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Review Article

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Introduction to Cannabis, Cannabinoids and the Endocannabinoidome (Ecbome): An -*Ome* of Interactions and Potential

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Abstract

Cannabis sativa L. produces a plethora of molecules with therapeutic potential, among which phytocannabinoids stand out as significant components. The search for endogenous mediators of cannabis effects in animals has led to the elucidation of cannabinoid receptors CB1/CB2, their endogenous ligands (endocannabinoids), and their enzymes responsible for their synthesis and degradation, collectively termed ''Endocannabinoid System (ECS). Cannabinoids, such as THC, contribute to both therapeutic efficacy and toxicity of the cannabis plant. Phytocannabinoids not only interact with the ECS but also engage with a diverse array of other receptors, ion membrane channels, nuclear receptors (orphan GPCRs, PPARs, and LGICs), endogenous ligands akin to endocannabinoids, metabolic enzymes, and other target molecules. These mediators, although described within other systems or families, may play a pivotal role in mediating the effects of cannabis products constituting an -ome broader than the ECS, referred to as the Endocannabinoidome (eCBome) by some authors. Understanding the role of the eCBome in health and disease, as well as its modulation, presents an interesting target for the development of therapeutic strategies. This review provides an overview of the historical and current knowledge of the endocannabinoidome and its exogenous modulation as a therapeutic approach.

Keywords: Cannabis sativa L., Phytocannabinoids, Endocannabinoids, Cannabinoids, Endocannabinoid system, Eendocannabinoidome, Nanopharmaceuticals

Introduction

The Cannabis plant (*Cannabis sativa* L.) has been utilized by humans for millennia due to its diverse benefits. Among these, its medical applications are particularly notable [1]. This plant exhibits a plethora of biological activities [2]. Despite its wide range of historical use, it wasn't until relatively recently that the biological properties of the molecular compounds of plants were studied from a modern scientific perspective. Research into the effects of "hashish" paved the way for the discovery of phytocannabinoids (pCBs), including tetrahydrocannabinol or Δ-9-Tetrahidrocannabinol (THC) [3]. Subsequent research aimed at elucidating the receptors through which cannabinoids like THC trigger psychoactive effects. Thereafter, the discovery of Endocannabinoid System (ESC) began [4]. The widespread presence of this system across species and within numerous animal tissues has led to the identification of a vast array of molecular mediators of cannabinoid biological activities, along with other compounds present in the plant [5]. Therefore, the real scope of the ESC and the therapeutic potential of cannabinoids and other compounds are being redefined. Some authors suggest a broader term to encompass include the myriad of endogenous mediators. As a result the concepts "Endocannabinoidome (eCBome)'' or "Expanded Endocannabinoid System" have emerged, which include not only the ESC, but also other mediators resembling endocannabinoids and cannabinoid target proteins [4,6-17]or endocannabinoidome, have both been implicated in diet-induced obesity and dysmetabolism. This study aims at identifying the potential interactions between these two fundamental systems—which form the gut microbiota-endocannabinoidome

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axis—and their involvement in the establishment of diet-induced obesity and related metabolic complications. We report here time- and segment-specific microbiome disturbances as well as modifications of intestinal and circulating endocannabinoidome mediators during high-fat, high-sucrose diet-induced glucose intolerance and subsequent obesity and hyperinsulinemia. This highlights the involvement of, and the interaction between, the gut microbiota and the endocannabinoidome during metabolic adaptation to high-fat and high-sucrose feeding. These results will help identifying actionable gut microbiome members and/or endocannabinoidome mediators to improve metabolic health. The intestinal microbiota and the expanded endocannabinoid (eCB. The mechanisms underlying the effects of cannabinoids on animal physiology are diverse and intricate. Although ongoing research continues to elucidate the extent and distribution of the eCBome, it has been found to be present in virtually every tissue, at least in mammals [18], and plays a role in both physiologic and pathologic processes [19] neurodegenerative, gastrointestinal, metabolic and cardiovascular diseases, pain, and cancer. It has been suggested that this phenomenon primarily serves an autoprotective role in inhibiting disease progression and/or diminishing signs and symptoms. Accordingly, enhancement of endogenous endocannabinoid tone by inhibition of endocannabinoid degradation represents a promising therapeutic approach for the treatment of many diseases. Importantly, this allows for the avoidance of unwanted psychotropic side effects that accompany exogenously administered cannabinoids. The effects of endocannabinoid metabolic pathway modulation are complex, as endocannabinoids can exert their actions directly or via numerous metabolites. The two main strategies for blocking endocannabinoid degradation are inhibition of endocannabinoid-degrading enzymes and inhibition of endocannabinoid cellular uptake. To date, the most investigated compounds are inhibitors of fatty acid amide hydrolase (FAAH. Approaches to modulate this system for understanding its pathophysiological role and therapeutic potential include the administration of cannabinoids (including synthetic cannabinoids), inhibition of endogenous cannabinoid degradation, inhibition of cellular reuptake to enhance its tone, and the utilization of nanotechnology, such as nanopharmaceuticals to improve its pharmacological properties and develop safer and more effective therapies [20]distribution in the mammalian body, receptor structure, and enzymatic degradation of the ECS. A closer look at ligand-receptor complexes, endocannabinoid tone, tissue distribution, and G-protein activity leads to a better understanding of the potential of the ECS toolkit for therapeutics. The signal transduction pathways examine the modulation of downstream effector proteins, desensitization, signaling cascades, and biased signaling. An in-depth and overall view of the targeted system is achieved through homology modeling where mutagenesis and ligand binding examine the binding site and allow sequence analysis and the formation of libraries for molecular docking and molecular dynamic simulations. Internalization routes exploring receptor-mediated endocytosis and lipid rafts are also considered for explicit signaling. Furthermore, the review highlights nanotechnology and surface modification aspects as a possible future approach for specific targeting.”,”author”:[{“dropping-particle”:””,”family”:”Dasram”,”given”:”Mendhi Henna”,”non-dropping-particle”:””,”parse-names”:false,”suffix”:””},{“dropping-particle”:””,”family”:”Walker”,”given”:”Roderick B.”,”non-dropping-particle”:””,”parse-names”:false,”suffix”:””},{“dropping-particle”:””,”family”:”Khamanga”,”given”:”Sandile M.”,”non-dropping-particle”:””,”parse-names”:false,”suffix”:””}],”container-title”:”International Journal of Molecular Sciences”,”id”:”ITEM-1”,”issue”:”21”,”issued”:{“date-parts”:[[“2022”]]},”title”:”Recent Advances in Endocannabinoid System Targeting for Improved Specificity: Strategic Approaches to Targeted Drug Delivery”,”type”:”article-journal”,”volume”:”23”},”uris”:[“http://www.mendeley.com/documents/?uuid=2846b48c-0127-42e8-b2d8-f9916e15119f”]}],”mendeley”:{“formattedCitation”:”[20]”,”plainTextFormattedCitation”:”[20]”,”previouslyFormattedCitation”:”[20]”},”properties”:{“noteIndex”:0},”schema”:”https://github.com/citation-style-language/schema/raw/master/csl-citation.json”}.

Discussion

History and botany

Cannabis (*Cannabis sativa* L.) stands as one of the oldest species cultivated by humans and boasts a cosmopolitan distribution [21]. Believed to originate from Central Asia, possibly the Himalayas [21], the plant’s history dates back approximately 12,000 years in China, where its seeds formed part of the basic grains of the region [1]. Throughout history, humans have utilized cannabis in several ways, including for natural fiber production, insulation boards, rope making, oils, paper, and clothing. Its medical properties have been recognized in numerous ancient civilizations, and it is currently a controversial and significant object of study [22,23]and this collective name is used to denote various botanical forms. Two varieties have economic significance: Cannabis sativa var. sativa and Cannabis sativa var. indica. They are commonly referred to as industrial cannabis/hemp and medicinal cannabis/medicinal marijuana, respectively. This paper reviews the available literature on the botanical aspects, cultivation, productivity, industrial applications, medicinal properties and environmental impacts of cannabis which influence agronomic standards for field cultivation of cannabis in north-eastern Europe. The processing suitability of cannabis is determined by the proportions of the major cannabinoids: Δ9-trans-tetrahydrocannabinol (THC. Its farming (hemp) dates back to 1000-2000 BC in Egypt and Western Asia, followed by its introduction to South America (Chile) in 1545 and North America in 1606 (Port Royal, Canada). The phylogenetic origin of the Cannabis genus, which, like its congener *Humulus lupulus* (Hop), belongs to the Cannabaceae family, has been determined using a “molecular watch” to assess DNA changes over time and to establish phylogenetic trees using specialized software. It has been estimated that Cannabis and Humulus diverghed from their common ancestors approximately 27.8 million years ago [24].

Cannabis sativa L. is a dicotyledonous, herbaceous, annual, apetalous, and dioecious plant. Its dioecious nature implies the existence of different female and male plants; however, under certain conditions, the occurrence of hermaphrodites or bisexual flowers is possible [25]. Among the constituents of interest, phytocannabinoids stand out. These are a class of ‘‘unique’’ terpenophenolic compounds from the *Cannabis sativa* L. plant found predominantly in the glandular trichomes of female flowers [26], although cannabinoids can be present in all plant structures except for the seeds [27].

Despite their significance, plant classification remains a subject of controversy. Plant classification has been assesed using morphology, chimiotaxonomy, and genetics. However, hybridization of the

plant have complicated efforts to establish taxonomic distinctions among varieties. It has been even proposed that this hybridization jeopardizes the biodiversity of Cannabis [28]. While it is commonly accepted that cannabis comprises a single species (Table 1) with two subspecies: *Cannabis sativa*, *C. sativa* subsp. *sativa*, and *C. sativa* subsp. *Indica*; some propose classifying cannabis varieties as botanical varieties instead of subspecies [29] (Table 1).

Table 1: Cannabis sativa taxonomy[25].

Kingdom:	*Plantae* (plants)
Subkingdom:	*Tracheobionta* (vascular plants)
Superdivision:	*Spermatophyta* (seed plants)
Division:	*Magnoliophyta* (flowering plants)
Class:	*Magnoliopsida* (dicotyledons)
Subclass:	*Hamamelididae*
Order:	*Urticales*
Family:	*Cannabaceae*
Genus:	*Cannabis*
Species:	*Cannabis sativa*
Taxonomic Authority Abbreviation:	L.

Plant Constituents

The first scientific effort to elucidate the chemical composition of cannabis dates back approximately 160 years. The earliest publication in the literature describes the active compounds found in hashish (a marijuana preparation), published in 1857 in the Journal of Chemical Society (Vol. 21, No. 47) by T. and Smith. In 1964, Gaoni and Mechoulam reported the isolation, structural elucidation, and partial synthesis of an active compound of hashish known as Δ1-3,4-trans-tetrahidrocannabinol [3]. Presently, over 500 compounds produced by cannabis plants have been identified, with approximately 120 classified as cannabinoids [30]. The remaining compounds encompass terpenes, hydrocarbons, carbohydrates, related compounds, nitrogen compounds, non-cannabinoid phenols, fatty acids, flavonoids, simple acids, simple ketones, simple esters and lactones, simple aldehydes, proteins, enzymes, glycoproteins, steroids, simple alcohols, vitamins, and pigments. Phytocannabinoids, terpenes, and flavonoids are of particular interest due to their biological activity and therapeutic potential [2].

Phytocannabinoids

These constituents of the cannabis have been defined as a class of structurally homogenous monoterpenoids, indicative of Cannabis sativa L. [31]. Another definition refers to these as pharmacological ligands of the human cannabinoid receptors. Contrary to popular belief, these compounds are not exclusive to cannabis but are also the main studied source. Phytocannabinoids are also found in other flowering plants, such as hepatic (Marchantiophyta) and fungi [32]liverworts, and fungi that can be beneficial for the treatment of human ailments such as pain, anxiety, and cachexia. Targeted biosynthesis of cannabinoids with desirable properties requires identification of the underlying genes and their expression in a suitable heterologous host. We provide an overview of the structural classification of phytocannabinoids based on their decorated resorcinol core and the bioactivities of naturally occurring cannabinoids, and we review current knowledge of phytocannabinoid biosynthesis in Cannabis, Rhododendron, and Radula species. We also highlight the potential in planta roles of phytocannabinoids and the opportunity for synthetic biology approaches based on combinatorial biochemistry and protein engineering to produce cannabinoid derivatives with improved properties.","author":[{"dropping-particle":"","family":"Gülck","given":"Thies","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Møller","given":"Birger Lindberg","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Trends in Plant Science","id":"ITEM-1","issue":"10","issued":{"date-parts":[["2020"]]},"page":"985-1004","publisher":"The Authors","title":"Phytocannabinoids: Origins and Biosynthesis","type":"article-journal","volume":"25"},"uris":["http://www.mendeley.com/documents/?uuid=45b2041e-69b8-4419-a890-40f3ac83b209"]}],"mendeley":{"formattedCitation":"[32]","plainTextFormattedCitation":"[32]","previouslyFormattedCitation":"[32]"},"properties":{"noteIndex":0},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. For the purpose of this review, we focus solely on phytocannabinoids produced by *Cannabis sativa* L. Over the last decade, approximately 150 phytocannabinoids have been identified and isolated[33]. These were divided into 11 chemical classes (Table 2).

Table 2: Phytocannabinoid chemical classes[34].

Chemical Class
Δ9-trans-tetrahydrocannabinol (Δ9-THC)-type
Δ8-tetrahydrocannabinol (Δ8-THC)-type
Cannabinol (CBN)-type
Cannabidiol (CBD)-type
Cannabichromene (CBC)-type
Cannabigerol (CBG)-type
Cannabinodiol (CBND)-type
Cannabielsoin (CBE)-type
Cannabicyclol (CBL)-type
Cannabitriol (CBT)-type
Miscellaneous type

pCBs have garnered significant interest for the treatment of several pathologies. Tetrahydrocannabinol (THC) and Cannabidiol (CBD), for instance, have been extensively studied for conditions such as cancer, Parkinson's disease, Alzheimer's disease, and notably for CBD, and their use as a treatment for certain types of refractory epilepsy in children has been approved in some countries [10]. These and other cannabinoids have been studied for their potential therapeutic effects on disorders including anxiety, diabetes, immunomodulation, inflammatory bowel disease, nausea, neuroprotection, among others [19,35,36]including the Cannabis major psychoactive compound-Δ9-tetrahydrocannabinol (Δ9-THC. While research indicates the biological activity of other lesser-known pCBs, information on these compounds is often scarce. Evidence is growing for cannabinoids such as Δ^8-THC [37-39]hashish and marihuana, both derived from the Indian hemp Cannabis sativa L., have been used for their medicinal, as well as, their psychotropic effects. These effects are associated with the phytocannabinoids which are oxygen containing C21 aromatic hydrocarbons found in Cannabis sativa L. To date, over 120 phytocannabinoids have been isolated from Cannabis. For many years, it was assumed that the beneficial effects of the phytocannabinoids were mediated by the cannabinoid receptors, CB1 and CB2. However, today we know that the picture is much more complex, with the same phytocannabinoid acting at multiple targets. This contribution focuses on the molecular pharmacology of the phytocannabinoids, including Δ9-THC and CBD, from the prospective of the targets at which these important compounds act.","author":[{"dropping-particle":"","family":"Morales","given":"Paula","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Hurst","given":"Dow P.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Reggio","given":"Patricia H.","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Progress in the chemistry of organic natural products","id":"ITEM-1","issued":{"date-parts":[["2017"]]},"title":"Molecular Targets of the Phytocannabinoids: A Complex Picture","type":"article"},"uris":["http://www.mendeley.com/documents/?uuid=845feead-ee5d-41bf-9b89-e7908f138a5d"]},{"id":"ITEM-2","itemData":{"DOI":"10.1186/s42238-021-00115-8","ISSN":"2522-5782","abstract":"The most important discoveries in pharmacology, such as certain classes of analgesics or chemotherapeutics, started from natural extracts which have been found to have effects in traditional medicine. Cannabis, traditionally used in Asia for the treatment of pain, nausea, spasms, sleep, depression, and low appetite, is still a good candidate for the development of new compounds. If initially all attention was directed to the endocannabinoid system, recent studies suggest that many of the clinically proven effects are based on an intrinsic chain of mechanisms that do not necessarily involve only cannabinoid receptors. Recent research has shown that major phytocannabinoids and their derivatives also interact with non-cannabinoid receptors such as vanilloid receptor 1, transient receptor ankyrin 1 potential, peroxisome proliferator-activated receptor-gamma or glitazone receptor, G55 protein-coupled receptor, and nuclear receptor, producing pharmacological effects in diseases such as Alzheimer's, epilepsy, depression, neuropathic pain, cancer, and diabetes. Nonetheless, further studies are needed to elucidate the precise mechanisms of these compounds. Structure modulation of phytocannabinoids, in order to improve pharmacological effects, should not be limited to the exploration of cannabinoid receptors, and it should target other courses of action discovered through recent research.","author":[{"dropping-particle":"","family":"Kruger","given":"Jessica S.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Kruger","given":"Daniel J.","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Journal of Cannabis Research","id":"ITEM-2","issue":"1","issued":{"date-parts":[["2022","12","4"]]},"page":"4","title":"Delta-8-THC: Delta-9-THC's nicer younger sibling?","type":"article-journal","volume":"4"},"uris":["http://www.mendeley.com/documents/?uuid=d306da0b-bc0b-473d-8b30-dd00aa6c2220"]},{"id":"ITEM-3","itemData":{"DOI":"10.1186/s42238-021-00115-8","ISSN":"25225782","abstract":"Background: Products containing delta-8-THC became widely available in most of the USA following the 2018 Farm Bill and by late 2020 were core products of hemp processing companies, especially where delta-9-THC use

remained illegal or required medical authorization. Research on experiences with delta-8-THC is scarce, some state governments have prohibited it because of this lack of knowledge. Objective: We conducted an exploratory study addressing a broad range of issues regarding delta-8-THC to inform policy discussions and provide directions for future systematic research. Methods: We developed an online survey for delta-8-THC consumers, including qualities of delta-8-THC experiences, comparisons with delta-9-THC, and open-ended feedback. The survey included quantitative and qualitative aspects to provide a rich description and content for future hypothesis testing. Invitations to participate were distributed by a manufacturer of delta-8-THC products via social media accounts, email contact list, and the Delta8 Reddit.com discussion board. Participants (N = 521, CBG [11,40-42]apparently, are devoid of this, otherwise, ubiquitous system that provides homeostatic balance to the nervous and immune systems, as well as many other organ systems. The endocannabinoid system (ECS , and CBN [2,34,43,44] the use of Cannabis sativa L., commonly referred to as marijuana, for medicinal purposes has been reported for more than 5000 years. Marijuana use has been shown to create numerous health problems, and, consequently, the expanding use beyond medical purposes into recreational use (abuse but relatively limited for compounds like CBC, CBND, CBE, CBT, and CBL [25,30,34,37,40,45]. Notably, it has been proposed that the therapeutic effects of whole cannabis plant extracts may surpass those of individual isolated phytocannabinoids, with an association made between synergic activities among plant compounds. This phenomenon, termed the "Entourage Effect," encompasses both "intra-entourage", referring to the interactions between different phytocannabinoids within a specific strain, and "inter-entourage" where other secondary metabolites of the plant, primarily terpenes, are involved [31].

The Endocannabinoid System (SEC) and the Endocannabinoidome (eCBome)

Findings regarding cannabis active compounds sparked investigations into endogenous animal mediators with which they were able to interact, inducing the characteristic ''psychoactive'' effects of cannabis. This research, although sporadic, persisted following the publication of Gaoni and Mecholaum (1964). It wasn't until the 1990s that the first endogenous mediators began to be discovered. First in 1988, cannabinoid receptors on the plasma membrane were identified; followed by the cloning of receptors CB1 and CB2, respectively, both of which are orphan receptors bound to protein G. And lastly, the search for their natural ligands, termed "endocannabinoids," as they were named in 1995, some years after their discovery [5].

According to Di Marzo and Piscitelli [4], the Endocannabinoid System is defined as:

"The assembly of 1) two G-protein-coupled receptors and seven transmembrane dominions (RAPG) for THC - the cannabinoid type 1 receptor *(CB_1R)* and cannabinoid type 2 receptor (CB_2R); 2) its two most studied endogenous ligands, the "endocannabinoids" N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), and 3) the five enzymes once thought to be the only ones responsible for the biosynthesis of endocannabinoids [e.g. N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase α and β (DAGL), for anandamide and 2-AG, respectively) and their hydrolytic inactivation (e.g. fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), for anandamide and 2-AG, respectively]."

The authors then highlight three primary issues with this definition:

I. only Δ^9-THC and its less abundant congener Δ^9-THCV (tetrahydrocannabivarin) can bind with high affinity to receptors CB1 and CB2 compared with other phytocannabinoids. In addition, the term "cannabinoid receptors" should also include the rest of the proteins that frequently bind to cannabinoids;

II. The term "endocannabinoids" should not only include the endogenous ligands of receptors CB1 and CB2, but also the rest of the ligands able to interact with receptors with affinity to cannabinoids, referred to by the authors as "endocannabinoid-like mediators and

III. "Endocannabinoid enzymes" where all enzymes responsible for biosynthesis and inactivation of the rest of the mediators that would form the endocannabinoid list should be included.

Previously, the presence of ECS components has been documented across most animal kingdoms, ranging from primates to more primitive species such as cnidarians. *Hydra vulgaris*, considered the oldest phylogenetic organism with a primitive nervous system, posseses a putative endocannabinoid system composed of 2-AG, anandamide, and biosynthesis and catabolism enzymes (lacking genes for CB1 and CB2 receptors), which play a role in the animal's feeding response [46]. CB1 receptors and other components of ESC have been identified in vertebrates such as mammals, birds, reptiles, and fish, as well as in invertebrates such as sea urchins, leeches, mussels, and nematodes [47]. In arthropods, the presence of CB1/CB2 receptors has not been found, and it is believed that they are only found in invertebrate groups intimately related to vertebrates. However, the presence of endocannabinoid biosynthesis and inactivation enzymes has been identified, which could indicate the presence of an EC-like system in numerous invertebrate phyla [46]. Additionally, in invertebrates, like the fruit fly *Drosophila melanogaster*, transient receptor potential (TRP) channels have been identified. These ionic channels are well-preserved among numerous species [48] and show affinity for cannabinoid ligands [49].

The endocannabinoid system is widely distributed in mammalian tissues and has several important functions in central and peripheral tissues [50]. Under pathological conditions, it is believed to play a major role in homeostasis. On the contrary, an imbalance in the ECS can contribute to the onset of symptoms or disease development [19,20,51]cannabinoids, as components of the cannabinoid system (CS. Receptors CB1 and CB2 possess endogenous ligands which are not considered as classical endocannabinoids, and some authors consider other lipidic compounds derived from long chain polyunsaturated fatty acids (C18 or longer) within the classical concept of "endocannabinoids". Classical endocannabinoids are considered as promiscuous compounds. They not only interact with G protein-coupled receptors CB1 and CB2 but can also modulate the activity of other GPCRs, ion channels (e.g., some TRPs), PPAR nuclear receptors (peroxisome proliferator-activated receptors), and some non-receptor targets [52], among others (Table 3).

Table 3: Endocannabinoidome Receptors.

System	Receptor	Family or Superfamily	References
Endocannabinoid system. (ECS)	Cannabinoid Receptors (CBRs)	G-protein coupled receptors (GPCRs)	
	CB1		[53–56]
	CB2		[53–55, 57]
Enlarged endocannabinoid system or Endocannabinoidome. (eCBome)	Peroxisome proliferator activated receptors (PPARs)	Nuclear receptors (NRs)	
	PPARα		[14, 58–63]
	PPARβ/δ		[14, 58, 59, 62, 64, 65]
	PPARγ		[14, 58–60, 63, 64]
	PPARα		[14, 58–63]
	PPARβ/δ		[14, 58, 59, 62, 64, 65]
	PPARγ		[14, 58–60, 63, 64]
	Transient receptor potential channels (TRPs)	Ionotropic cannabinoid receptors	
	TRPV1, TRPV2, TRPV3, TRPV4 (vanilloid type)		[47, 49, 66–71]
	TRPM8 (melastatin type)	Ligand-gated ion channels (LGIC)	[34, 47, 49, 66–68, 71]
	TRPA1		[49, 66–71]

	(ankyrin type)		
	GlyR (Glycine receptors)	LGIC; Cys-loop	[37, 65, 72–77]
	$GABA_A$ (γ-amino butiric acid receptors)		[72–74, 78–80]
	5-HT receptors		[8,34,37,72–74,81–85]
	nAChR (Nicotinic acetylcholine receptors)		[72–74, 78, 86]
	Sodium channels NaV	Voltage-gated ion channels (VGIC)	[77, 87–91]
	Calcium channels CaV		[69,77,86–89,91–95]
	Potasium channels KV		[77, 86–90]
	Orphan receptors	G-protein coupled receptors (GPCRs)	
	GPR18, GPR55, GPR119		[2, 9, 37, 52, 54, 68, 69, 73, 78, 91, 96–102]
	GPR3, GPR6, GPR30, GPR35, GPR40, GPR41, GPR43, GPR23, GPR12,		[2, 9, 37, 47, 103]
	GPR72, GPR92, GPR120		

This broad vision of the endocannabinoid system has led to the recognition of numerous mediators that fall outside the classical definition of the ECS. Consequently, there is a growing consensus to refer this *-ome* of cannabinoid mediators as "Endocannabinoidome" (eCBome)'' or occasionally as the "Expanded Endocannabinoid System" [4,6-17]or endocannabinoidome, have both been implicated in diet-induced obesity and dysmetabolism. This study aims at identifying the potential interactions between these two fundamental systems—which form the gut microbiota-endocannabinoidome axis—and their involvement in the establishment of diet-induced obesity and related metabolic complications. We report here time- and segment-specific microbiome disturbances as well as modifications of intestinal and circulating endocannabinoidome mediators during high-fat, high-sucrose diet-induced glucose intolerance and subsequent obesity and hyperinsulinemia. This highlights the involvement of, and the interaction between, the gut microbiota and the endocannabinoidome during metabolic adaptation to high-fat and high-sucrose feeding. These results will help

identifying actionable gut microbiome members and/or endocannabinoidome mediators to improve metabolic health. The intestinal microbiota and the expanded endocannabinoid (eCB.

Endocannabinoid-like mediators have been defined as "mediators that belong to the same chemical class as the endocannabinoids (e.g., amides or long chain fatty acid esters) which are not necessarily metabolically related to anandamide or 2-AG and have protein receptors different to CB1R y CB2R" [4]. Endogenous ligands recognized as ''endocannabinoid-like mediators'' are members of the classes of N-acylethanolamines (NAEs), monoacylglycerols (MAGs), N-acyl amino acids (lipoamino acids or NAAAs), N-acyl dopamines, and N-acyl serotonins [17]. For instance, endocannabinoid-like mediators may exert an effect on eCBs and receptors by preventing their degradation by metabolic enzymes [47]. For example, the release of molecules, such as palmitoyl-ethanolamide (PEA) or oleoyl-ethanolamide (OEA), can enhance the activity of AEA by inhibiting enzymatic hydrolysis by FAAH, increasing the sensitivity of cannabinoids, other receptors, or other molecular mediators targeting anandamide by various mechanisms. Similarly, the release of other non-eCB 2-MAGs, such as 2-linoleyl glycerol and 2-palmitoylglycerol, can enhance the activity of 2-AG [104].

The ECS and the eCBome are involved involved in diverse physiological and pathological activities where cannabinoids and other treatments that aim to modulate this system could play promising and interesting roles. Stimulation of cannabinoid receptors CB1/CB2 by ligands like natural, endogenous, and synthetic cannabinoids lead to signaling events, including the inhibition of adenylyl cyclase, MAPK activation, and ionic channel activity modulation [54]. Physiological effects encompass a wide range of functions, from antinociception, cognition, memory, locomotive activity, endocrine function, temperature control, cardiac rhythm, vomiting and nausea, intraocular pressure, inflammation, immune recognition, and antitumor effects [55].

PPARs, a family of ligand-activated transcription factors, contain a range of endogenous lipid ligands [16]. They play an important role in homeostasis and energy metabolism, and their dysregulation is associated with a variety of metabolic diseases such as obesity and carcinogenesis [14]. Their modulation is of therapeutic importance in diseases associated with cancer, such as diabetes, obesity, dyslipidemia, and chronic inflammation and represents interesting targets for its prevention [64]. Studies have shown that part of the therapeutic and biological activity of cannabinoids are related to the activation of PPARα and PPARγ in diseases such various diseases including neurodegenerative disorders [103].

Transient receptor potential (TRP) channels belong to a superfamily of transmembrane ionic channels that serve as mediators of diverse physical and chemical stimuli, and they also play a role in cannabinoid activity [49]. The TRP family is composed of seven subfamilies with 27 channels in humans [71]. They are widely distributed in cells and tissues and are important for vision, touch, hearing, pain, and temperature sensation [66]. Functional failures of TRPs can result in neurological disorders, pain, inflammation, and respiratory disorders. Among TRPs, TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8 can be modulated by ligands (cannabinoids include), earning them them designation of 'ionotropic cannabinoid receptors'. Ligand activation induces a desensitization state, rendering the channel insensitive to subsequent stimuli [49]. It is proposed that through these channels, phytocannabinoids exert some of their biological and therapeutic activities in seizures [101], pain, and inflammatory disorders [34,49].

Therapeutic Perspectives

The understanding of the ESC and the eCBome offers diverse therapeutic perspectives, given their they role in numerous physiological and pathological activities. Cannabinoids, along with other treatments (e.g., enzyme inhibitors) could play an important and promising role. Several studies have reported that ESC play an important role in controlling, maintaining, and regulating homeostasis when disrupted. However, it has also been observed that under certain conditions, its normal function can be disrupted, contributing to the development of imbalance or disease. Because of the number of components of the endocannabinoidome that can be modulated, its study and manipulation have turned out to be of scientific interest for understanding and treating numerous diseases. Modulation of its most studied components is being analyzed as an alternative for the treatment of pathological conditions. Several approaches have been explored with variable results, including the administration of phytocannabinoids (isolated or in a group), synthetic cannabinoids or cannabimimetic analogs, inhibition of metabolic enzymes or other proteins, and the development of strategies to administer therapies using nanotechnology [19,20].

The development of synthetic cannabinoids and cannabimimetics has yielded drugs like nabilone, an FDA-approved synthetic cannabinoid for the treating chemotherapy-induced nausea and vomiting refractory to standard antiemetics. Other synthetic cannabinoids target various types of pain [105]. Synthetic cannabinoids have emerged because of the need to explore the endocannabinoid system and its potential to be modulated for the treatment of conditions such as neurodegenerative diseases, emesis, obesity, and cancer. Despite their therapeutic effects, synthetic cannabinoids can lead to adverse neurological effects [32], associated to the direct activation of CBRs. For example, CB1 activation can result in side effects such as hypomotility, hypothermia, catalepsy, sedation, hyperphagia, and drug dependence. Additionally, the anti-inflammatory and immunosuppressive benefits of CB2 activation in neurons are desired; however, its activation in T cells could only be slightly beneficial in pathogen- and cancer-related inflammation [20]. Another approach to modulate the endocannabinoidome involves enhancing endocannabinoid tone by selectively inhibiting endocannabinoid catabolic enzymes, primarily FAAH and MAGL, and by inhibiting endocannabinoid reuptake [19]. While promising, commercial treatments based on this strategy are lacking, with a reported failed clinical trial carried out in France, where an FAAH inhibitor was used in 90 of 128 subjects, resulting in four individuals with permanent brain damage and one deceased. The exact mechanism that led to this result was not determined, but it was speculated that it was due to both human error and off-target effects of the experimental drug [20,106]"id":"ITEM-1","issue":"3","is-

sued":{"date-parts":[["2016","9"]]},"page":"120-126","title":"What failed BIA 10-2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trials","type":"article","volume":"7"},"uris":["http://www.mendeley.com/documents/?uuid=e943b822-25e3-4c54-8f65-d0cda0ed0c21","http://www.mendeley.com/documents/?uuid=47833177-41ab-48d0-9b03-bb5bdb59a016"]},{"id":"ITEM-2","itemData":{"DOI":"10.3390/ijms232113223","ISSN":"14220067","PMID":"36362014","abstract":"Opportunities for developing innovative and intelligent drug delivery technologies by targeting the endocannabinoid system are becoming more apparent. This review provides an overview of strategies to develop targeted drug delivery using the endocannabinoid system (ECS.

As explained before, phytocannabinoids are multi-target compounds. In addition to modulating the activity of cell surface receptors/membrane receptors, such as GPCR, and intracellular transcription factors, such as PPARs. The ability of a ligand to bind to multiple targets (magic shotgun) instead of having high selectivity (magic bullet) is generally considered an undesired property [107]. The side effects of THC, including psychosis and impaired memory, and cognitive function, as well as poor short-term judgement, among others; deter patients from using plant extracts despite their possible benefits [20]. Nevertheless, "non-psychotropic" phytocannabinoids, such as CBD and CBG, show therapeutic potential with a broad safety margin, even when used at a high dosage for extended periods of time [41,108]this article focuses on clinical studies and CBD potential interactions with other drugs. Results: In general, the often described favorable safety profile of CBD in humans was confirmed and extended by the reviewed research. The majority of studies were performed for treatment of epilepsy and psychotic disorders. Here, the most commonly reported side effects were tiredness, diarrhea, and changes of appetite/weight. In comparison with other drugs, used for the treatment of these medical conditions, CBD has a better side effect profile. This could improve patients' compliance and adherence to treatment. CBD is often used as adjunct therapy. Therefore, more clinical research is warranted on CBD action on hepatic enzymes, drug transporters, and interactions with other drugs and to see if this mainly leads to positive or negative effects, for example, reducing the needed clobazam doses in epilepsy and therefore clobazam's side effects. Conclusion: This review also illustrates that some important toxicological parameters are yet to be studied, for example, if CBD has an effect on hormones. Additionally, more clinical trials with a greater number of participants and longer chronic CBD administration are still lacking.","author":[{"dropping-particle":"","family":"Iffland","given":"Kerstin","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Grotenhermen","given":"Franjo","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Cannabis and Cannabinoid Research","id":"ITEM-1","issue":"1","issued":{"date-parts":[["2017","1"]]},"page":"139-154","title":"An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies","type":"article-journal","volume":"2"},"uris":["http://www.mendeley.com/documents/?uuid=7aad2684-210d-4270-97ab-b001c9578ff6"]},{"id":"ITEM-2","itemData":{"DOI":"10.1007/s00213-016-4397-4","ISSN":"14322072","PMID":"27503475","abstract":"Rationale: The appetite-stimulating properties of cannabis are well documented and have been predominantly attributed to the hyperphagic activity of the psychoactive phytocannabinoid, Δ9-tetrahydrocannabinol (Δ9-THC.

However, important limitations in the use of phytocannabinoids as medical agents occur due to their physicochemical properties, such as low water solubility and stability. Phytocannabinoids break down in response to heat, light, and storage [109]. CBD is a good example. As it is a highly lipophilic compound, it is difficult to administer orally [110]and their clinical potential may be limited without adequate formulation strategies. Cannabidiol (CBD. Furthermore, it has low bioavailability and a variable pharmacokinetic profile. Because it is highly lipophilic, it is typically used in oily or alcoholic formulations, soft gel capsules, sublingual drops, and oro-mucosal sprays. Its high lipophilicity is responsible for its low absorption rate in the gastrointestinal tract owing to precipitation, and both CBD and THC have a high degree of first-pass metabolism. These properties contribute to the poor, erratic, and variable absorption profiles of phytocannabinoids. The encapsulation of fCBs in nanocarriers can protect them from degradation and improve their qualities [109].

Administration therapy strategies using nanotechnology are gaining popularity and being used in nanopharmaceutical development. These nanotechnology-based pharmaceutical systems can improve the properties of a drug, such as extending its circulation, location, and efficiency. Nanopharmaceuticals can take different shapes, such as polymeric, metallic, and magnetic nanoparticles; liposomes, carbon nanotubes, quantum dots, and dendrimers [111]. Nanotechnology has been used in a variety of nanocarriers for the delivery of highly lipophilic drugs, such as cannabinoids, which would allow an increase in solubility and bioavailability, in addition to reducing the required dose and off-target effects [20, 112]. Some of these studies have assessed the potential use of gold nanoparticles with cannabinoids to treat cancer [112], as well as nanoparticles with natural [113-116]usually by oral delivery. Animal studies suggest oral bioavailability is low, but literature in humans is not sufficient. The aim of this review was to collate published data in this area. Methods: A systematic search of PubMed and EMBASE (including MEDLINE or synthetic [117] cannabinoids, to evaluate and compare their pharmacological properties, their therapeutic potential, and key issues regarding applicability and safety.

Conclusion

Cannabis sativa L. has been cultivated by humans for thousands of years due to its broad range of applications. Evidence of its medical uses dates back to several ancient civilizations. Research into the active compounds of marijuana, or hashish, has led to the discovery of the animal endogenous system by which they interact, initially named the endocannabinoid system, and later extended to the endocannabinoidome. Once again, the development of cannabinoid therapies has become a focus of modern medicine. The Endocannabinoidome, and consequently the endocannabinoid system, is a crucial homeostatic system found widely throughout the animal kingdom, operating in numerous tissues. This system can promote homeostasis when imbalances occur. However, eCBome imbalances

can also contribute to disease progression.

Cultural acceptance and scientific advancements have enabled the study of the mechanisms of action of the endocannabinoidome in health and disease, leading to the development of therapies aimed at modulating it. However, these therapies have important advantages and disadvantages when a therapeutic strategy is pursued. The development of nano-pharmaceuticals is seen as a promising approach to enhance pharmacological properties of cannabinoids, such as improving solubility and bioavailability, offering a potentially efficient pathway forward.

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Conflict of Interest

The authors have declared that no competing interests exist.

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