like obesity and type 2 diabetes	[52], [110]
Cardiovascular System	Influences blood pressure regulation, vasodilation/vasoconstriction	CB1 modulation occurs through vmPFC, impacts baroreflex activity. Endocannabinoids affect vascular tone.	Affects heart health and could offer therapeutic potential in hypertension and atherosclerosis	[111], [34], [35]
Myocardial Metabolism	Affects myocardial metabolism and energy substrate utilization	CB1/CB2 interact with cardiomyocytes. CB2 maintains ATP levels, CB1 linked to lipogenesis and steatosis.	Critical in cardiovascular diseases and metabolic health, targeting CB2 may be cardioprotective	[112], [113]
Bone Metabolism	Regulates bone metabolism and remodeling	CB1, CB2, and GPR55 receptors in bone tissue. Endocannabinoids produced in synovial tissues.	Potential in treating osteoporosis and joint diseases like arthritis by modulating bone turnover	[114], [115]
Gastrointestinal System	Maintains intestinal homeostasis, regulates appetite	Endocannabinoids influence gut permeability and fluid secretion. Modulates appetite via CB1 in hypothalamus.	Essential for digestive health, managing eating disorders, and gut-brain axis regulation	[116], [32], [52]
Respiratory System	Modulates respiratory rhythm and intensity	CB1 and CB2 in preBötzinger complex influence central rhythm generators. Interacts with peripheral components.	Targeting the eCBome could potentially help manage respiratory conditions. CB2 activation mitigates opioid-induced respiratory depression.	[104], [117], [118]
Reproductive Systems	Influences maternal processes, spermatogenesis, and fetal brain development	CB1 present in placental tissues, affects male and female reproductive organs. Shapes neural development.	Implications in fertility, pregnancy complications, and neurodevelopmental disorders	[119], [120], [37]
Other Systems	Regulates various specialized physiological systems	Impacts musculoskeletal, urinary, integumentary systems. Modulates wound healing and chronic pain conditions.	Broadens the scope of eCBome therapeutic applications in diverse pathologies	[38], [121], [122]

Table 4 *Physiological Functions and Homeostatic Mechanisms of the ECS/eCBome*

Neuromodulation and Pain Management

Endocannabinoids like AEA and 2-AG modulate neurotransmitter release and neuronal excitability by interacting with CB1, CB2, and TRPV1 receptors, influencing pain perception, mood, and cognition [7,23]. N-acylethanolamines such as PEA and OEA exert analgesic and anti-inflammatory effects via PPARs and TRPV1 [24,25]. Preclinical studies demonstrate the therapeutic potential of targeting the eCBome for pain management, with eCBome modulators exhibiting analgesic effects in neuropathic, inflammatory, and migraine pain models [24].

Moreover, the formation of heterodimeric complexes like CB1-μ-Opioid (Table 3) suggests potential implications for the eCBome in modulating pain perception through interactions with the endorphin-based analgesic system.

Neuroplasticity, Neuroprotection, and Circadian Rhythms

The eCBome regulates neuroplasticity through endocannabinoids acting as retrograde messengers, modulating synaptic processes crucial for learning, memory, and cognition [26,27]. Disruptions in eCBome signaling are implicated in neurodegenerative disorders [28]. N-acylethanolamines like PEA and OEA exhibit neuroprotective antioxidant and anti-inflammatory effects, potentially mitigating neuronal damage [28].

The eCBome's influence extends to circadian rhythms and sleep architecture. Endogenous mediators like N-arachidonoyl-serotonin (AA-5-HT), AEA, PEA, and OEA interact with the sleep-wake cycle, influencing sleep homeostasis and neurotransmitter regulation through receptors like CB1, CB2, TRPV1, and PPARs [29,30,31].

Immune System Regulation

The eCBome modulates immune responses through pro- and anti-inflammatory effects. Endocannabinoids like AEA and 2-AG exert immunosuppressive actions via CB2 receptors, while N-acylethanolamines like PEA and OEA exhibit anti-inflammatory properties through PPARs and TRPV1 [9,32]. This dual role is relevant for inflammatory and autoimmune diseases (Table 4). The eCBome also regulates oxidative stress and inflammation resolution [32]. Interestingly, this concept aligns with the findings of recent studies demonstrating the eCBome's involvement in the gut-brain axis. The eCBome exhibits bidirectional communication with the gut microbiome, as certain gut bacteria produce bioactive short-chain fatty acids (SCFAs) and endocannabinoid-like molecules that modulate endocannabinoid levels. Conversely, the eCBome influences the gut microbiome composition and function [33,34].

Metabolic Functions and Energy Homeostasis

Endocannabinoids like AEA and 2-AG stimulate appetite via CB1 receptors in the hypothalamus [35]. However, the eCBome's influence extends beyond appetite, with mediators like OEA and N-acyl-dopamines modulating lipid and glucose metabolism, insulin sensitivity, and energy expenditure through PPARs, GPR119, and TRPV1 (Table 1). This interplay between the eCBome and metabolic processes has implications for obesity, diabetes, and metabolic syndrome.

The health of the eCBome is highly dependent on the dietary precursors we provide. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are essential dietary components that significantly influence the eCBome. Figure 2 illustrates the metabolic pathways of omega-3 and omega-6 PUFAs and their impact on the eCBome. The balance between omega-3 and omega-6 PUFAs is critical for maintaining optimal eCBome function. A diet high in omega-6 PUFAs, as depicted by the increasing red area in the figure, can lead to elevated levels of AEA and 2-AG, promoting metabolic dysfunction and chronic disease. Conversely, omega-3 PUFAs can help modulate these effects, highlighting the importance of dietary interventions in managing eCBome-related metabolic disorders.

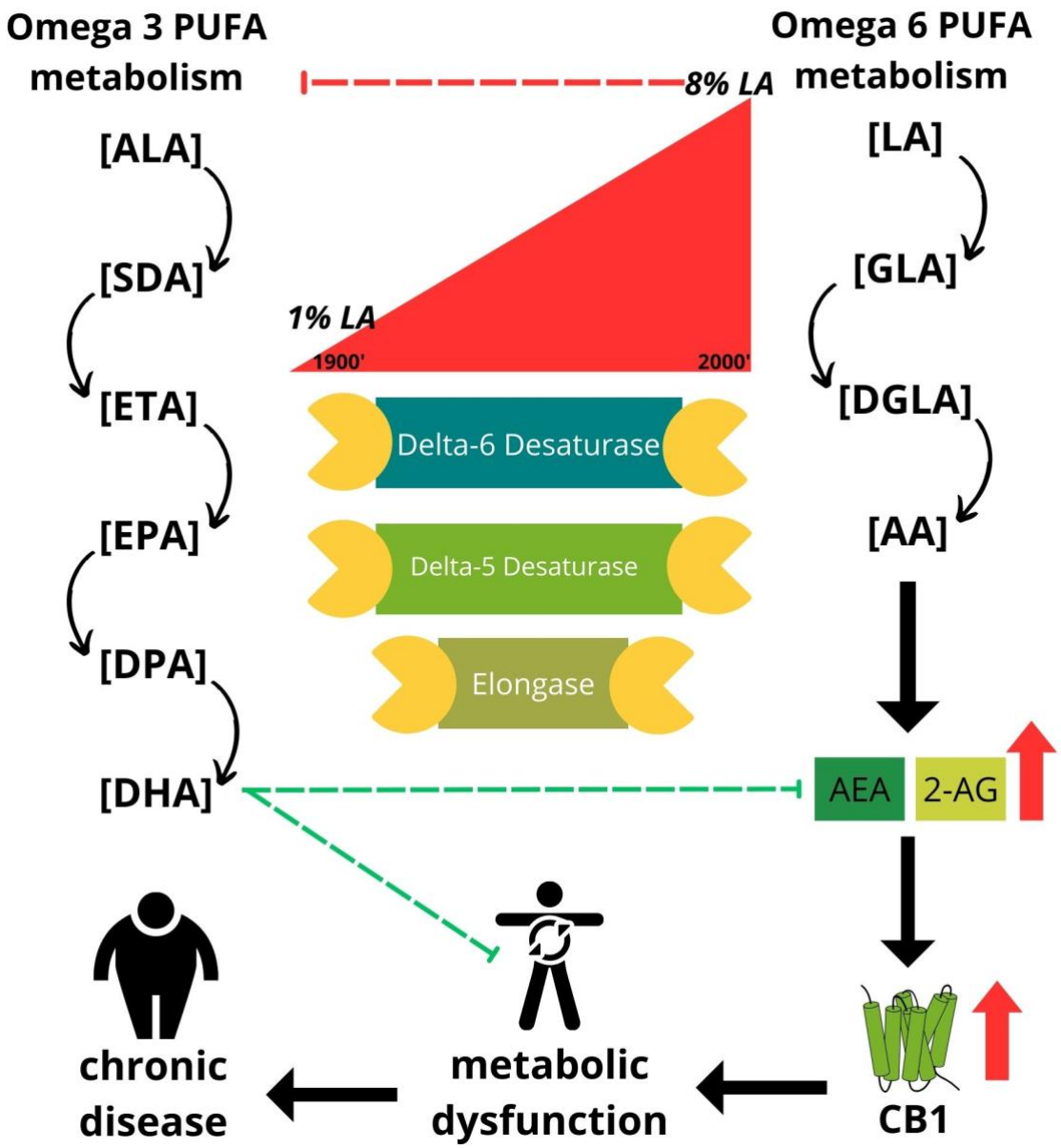


Figure 2 *Metabolic pathways of Omega-3 and Omega-6 PUFAs and their impact on the eCBome.*

The diagram highlights the conversion of alpha-linolenic acid (ALA) to various omega-3 PUFAs and linoleic acid (LA) to omega-6 PUFAs, with key enzymes such as Delta-6 Desaturase, Delta-5 Desaturase, and Elongase playing crucial roles. The figure also shows the downstream effects of these metabolic pathways on the production of endocannabinoids like AEA and 2-AG, which interact with CB1 receptors and influence metabolic dysfunction and chronic disease.

Cardiovascular System Interactions

Endocannabinoids like AEA and 2-AG interact with CB1, CB2, and TRPV1, modulating processes that influence blood pressure, vascular tone, and myocardial contractility [36,37]. The eCBome is implicated in atherosclerosis development, with endocannabinoids contributing to inflammatory processes and plaque formation. Conversely, N-acylethanolamines like PEA and OEA exhibit cardioprotective anti-inflammatory and antioxidant effects through PPARs and TRPV1 [36,37] (Table 1).

Gastrointestinal System and Gut Microbiome

The eCBome regulates gastrointestinal function and gut homeostasis, with endocannabinoids and receptors expressed in the gastrointestinal tract, modulating motility, secretion, and intestinal permeability [34]. The eCBome exhibits bidirectional communication with the gut microbiome, as certain gut bacteria produce bioactive SCFAs and endocannabinoid-like molecules that modulate endocannabinoid levels. Notably, a recent study demonstrated that KetoA (10-oxo-12(Z)-octadecenoic acid), a linoleic acid metabolite produced by gut lactic acid bacteria, can enhance energy metabolism by activating TRPV1 [35]. Conversely, the eCBome influences the gut microbiome composition and function [33,34]. Additionally, a recent clinical ex-vivo study demonstrated that supplementation with Buglossoides arvensis oil, rich in the omega-3 fatty acid stearidonic acid (SDA), directly impacts the gut microbiome and stimulates the production of endocannabinoid-like molecules, including N-stearidonoyl-ethanolamine (SDEA) and commendamide, by gut bacteria [38]. These studies highlight the ability of dietary interventions to modulate the eCBome through gut microbiome-mediated mechanisms.

Other Specialized Systems

The eCBome is implicated in reproductive functions like fertility, embryo implantation, and parturition, with endocannabinoids and receptors expressed in reproductive tissues [39,40]. Additionally, the eCBome modulates bone metabolism and musculoskeletal function, with potential implications for osteoporosis and arthritis [40,41].

To summarize the key points, the eCBome orchestrates a delicate balance of regulatory mechanisms across various physiological processes and organ systems, underscoring its pivotal role in maintaining overall homeostasis and its vast therapeutic potential.

IV. Lifestyle interventions and eCBome Manipulation

Emerging evidence suggests that various lifestyle factors can modulate the eCBome, offering potential avenues for personalized medicine approaches that complement and potentiate the therapeutic effects of CBMPs.

Diet and Nutrition

Dietary components influence the eCBome's signaling pathways, as illustrated in Table 5 and Figure 1. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) modulate endocannabinoids and related lipid mediators like AEA, 2-AG, OEA, and PEA (Table 1), which interact with receptors including CB1, CB2, PPARs, GPR119, and TRPV1 [42]. A Mediterranean diet increases omega-3 derived eCBome mediators while decreasing omega-6 derived endocannabinoids like 2-AG and AEA (43). These dietary modulations can enhance CBMPs' therapeutic effects by optimizing the eCBome's signaling environment. Additionally, in a recent study, researchers demonstrated that supplementation with Buglossoides arvensis oil, rich in the omega-3 fatty acid stearidonic acid (SDA), can stimulate the production of endocannabinoid-like molecules, including N-stearidonoyl-ethanolamine (SDEA) and commendamide, by gut bacteria, further highlighting the potential of dietary interventions to modulate the eCBome [38].

Figure 1 depicts how dietary sources like olive oil, omega-3/6 foods, and fibers influence eCBome mediator production and activity. Dietary fibers modulate the eCBome by producing bioactive short-chain fatty acids (SCFAs) that influence endocannabinoid levels [33]. The balance between omega-3 and omega-6 PUFAs affects lipid mediator production and inflammatory responses.

Exercise and Physical Activity

Regular exercise modulates plasmatic endocannabinoid levels like AEA and 2-AG (Table 1), which interact with CB1, CB2, and TRPV1, affecting neurotransmission, neuronal excitability, and pain perception [44,45]. Remarkably, exercise interventions modulate gut microbiome composition, influencing endocannabinoid and endocannabinoid-like molecule levels like AEA, 2-AG, and OEA, partially mediated by SCFAs produced by gut microbes [33]. This underscores the interplay between exercise, gut microbiome, and eCBome.

Figure 1 and Table 5 detail how exercise-induced changes in AEA and 2-AG levels can modulate their interactions with CB1, CB2, and TRPV1, contributing to exercise's effects on the eCBome. Tailoring exercise regimens to individual profiles can optimize eCBome modulation and potentially enhance CBMPs' therapeutic effects by synergistically modulating the eCBome.

Mind-Body Practices

Practices like meditation, yoga, and acupuncture may influence the eCBome and signaling pathways involving AEA and 2-AG (Table 1, Table 5, Figure 3), which modulate neurotransmission, neuronal excitability, and pain perception via CB1, CB2, and TRPV1 [46,47,48]. Acupuncture has been linked to modulating endocannabinoid levels and cannabinoid receptor activation, suggesting potential synergies with CBMPs in managing pain, inflammation, and other conditions by targeting eCBome components [49].

Multimodal manipulation of eCBome

By integrating knowledge of lifestyle and dietary factors that modulate the eCBome, as exemplified by the diverse components and their physiological relevance shown in Table 1 and Table 4, healthcare professionals can learn and teach multimodal personalized approaches that complement and potentiate the therapeutic effects of CBMPs. These interventions may enhance the response to cannabinoids by synergistically modulating the eCBome components and signaling pathways, while potentially reducing adverse effects and optimizing overall patient outcomes.

For example, a patient with chronic pain or neurological conditions could benefit from a personalized regimen that combines CBMPs with a Mediterranean-inspired diet rich in omega-3 fatty acids to modulate eCBome mediators like those derived from omega-3 PUFAs. This could be combined with regular exercise tailored to their fitness level to increase AEA and 2-AG levels, and mind-body practices like meditation or yoga to further modulate endocannabinoid signaling pathways involving compounds like AEA

and 2-AG. As shown in Table 1, these mediators interact with receptors like CB1, CB2, TRPV1, contributing to processes like pain modulation, neuroplasticity, and neuroprotection. This multifaceted approach could synergistically modulate the eCBome, potentially improving pain management, reducing inflammation, and promoting overall well-being by targeting the diverse components and signaling pathways of the eCBome.

ECS Intervention	Main APIs	Molecular Targets	Indications	References
Type I (THC-Dominant)	High THC, Low CBD	CB1, CB2, GPR55, TRPV1, PPARs, opioid receptors, others	- Chronic pain - Chemotherapy-induced nausea/vomiting - Appetite stimulation - Neurological conditions (e.g. multiple sclerosis spasticity, neurodegenerative disorders) - Immune modulation - Cardiovascular regulation	[12], [13], [49]
Type II (Balanced THC:CBD)	Roughly equal THC and CBD	CB1, CB2, TRPV1, GPR55, 5-HT1A, PPARs, negative allosteric modulation of CB1, others	- Chronic pain - Muscle spasticity (e.g. multiple sclerosis) - Inflammatory conditions - Certain neurological conditions	[49]
Type III (CBD-Dominant)	High CBD, Very low THC	Primarily TRPV1, GPR55, 5-HT1A, PPARs, negative allosteric modulation of CB1	- Seizure disorders (e.g. Dravet, Lennox-Gastaut syndromes) - Potentially other neurological/psychiatric conditions	[49], [14]
Mediterranean Diet	Increases omega 3-derived eCBs Decreases omega 6-derived eCBs	CB1, CB2, TRPV1, PPARs, others	Modulation of eCBome, anti-inflammatory effects, potential synergy with medical cannabis	[40], [41]
Ketogenic Diet	High-fat low-carbohydrate diet. ketone bodies	CB1, CB2, TRPV1, PPARs, N-acylethanolamines (e.g.,OEA)	Refractory epilepsy, Irritable Bowel Syndrome (IBS), potential neuroprotective effects, modulation of glucose metabolism and intestinal membrane permeability	[123], [124]
Intermittent fasting	Time-restricted eating	CB1, CB2, TRPV1, PPARs, others	Analgesia, modulation of eCBome and gut microbiome composition, potential synergy with medical cannabis	[125], [126]
Exercise	Increases AEA and 2-AG levels	CB1, CB2, TRPV1, PPARs, others	Modulation of eCBome and gut microbiome composition, potential synergy with medical cannabis	[42], [43], [133]
Mindfulness	Increases AEA, 2-AG, BDNF levels	CB1, CB2, TRPV1, PPARs, others	Improved mood, well-being, stress reduction via eCBome modulation, potential synergy with medical cannabis	[44], [45], [46], [47]

Table 5 *Summary of ECS interventions, their main active pharmaceutical ingredients (APIs), molecular targets engaged, potential therapeutic indications, and supporting references.*

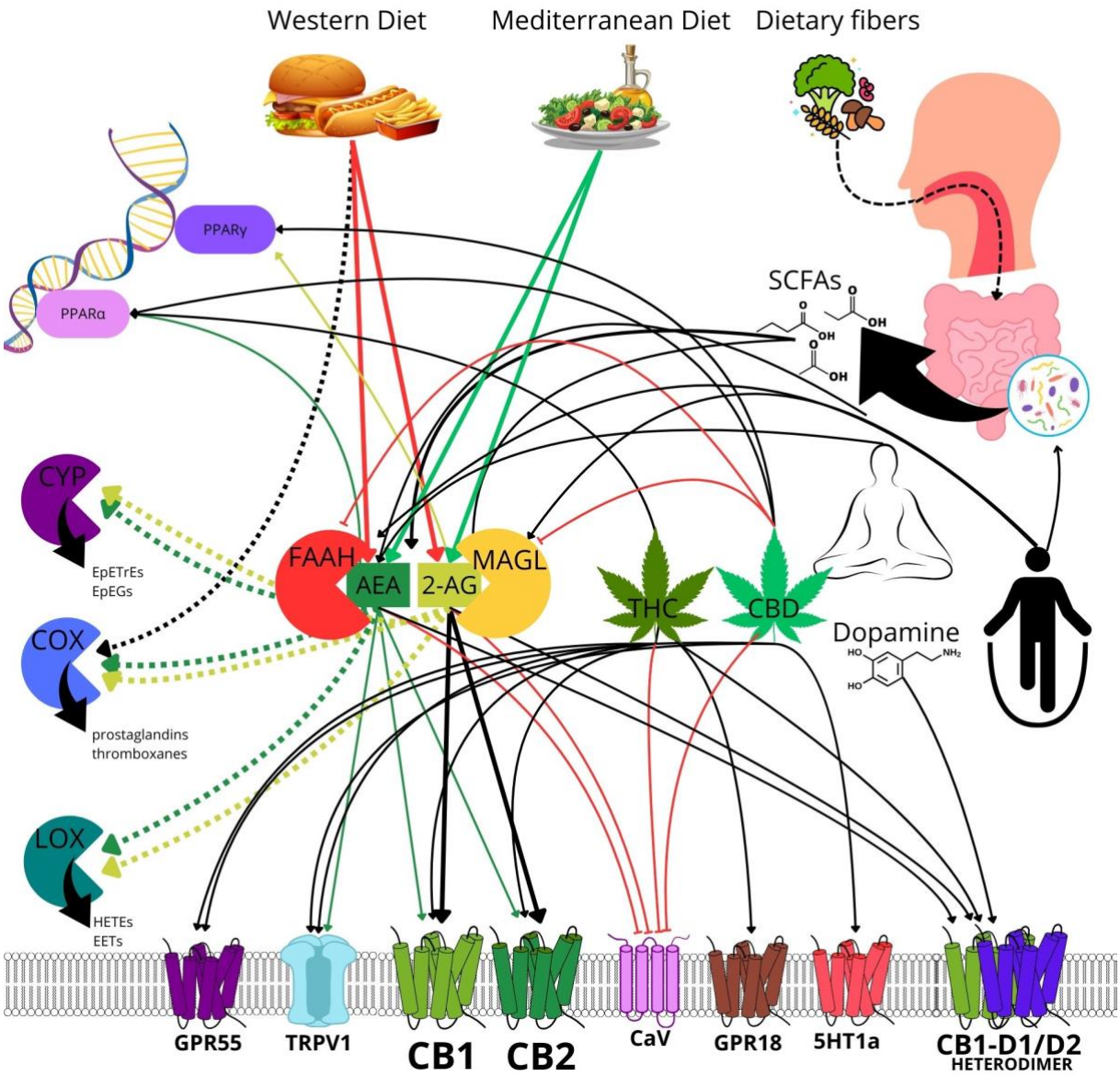


Figure 3 *Nutritional, Behavioral, and Pharmacological Modulation of the ECS and related pathways.*

This figure delineates the influence of dietary patterns, exercise, mindfulness, and cannabinoids on the ECS. The Western Diet, rich in omega-6 fatty acids, is shown to elevate AEA and 2-AG levels, while the Mediterranean Diet, with its higher omega-3 content, normalizes ECS signaling. Dietary fibers, through gut microbiome modulation, lead to SCFA production, indirectly affecting ECS activity. The microbiome also directly produces bioactive NAEs like SDEA. Exercise is depicted as a dual modulator of the ECS, both through SCFA-mediated microbiome changes and direct dopamine regulation, impacting the CB1-D1/D2 heteromer. Cannabinoid interactions are detailed, with THC binding to CB1 and CB2 receptors and influencing GPR55 and GPR18, while CBD activates PPARs, TRPV1, and CaV3 channels, and uniquely targets 5HT1a and FAAH inhibition.

V. Medical Cannabis and the eCBome

Phytocannabinoids found in cannabis, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with various eCBome targets, including CB1, CB2, GPR55, TRPV1, and PPARs (Table 1). These interactions allow phytocannabinoids to potentially mimic or modulate the effects of endocannabinoids and endocannabinoid-like molecules on processes like pain, appetite, inflammation, and immunity [13,14,15]. Cannabis-based medicinal products (CBMPs) containing THC, CBD, or a combination

of both, therefore hold therapeutic potential by targeting components of the eCBome system.
Evidence supporting the use of cannabis/cannabinoids for specific conditions:

Chronic Pain

Endocannabinoids like AEA and 2-AG modulate pain perception by interacting with CB1, CB2, and TRPV1 receptors, inhibiting nociceptive signaling [7,23]. Phytocannabinoids like THC from Type 1 CBMPs and CBD from Type 3 CBMPs can mimic these analgesic effects by engaging the same targets [13,14]. Typical dosing involves combining THC (2.5-10 mg) and CBD (5-20 mg) orally or via oromucosal sprays, individualized based on response and tolerability [50].

Seizure Disorders

CBD exhibits anticonvulsant effects by modulating TRPV1 and GPR55 (Table 1). The licensed CBMP Epidyolex (CBD isolate) targets TRPV1, GPR55, 5-HT1A, and PPARs for treating seizures in Lennox-Gastaut and Dravet syndromes [51]. Typical dosing starts at 2.5 mg/kg CBD twice daily, gradually increasing to 10-20 mg/kg/day based on response [51].

Muscle Spasticity (e.g., Multiple Sclerosis)

The licensed CBMP Sativex (THC:CBD spray) engages CB1, CB2, TRPV1, GPR55, and 5-HT1A (Table 1), recommended for moderate to severe spasticity in multiple sclerosis when other treatments are ineffective [51]. Dosing starts with one spray/day, gradually increasing to a maximum of 12 sprays/day, with each spray containing 2.7 mg THC and 2.5 mg CBD [51].

Nausea and Vomiting (Chemotherapy-induced)

Type 1 CBMPs containing THC interact with CB1, CB2, GPR55, TRPV1, and opioid receptors (Table 1) to stimulate appetite and reduce nausea/vomiting by modulating CB1 in the hypothalamus and brainstem [52,53].

Appetite Stimulation

The eCBome regulates appetite and energy homeostasis through the interplay of components listed in Tables 1 and 4. Endocannabinoids like AEA and 2-AG stimulate appetite via CB1 receptors in the hypothalamus [54]. Type 1 CBMPs containing THC mimic these effects by interacting with various eCBome targets, including CB1, CB2, GPR55, TRPV1, and PPARs, as presented in Table 1 [13].

CNS Disorders

The eCBome's roles in neuroplasticity, neuroprotection, immune regulation, and signaling pathways implicated in cancer cell migration and tumor progression (Table 4) make it a potential target for many CNS disorders including neurodegenerative diseases, traumatic brain injury, stroke, and various cancers [19,32,55].

Preclinical studies show CBD and other eCBome modulators can exert neuroprotective effects in Parkinson's disease by reducing oxidative stress, neuroinflammation, and excitotoxicity, potentially alleviating motor symptoms and cognitive impairments [15]. A recent mixed studies systematic review on cannabinoids in behavioral, psychological, and motor symptoms of neurocognitive disorders confirm that Type III CBMPs (1:20, THC:CBD) are associated with improved motor symptoms in conditions like Huntington’s disease (HD) and Parkinson’s disease (PD) [56].

In post mortem brain biopsies from deceased Alzheimer's patients, AEA and its lipid precursor NArPE have been found to be significantly reduced in the mid-frontal and temporal cortices [57]. Furthermore, both CB2 and GPR55 were recently discovered to be upregulated very early on in advanced AD disease mouse models [58]. The researchers also found that CB2 expression levels in astrocytes and glia cells, as well as GPR55 expression levels in neurons, were upregulated in response to Aβ42-treatment, the toxic prion-like molecule associated with neuronal loss in advanced Alzheimer's disease. In a recent preclinical animal study, researchers showed that APP-PS1 mice in chronic intermittent cannabinoid treatment (5 days on, 2 days off) with either a CB2 agonist, JWH-133, or whole plant cannabis (15% THC, <1% CBD) (63), reduced anxiety, partially reversed cognitive defects, reduced number and size of amyloid plaques, and improved cerebral glucose metabolism [59]. eCBome modulation in patients with Alzheimer's holds enormous therapeutic potential and clinical research desperately needs to catch up.

Psychiatric Disorders

The use of medical cannabis for treating psychiatric disorders remains controversial due to limited high-quality evidence supporting its efficacy and safety. While some studies suggest potential benefits of cannabinoids like CBD for anxiety, depression, PTSD, and sleep disorders, systematic reviews conclude that current evidence is of poor quality and inconsistent.

Concerns exist about cannabis worsening certain psychiatric conditions like anxiety, depression, and bipolar disorder in some individuals. Clinicians need to carefully weigh the risks and benefits, monitor for side effects, and base treatment decisions on the best available evidence. More rigorous research is warranted to establish the therapeutic role of medical cannabis in psychiatry.

Autism Spectrum Disorder (ASD)

Emerging evidence suggests that the eCBome may be involved in the pathophysiology of neurodevelopmental disorders like autism spectrum disorder (ASD). A large number of eCBome alterations in endocannabinoid signaling have been linked to mechanisms and symptoms of ASD, such as abnormal neural development, immune dysfunction, social deficits, and repetitive behaviors [60]. The endocannabinoid-microbiota axis is also often altered in patients with ASD which has sparked interest in exploring the axis using cannabinoids, nutritional interventions, and "gut-therapy" as potential treatment options for ASD. Research on medical cannabis for neurodevelopmental disorders is still very limited but holds much future promise.

Cancer

The eCBome's involvement in immune regulation and its interactions with signaling pathways implicated in cancer cell migration and tumor progression make it a potential target for cancer therapy [19,55].

In breast cancer, targeting CB2-GPR55 heterodimers inhibits cancer cell migration and metastasis [17,61]. CBD exerts anti-proliferative and pro-apoptotic effects in breast cancer cells, potentially through TRPV1 and GPR55 modulation [14]. In glioblastoma, eCBome modulators like AEA and CBD inhibit tumor growth, angiogenesis, and invasion, potentially through CB1, CB2, and TRPV1 [32].

In glioblastoma, a highly aggressive form of brain cancer, the eCBome has been implicated in regulating tumor growth, angiogenesis, and invasion [32]. Preclinical

studies have shown that eCBome modulators like AEA and CBD can inhibit glioblastoma cell proliferation and induce apoptosis, potentially through modulation of CB1, CB2, and TRPV1 receptors [32]. While promising, further research is needed to translate these findings into clinical applications, optimizing dosing, formulations, and delivery methods for targeting specific eCBome components and signaling pathways in different conditions.

Potential Challenges and Limitations

While the CBMPs present promising therapeutic opportunities, several challenges and limitations need to be addressed when targeting the eCBome system for therapeutic interventions:

Regulatory Hurdles

The regulatory landscape surrounding medical cannabis and eCBome modulators varies widely across regions, posing challenges for researchers, healthcare professionals, and patients. Addressing issues like product standardization, potential adverse effects, medical education, and the need for further research to establish optimal dosing and formulations is essential for advancing our understanding of the eCBome's therapeutic potential. In the United Kingdom, CBMPs were rescheduled in 2018, allowing specialist clinicians to legally prescribe them for certain conditions. However, CBMPs remain tightly regulated, with strict guidelines on prescribing, manufacturing, and supply chain controls. The regulatory framework is overseen by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Home Office.

Potential Adverse Effects

While cannabinoids and other eCBome modulators have demonstrated therapeutic benefits, they may also be associated with potential adverse effects, such as cognitive impairment, psychoactive effects, and cardiovascular or respiratory complications. These adverse effects may vary depending on the specific compounds, dosages, and individual patient factors, necessitating careful monitoring and risk-benefit assessments.

Need for Further Research

Despite the growing body of knowledge surrounding the eCBome, there is still a need for extensive research to fully understand the complex interactions between its various components, receptors, and signaling pathways. Elucidating these intricate mechanisms is crucial for developing targeted and personalized therapeutic interventions with optimal efficacy and minimal side effects.

VI. Educational and Clinical Implications

Need for Education on CBMPs and the eCBome

Traditionally, medical curricula and mainstream literature have largely overlooked the ECS and its expanded eCBome components due to stigma associated with cannabis. Integrating eCBome knowledge into medical education is crucial for equipping future professionals to recognize conditions influenced by this system, such as chronic pain, neurodegenerative disorders, and metabolic diseases [21,61].

As illustrated in Table 2, the eCBome encompasses a broader range of ligands, receptors, enzymes, and signaling pathways than the classical ECS, demonstrating far-reaching health implications. Providing a holistic eCBome perspective will foster appreciation for its interconnectedness with regulatory networks like the immune, nervous, and endocrine systems. This understanding is crucial for developing comprehensive patient care approaches, particularly regarding medical cannabis applications highlighted by the diverse 'ECS Interventions' in Table 5 and Figure 3.

Guidelines for Authorizing Cannabis and Monitoring Patients

Clear guidelines based on scientific evidence are needed for authorizing and monitoring CBMP use. These should address conditions where CBMPs demonstrate efficacy, like chronic pain, seizures, muscle spasticity, and chemotherapy-induced nausea/vomiting [50,62]. Emphasizing precise dosing, formulation, and administration routes is vital, as these factors impact CBMP efficacy and safety [62,63].

As presented in Table 1, phytocannabinoids interact with various eCBome targets, leading to diverse effects [13,14]. Understanding the eCBome's complexity and cannabinoid pharmacokinetics is essential for developing targeted, personalized interventions. Guidelines should outline protocols for monitoring patient responses, adverse effects, and drug interactions, considering the eCBome's intricate physiological interactions highlighted in Table 4 [33,35,36].

Addressing Common Misconceptions and Stigma Surrounding CBMPs

Despite scientific evidence supporting CBMP therapeutic potential, misconceptions and stigma persist. Addressing these within medical curricula is crucial for promoting evidence-based decision-making and fostering informed understanding of medical cannabis.

A common misconception is perceiving medical cannabis as a recreational drug with limited therapeutic value. However, as demonstrated in Table 5 and Figure 3, phytocannabinoids and lifestyle interventions modulate various eCBome targets, affecting diverse processes and offering therapeutic benefits [13,14,15,42,43].

Stigma may stem from cannabis' historical association with substance abuse and legal restrictions. However, as eCBome understanding evolves, an objective, scientific approach to medical cannabis is essential. Incorporating the latest research into curricula and fostering open discussions can develop informed, unbiased perspectives on its potential benefits, risks, and therapeutic applications alongside other lifestyle ECS interventions outlined in Table 5 and Figure 3.

In summary, integrating the eCBome and medical cannabis into medical education is crucial for equipping future professionals with knowledge for informed decision-making and optimal patient care. Addressing education needs, establishing clear guidelines, and combating misconceptions and stigma will enable harnessing this system's full potential and leveraging a range of diverse ECS-modulating interventions for human health and well-being.

VII. Future Directions

Ongoing Research and Longitudinal Studies

While providing invaluable insights, longitudinal human studies and well-designed clinical trials are crucial to fully capture the eCBome's dynamic nature and long-term implications [20,21,61,64]. Longitudinal studies could elucidate the eCBome's roles in physiological processes, potential dysregulation in pathological conditions, and the impact of lifestyle factors like diet and exercise, as highlighted in Table 5.

Exploring Endogenous eCBome Mediators for Therapeutic Applications

As poignantly highlighted by the late great Professor Raphael Mechoulam in his final scientific article before passing, "although extensive data are available for the endocannabinoids, they have not been investigated in, or even administered to, humans—more than 25 years since they were reported! Are we missing something?" [66]. This sentiment underscores the urgency to bridge the gap between our increased understanding of the eCBome and its practical exploration in human subjects, which has largely been limited to phytocannabinoids and medical cannabis.

In line with the principles of modern polypharmacology, leveraging multiple mechanisms of action acting on the eCBome is likely to improve therapeutic outcomes. One promising avenue is the methodical exploration of the therapeutic potential of endogenous eCBome mediators. As endogenous compounds, these mediators intrinsically possess high selectivity, low off-target effects, and favorable safety profiles. Future research should focus on investigating the therapeutic applications of endogenous eCBome components, such as endocannabinoids, N-acylethanolamines, and other lipid mediators, as well as their interactions with various receptors and signaling pathways.

Supplementation with compounds like PEA and OEA, which are known to interact with eCBome targets like PPARs, TRPV1 [24,27], should be explored with regards to their ability to further modulate the eCBome and enhance therapeutic outcomes of CBMPs (Table 1). However, the availability of pharmaceutical-grade formulations of such compounds is currently limited, and their practical implementation may face regulatory and accessibility challenges that need to be addressed.

The discovery of endogenous ligands and their interactions with eCBome heterodimers (Table 3) could pave the way for innovative therapeutic agents mimicking or modulating these effects [11,12,17,19,54].

Development of Novel Cannabinoid-Based Medications

Complementing the exploration of endogenous mediators, the eCBome represents a promising target for novel phytocannabinoid-based medications. The data presented in Table 1 illustrate how phytocannabinoids like THC and CBD interact with various eCBome targets, modulating diverse physiological processes [13,14,15]. Future research should focus on developing more selective and targeted compounds with higher precision and reduced side effects, as well as extensively exploring the therapeutic potential of minor cannabinoids [20,63].

Clinical Trials and Personalized Approaches

As novel cannabinoid-based medications progress, well-designed clinical trials are crucial for evaluating safety, efficacy, and therapeutic applications across diverse populations, enabling personalized treatment approaches [61,64]. Trials should investigate optimal dosing, formulation, and administration routes, considering the diverse eCBome targets and potential interactions with lifestyle interventions (Table 5 and Figure 3).

Elucidating Molecular Mechanisms and Signaling Pathways

Further elucidating the eCBome's molecular mechanisms and signaling pathways is vital for developing targeted interventions [20,21]. Advanced techniques like proteomics, metabolomics, and computational modeling could provide insights into complex signaling cascades and regulatory networks involving lipid mediators, enzymes, and molecular targets (Tables 1 and 3) [61,64]. Exploring epigenetic and genetic factors influencing eCBome component expression and activity could pave the way for personalized medicine approaches [20].

Interdisciplinary Collaborations and Computational Approaches

The eCBome's intricate nature necessitates interdisciplinary collaborations and computational approaches, fostering knowledge exchange and innovative solutions [61,64]. Integrating machine learning and artificial intelligence can accelerate discovery processes, facilitate data analysis from omics studies and clinical trials, identify patterns, predict outcomes, and generate hypotheses for experimental validation [61].

The Dynamic eCBome

As understanding evolves, embracing the eCBome's fluid and dynamic nature is crucial. Future research should remain open to expanding boundaries, incorporating newly identified lipid mediators, enzymes, or molecular targets playing a role in its functioning [20,21]. Researchers should adapt their understanding of the eCBome's interactions with other physiological systems as new evidence emerges, enabling a comprehensive exploration of its regulatory roles [20,21]. By adopting a dynamic and adaptable approach, the scientific community can ensure the eCBome remains at the forefront of scientific inquiry, continuously evolving to reflect cutting-edge research [20,61].

VIII. Conclusion

The eCBome has emerged as a pivotal physiological regulator, orchestrating a multitude of processes essential for maintaining homeostasis within the human body [2,61]. Its far-reaching influence spans diverse domains, as highlighted in Table 4, including neuromodulation, pain management, neuroplasticity, immune regulation, metabolic homeostasis, cardiovascular regulation, and specialized systems like reproduction and musculoskeletal function.

The eCBome's complexity arises from its expanded array of lipid mediators, enzymes, molecular targets, and signaling pathways beyond the classical ECS components, as illustrated in Figure 1 [4,20]. This intricate network modulates physiological equilibrium through interconnections with various systems, including the immune, nervous, and metabolic systems [20,21].

Moreover, the formation of receptor heterodimers, such as CB1-D1/D2, CB1-μ-Opioid, and CB2-GPR55 (Table 3), further amplifies the eCBome's regulatory scope, influencing processes like motor function, pain perception, cancer cell migration, and tumor progression [11,12,17,18,19,54,67].

As our understanding deepens, the eCBome's therapeutic potential becomes increasingly apparent. Targeted interventions like CBMPs and other eCBome modulators offer opportunities for developing innovative treatments across various pathological conditions, including chronic pain, neurodegenerative disorders, metabolic diseases, and inflammatory conditions [21,61].

The eCBome's diversity of molecular targets and signaling pathways (Tables 1 and 4) enables personalized therapeutic approaches tailored to individual patient profiles, enhancing treatment efficacy while minimizing adverse effects. However, realizing this potential requires promoting evidence-based decision-making when considering medical cannabis, addressing misconceptions, and fostering an objective, scientific perspective [13,14,15,62].

In conclusion, the eCBome stands as a testament to the intricate complexity of human physiology and the vast potential for therapeutic innovation. By embracing a dynamic and inclusive understanding of this pivotal system, and promoting evidence-based decision-making, the medical and scientific communities can unlock new frontiers in personalized medicine, ultimately improving human health and well-being on a global scale [21,61].

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