The Endocannabinoid System

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The Endocannabinoid System (ECS) is primarily responsible for maintaining homeostasis, a balance in internal environment (temperature, mood, and immune system) and energy input and output in living, biological systems. In addition to regulating physiological processes, the ECS directly influences anxiety, feeding behaviour/appetite, emotional behaviour, depression, nervous functions, neurogenesis, neuroprotection, reward, cognition, learning, memory, pain sensation, fertility, pregnancy, and pre-and post-natal development. The ECS is also involved in several pathophysiological diseases such as cancer, cardiovascular diseases, and neurodegenerative diseases.

Keywords: Cannabis sativa L. ; endocannabinoid system ; cannabinoids ; phytocannabinoids ; endocannabinoids

1. Introduction

1.1. History

The Endocannabinoid System (ECS) is a complex molecular/biological system discovered in 1988 by scientists Allyn Howlett and W.A. Devane [1][2]. The word “Endocannabinoid” was first coined after the discovery of membrane receptors for Δ^9-tetrahydrocannabinol (Δ^9-THC or simply “THC”) in 1988 [3]. The ECS plays critical roles in multiple physiological processes such as homeostasis, anxiety, feeding behaviour/appetite, emotional behaviour, depression, nervous functions, neurogenesis, neuroprotection, reward, cognition, learning, memory, pain sensation, fertility, pregnancy, and pre-and post-natal development [4][5][6].

In recent years, there has been increasing interest in the role of the ECS in health and disease processes, and its components have been implicated as an emerging target of pharmacotherapy for a wide range of diseases including, but not limited to, general pain, headache, migraine, glaucoma, mood and anxiety disorders, obesity/metabolic syndrome, osteoporosis, neuromotor, neuropsychological and neurodegenerative diseases, respiratory diseases such as asthma, cardiovascular diseases such as stroke, atherosclerosis, myocardial infarction, metabolic disorders, arrhythmias, and hypertension [7][8][9].

Due to the involvement of the ECS in multiple pathophysiological processes, it offers promising opportunities for the development of novel cannabinoids-based therapeutic drugs that may be designed to target different components and/or cell-signalling pathways of the ECS, which may ultimately be of therapeutic benefit.

Cannabimimetic drugs such as small-molecule cannabinoid receptor agonists and antagonists may be designed to target the ECS and its enzymes and either enhance the bioactivity or activation of endocannabinoids or inhibit their inactivation [3][10]. On the same tangent, blockade of cannabinoid receptor-type 1 (CB_1R) has been shown to reduce body weight, activation of extracerebral cannabinoid receptors has been shown to alleviate pain, and inhibition of endocannabinoid degradation has been implicated in the modulation of pain and anxiety [11].

1.2. Components of the ECS

The ECS has increasingly become a favourable target for the treatment of various diseases as many of its components are distributed widely throughout the body and take part in cell-signalling pathways involved in the pathophysiology of many types of diseases.

The components (proteins) of the ECS include receptors, their ligands, and enzymes responsible for their biosynthesis and degradation/deactivation and are widely distributed throughout mammalian tissues and cells [12]. Components of the ECS include: (1) the three main receptor classes that cannabinoids interact with (i) G-Coupled Protein Receptors (GPCRs) (e.g., CB_1R and Cannabinoid-receptor type 1 (CB_2R)) and which share 44% overall homology [13], (ii) Ligand-sensitive ion channels (e.g., Transient Receptor Potential Vanilloid 1—TRPV1). TRPV1 is also activated by chemical agents, physical stimuli, capsaicin, and ions, and (iii) Nuclear receptors (e.g., PPARs) [14][15]; (2) the endogenous ligands

anandamide or N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG); and (3) the endocannabinoid metabolic enzymes responsible for endocannabinoid synthesis and degradation such as diacylglycerol lipase isozymes α and β, fatty acid amide hydrolase, monoacylglycerol lipase, and *N*-acylphosphatidylethanolamine-selective phospholipase D [3][16]. Refer to **Table 1** for components of the ECS.

Table 1. Components of the ECS and possible targets for the treatment of various diseases.

Endo-Cannabinoids ("Endogenous Cannabinoids"/ eCBs)	Enzymes		Receptors	Transport Proteins
	Synthesizing	Degradative		
- 2-AG [17] - AEA [17] - PEA [17] - OEA [17]	- DAGL (2-AG) [18] - NAPE-PLD (AEA) [19]	- FAAH (AEA) [19] - NAAA (AEA) [19] - ABHD6 and ABHD12 (2-AG) [18] - MAGL (2-AG) [18]	- CB_1R/CB_2R - (2-AG and AEA) - GPR18 [20] - GPR55 [21][22], - GPR119 [23], - TRPV1 (AEA) [24] - PPARγ [15]	- FABPs [25][26] - HSP70s [27] - Serum albumin [27] - FAAH-like AEA transporter (FLAT) [28] - AMT aka EMT [19][29][30].

2. The ECS as a Therapeutic Target

In recent years, genetic and pharmacological manipulation of the ECS has gained significant interest in medicine, research, and drug discovery and development. It's important physiological and pathophysiological roles offer promising opportunities for the development of novel cannabinergic, cannabimimetic, and cannabinoid-based therapeutic drugs that, genetically or pharmacologically, modulate the ECS via inhibition of metabolic pathways and/or agonism or antagonism of the receptors of the ECS. This modulation results in the differential expression/activity of the components of the ECS—beneficial in a number of diseases.

2.1. Mood and Anxiety Disorders

Anxiety is the body's natural survival response to harm or dangerous situations, and is characterized by increased responsiveness, defensiveness, and vigilance. Neuropsychiatric/anxiety-related disorders include Panic Disorder (PD), Social Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD), Post Traumatic Stress Disorder (PTSD), and Obsessive-Compulsive Disorder (OCD) [31]). Globally, these anxiety-related disorders are the most prevalent of any mental disorder. As a result, they are of great social and economic burden. Currently available anxiolytic and anti-depressant agents have limited response rates, limited tolerability, and unfavourable side-effect profiles, thus, cannabinoids may be promising novel alternative therapeutic agents to traditional anxiolytics and anti-depressants.

Activation of the cannabinoid 1 receptor (CB_1R) mediates natural rewards (such as social interaction, sexual intercourse, and delicious food) and drug rewards (desirable effects) [32]. As such, the CB_1R may be a promising, novel drug target for the treatment of mood and anxiety disorders. It is via this receptor that Δ^9-THC produces the desirable effects on an individual's mental health, however fleeting. The ECS also potentially modulates synaptic transmission of neurotransmitters, such as mesocorticolimbic dopamine, acetycholine, glutamate, opiate peptides, and GABA, which play significant roles in the control of our emotions and behaviours [33]. The CB_1R is densely populated in the brain, in areas responsible for the mediation of reward, such as the amygdala, hippocampus, and orbitofrontal cortex [34][35] and, thus, the ECS also plays a role in "emotional metastasis" [32][33]. On the same tangent, single nucleotide polymorphisms (a type of mutation) in the cannabinoid receptor 1 (CNR1) gene that that encodes the CB_1R has been linked to depression [36][37], nicotine dependence [38], alcohol dependence [39], and possibly other substance-use disorders that are the result of mood and anxiety disorders.

Cannabidiol (CBD) was first observed to be anxiolytic when it was shown to reverse Δ^9-THC's psychotic and anxiogenic effects, via a CB_1R-independent mechanism [40]. There is strong preclinical evidence that supports CBD's great potential as an anxiolytic, panicolytic, and anti-compulsive agent. Pre-clinical and animal studies have shown that CBD's activity decreased condition fear, mitigated the adverse effects of chronic stress, decreases autonomic arousal, prevents fear reconsolidation, and promotes fear extinction [31]. CBD is postulated to regulate fear and anxiety through interaction with the serotonin $5\text{-}HT_{1A}$, the TRPV-1 receptor, and, to a lesser extent, CB_1R [31]. CB_1R activation results in anxiolytic effects and plays a role in regulating/preventing fear and preventing chronic stress. CB_1R seems to mediate the anti-compulsive activity of CBD [31]. Activation of the serotonin $5\text{-}HT_{1A}$ receptor ($5\text{-}HT_{1A}R$) by CBD has been implicated in the regulation of fear and prevention chronic stress [31]. Another proposed mechanism of action by which CBD may produce anxiolytic effects is by upregulating hippocampal AEA, an endogenous cannabinoid with anxiolytic properties [41].

A 2011 preliminary study by Bergamaschi and colleagues investigated the effect of a single dose of CBD on subjects undertaking a simulation public speaking test (SPST). A total of 24 patients with Social Anxiety Disorder (SAD), who were never treated prior, received a single 600 mg dose of CBD before the SPS test. There was an improvement in speech performance, a reduction in anxiety, cognitive impairment, and alert anticipatory speech [42].

In murine models, CBD was able to reduce the depression induced by the Forced Swimming Test (FST), tests of conditioned fear, conflict tests, and restraint stress tests [31]. The mechanism of action is suggested to be by activation of the $5\text{-}HT_{1A}$ receptor. It has also been postulated that CBD increases brain-derived neurotropic factor (BDNF), thereby reducing depression [43]. The BDNF protein is responsible for neurogenesis (formation of nerve cells), and the growth, maintenance, and survival of nerve cells.

2.2. Pain Management

Pain is a symptom of many diseases. Both anecdotal and scientific evidence support the use of *C. sativa* L. and its secondary metabolite for overall pain management, and is effective even against chronic pain—both as a stand-alone drug and as an adjuvant, and there is record of the use of *C. sativa* L. in pain management in Chinese pharmacopoeia—some 5000 years ago.

More recently, the ECS has been implicated in the management of pain as cannabinoids have been shown to target components of the ECS [44] such as the CB_1R, CB_2R, non-CB_1R/CB_2R cannabinoid G protein-coupled receptor (GPCR) 55 (GPR55) [45], GPCR 18 (GPR18) aka *N*-arachidonoyl glycine (NAGly) receptor [46], opioid/serotonin (5-HT) receptors [47][48][49], TRPV1 [50][51], and PPARα and γ [15]. Additionally, it is notable that, in a murine model, the GPR55 receptor modulates the proinflammatory cytokines IL-4, IL-10, IFN gamma, and GM-CSF, thereby mitigating hyperalgesia [45].

Antagonists of CB_2R have been reported to demonstrate antinociceptive properties in models of inflammatory and nociceptive pain [52]. One mechanism of action is possibly by inhibition of AEA metabolism; another possibility is via modulation of peroxisome proliferator-activated receptor α agonists, TRPV1 antagonists, and/or α_2-adrenoceptor modulators [52]. In some cases, this is accomplished via activation of opioid system/enhancement of μ-opioid receptor agonists [52]. On the same tangent, cannabinoid and opioids, and cannabinoids and non-steroidal anti-inflammatory drugs (NSAIDs), have been shown to act synergistically [52]. Current evidence suggests that CBD, in particular, may have therapeutic benefits in treating Rheumatoid arthritis, Fibromyalgia, arthritis, chronic back pain, chronic abdominal pain due to surgery, and chronic pancreatitis, headache, and facial pain.

Studies in murine models of arthritic pain have also shown great promise [53]. In one animal model, cannabinoids were shown to inhibit neuropathic nociception caused by traumatic nerve injury, disease, and toxic insults [54]. In yet another animal model, cannabinoids demonstrated therapeutic efficacy against thermal pain, noxious pain, post-operative pain, cancer pain, and spinal cord injury-related pain [55]. On the same tangent, the endocannabinoid AEA demonstrated antinociceptive properties at the spinal level [50].

In general, *C. sativa* L., and its secondary metabolites thereof, may be a safer, non-addictive alternative to opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and most painkillers. This has contributed to CBD's growing popularity, particularly in professional sports and cancer-management. Furthermore, CBD is well-tolerated across wide dose ranges.

CBD could be particularly useful in cases where chronic cancer pain is refractory to treatment with traditional analgesics. A 2018 review article/meta-analysis by Vučković and colleagues explored scientific studies conducted between 1975 and March 2018 to examine CBD's therapeutic applicability in treating cancer-associated pain, fibromyalgia, and neuropathic pain, and concluded that the current scientific evidence supports the use medical cannabis in pain management [44]. There are many components to the many different types of pain. Vučković and colleagues, 2018, also postulate a number

of possible mechanisms of action of CBD-induced analgesia [44]. These include the reduction in inflammation, activation of some pain inhibition pathways, inhibition of neuropeptide and neurotransmitter release, and/or regulation of neuron excitability (particularly in the case of neuropathic pain).

In the present day, Nabiximols (Sativex®), a synthetic cannabinoid oromucosal spray, has been approved in some European countries and in Canada for the treatment of cancer-related pain. It is also used for spasticity and neuropathic pain in patients with Multiple Sclerosis.

Components of the ECS are also expressed in migraine-related structures [56] and, as such, the ECS may also be a target for the treatment of migraines. Refer to **Table 2** for a list of synthetic cannabinoids and their therapeutic window for pain.

Table 2. Synthetic cannabinoids and their therapeutic window for pain.

Synthetic Cannabinoids	Therapeutic Window	References
1.	**HU-308 and AM-124 (CB_2R agonists)**	**Pain and inflammation** [6]
2.	**Pyrimidinecarboxamide (and its derivatives) (CB_2R modulators)**	**Acute, chronic, and inflammatory pain** [6]
3.	**JWH-133 (intrathecal administration)**	**Reduction in post-operative hypersensitivity** [57]
4.	**Peripherally restricted CB_1R agonists**	**Chronic pain** [58]

2.3. Cannabinoids as an Alternative to Opioids

Opioid overdose (OOD) is a worldwide crisis, primarily due to over-prescription of opioids for the management of chronic pain, and also to the illicit drug market. Opioid overdose accounts for approximately 69,000 deaths worldwide, whereas some 15 million people are addicted [59].

An opioid (narcotic) is a class of drugs manufactured synthetically or from the opium plant. The mechanism of action is by binding to opioid receptors (G protein-coupled) located primarily in the central and peripheral nervous system and the gastrointestinal system. Ligands, the endogenous opioids that bind to said receptors, include endorphins, endomorphins, enkephalins, and dynorphins. These receptors mediate analgesia and nociception, and are typically used as pain relievers and anaesthetics. Other uses are to suppress diarrhoea and coughing, and to relieve shortness of breath. This class of drugs include heroin and synthetic opioids such as Fentanyl (Actiq®, Duragesic®, Fentora®, Abstral®, and Onsolis®), codeine, Hydrocodone (Hysingla® and Zohydro ER®), Hydrocodone/acetaminophen (Lorcet®, Lortab®, Norco®, and Vicodin®), Hydromorphone (Dilaudid® and Exalgo®), Meperidine (Demerol®), Methadone (Dolophine® and Methadose®), Morphine (Kadian®, MS Contin®, and Morphabond®), Oxycodone (OxyContin®, and Oxaydo®), Oxycodone and Acetaminophen (Percocet® and Roxicet®), and Oxycodone and naloxone. Fentanyl is 50 to 100 times more potent than morphine [60]. Side effects of opioid abuse include nausea, respiratory depression, sedation, euphoria, constipation, urinary retention, and itchiness. Side effects of opioid overdose include pinpoint pupils, drowsiness, cyanosis, slow breathing, loss of consciousness, and even death.

The analgesic effects of *C. sativa* L. and its secondary metabolites have made them promising tools in combatting the opioid crisis. This if further confirmed by the presence of cannabinoid receptors in peripheral, spinal, and supraspinal neurons associated with modulation of nociceptive signalling [61][62][63][64][65] and the implication of ECS in opiate dependence withdrawal [48]. In a sample of 4,840,562 persons, the legalization of medical cannabis directly correlated with lower chances of opioid use [66].

A preliminary cohort study reported a clinically and statistically significant relationship between enrolment in a New Mexico Medical Cannabis Program (MCP) and pain reduction, opioid prescription cessation (no prescription of opioid medication within the last 3 months), reduction in daily intravenous (IV) injection of opioid medications, reduced hospitalization due to prescription opioid medications (POMs) [67], reduced health care costs [67], and improvements of overall quality of life, social life, concentration, and activity levels [68]. A 41% opioid dose reduction (ODR) was also achieved using medical cannabis in cancer and rheumatological patients [69].

An association was also found between a reduction in opioid related deaths in Colorado and the legalization of recreational cannabis in Colorado (increasing access to medical cannabis via dispensaries) [70][71][72][73]. Another found a direct relationship between the implementation of medical cannabis access laws and the reduction in the probability a

provider prescribes any opioids net of any offsetting effects, the total number of patients receiving opioids and total days' supply of opioids prescribed [74]. Other studies suggest that the implementation of more flexible medical and adult-use marijuana laws may directly correlate with a reduction in opioid overdose death rates [75][76] and lower opioid prescribing rates (5.88% and 6.38% lower, respectively) [77].

A 2020 study by Blake explored the prescription rates of opioids in 19 states where medical cannabis is legal [78]. Results of this study show that, in these states, opioid prescriptions decreased. In another study, the decreased opioid use (in persons aged 18–55—Medicare/Medicade populations) was only associated with the implementation of a medical cannabis law (as opposed to a recreational cannabis law) [73][79]. On the same tangent, a 2019 study by Flexon and colleagues report no relationship between medicinal cannabis legislation and opioid misuse [80]. In another study, medical cannabis access and use directly correlated with and increased rate of cessation of injection of opioids [81]. Cannabis may also have a safer side-effect profile, lower abuse potential, and may even be used to treat some side effects of opioid use such as nausea [82].

At this point, it is suggested that cannabinoid-based analgesics may be used as an adjuvant, rather than an alternative form of therapy, and may even produce a synergistic result when used in combination with opioid analgesics [83][84][85]. A 2019 study by Capano and colleagues evaluated the effects of CBD hemp extract on opioid use and quality of life in a prospective cohort study in patients suffering from chronic pain. Patients given a CBD-rich extract were able to significantly improve their quality of life, and significantly reduce, or completely cease, the use of opioids [86]. No positive correlation between frequent cannabis use and frequent opioid use (whether illicit or prescribed) for pain was reported in this study.

On a different tangent, in contrast to opioids, the primary analgesic used to treat cancer-induced bone pain (CIBP) caused by malignant cancers such as breast cancer that tend to invade bone, peripherally restricted CB_1R agonists such as 4-{2-[-(1E)-1[(4-propylnaphthalen-1-yl)methylidene]-1H-inden-3-yl]ethyl}morpholine (PrNMI), have demonstrated significant alleviation of CIBP [87].

2.4. Inflammation

Inflammation may accompany many diseases, including many types of cancers, asthma, and autoimmune disorders such as rheumatoid arthritis, hepatitis, colitis, multiple sclerosis, and common dermatologic conditions. Cannabinoids, in general, are very potent anti-inflammatory agents. Endocannabinoids, such as AEA and 2-AG, and phytocannabinoids, such as Δ^9-THC and CBD, have demonstrated anti-inflammatory and immune-suppressive properties via CB_1R and CB_2R [88]. Cannabinoids have demonstrated the ability to downregulate cytokine and chemokine production and, in doing so, are able to suppress inflammatory responses [88]. As such, both endocannabinoids and phytocannabinoids may be promising tools in the treatment of inflammatory disorders.

It has been postulated that CBD binds to an adenosine A2A receptor, and decreases inflammation by way of inhibition of adenosine uptake. This has been confirmed in murine models. In another murine model, CBD was able to mitigate LPS-induced inflammation through said A2A receptors. CBD also had the same effect on inflammation in animal models for multiple sclerosis. In yet another murine model, CBD, by way of the TRPV-1 receptor, was able to reduce the levels of pro-inflammatory cytokines (eotaxin1, IL-2, IL-6, IL-12, IL-17, TNF-α, IFC-c, and MCP-1) [89]. AEA is also implicated in the treatment of inflammation [90].

It has also been postulated that CBD is a functional antagonist to the GPR55 receptor [91]. Via inhibition of GPR55 receptor activity, CBD may mediate levels of inflammation by controlling the release of pro-inflammatory cytokines IL-12 and TNF-α [92]. Additionally, by binding to and blocking the GPR55 receptor, CBD may exhibit analgesic effects in neuropathic pain, and anti-inflammatory activity in Inflammatory Bowel Disease [92].

CBD interacts with the PPAR-y receptor to mitigate beta-amyloid (Aβ)-induced neuroinflammation [92]. Through said receptor, CBD also promotes neurogenesis in the hippocampus. The anti-inflammatory actions of CBD were also reported in murine models of Type 1 Diabetic Cardiomyopathy, Pneumococcal meningitis, Colitis, Alzheimer's, and Inflammatory Bowel Syndrome [92]. In murine models, CBD also has the ability to decrease Reactive Oxygen Species (ROS), thereby inhibiting inflammation [92]. The extent to which these results in murine models may be applied to humans requires further study.

2.5. Cardiovascular Disorders

Studies have shown that cannabinoids, including CBD, have a cardioprotective role—preventing heart damage, reducing the risks thereof, and maintaining a “healthy” heart and vasculature [93]. Cannabinoids have also shown promise against arrhythmias, atherosclerosis, and stroke [94][95]. Studies also show that cannabinoids may lower the risk of cardiovascular diseases, heart attack (myocardial infarction), and injury as a result of reduced/restricted blood flow (ischaemia) [93]. CBD and other cannabinoids have also been shown to cause relaxation of the blood vessel walls (vasorelaxation) [93]. It is suggested that CBD decreases blood pressure, attenuates atherosclerosis, and increases the available nitric oxide by way of PPARγ antagonism [93]. Nitric oxide is a neurotransmitter and blood vessel relaxant, that improves blood circulation, reduces blood pressure, regulates heart rate, prevents clogged arteries, regulates contractility of the heart and vascular tone, prevents adhesion of cells to the endothelium, and prevents the formation of blood clots by inhibiting platelet activation. As an anxiolytic agent, CBD mitigates the cardiovascular response when we become anxious or stressed.

Proposed mechanisms of action by which CBD exerts its activity on the cardiovascular system are by TRPV channel activation, nuclear factor-kB (NFκB), and map kinase (MAPK) pathways [93]. AEA also activates TRPV1, and is implicated in the treatment of cardiovascular disorders [90]. Other cannabinoids may act by way of CB_1R activation. CBD is also shown to prevent hypotension by inducing arteriolar and venular vasodilation [93].

2.5.1. Diabetes

Diabetes is a metabolic disease characterized by high blood-sugar levels and is a significant risk factor for cardiovascular diseases (CVD) such as stroke, blood vessel disease, and coronary artery disease, as it damages the nerves and the blood vessels of the heart/cardiovascular system and possibly other organs, such as the eyes and kidney [96][97]. The hormone responsible for the regulation of blood glucose is insulin. In Type 1 diabetes, an autoimmune disease, the pancreatic cells that make insulin are attacked and destroyed by the individual’s own immune system. In Type 2 diabetes, the individual becomes resistant to insulin and, as a result, there is an accumulation of sugar in the blood [98].

Both CBD and Δ^9-tetrahydrocannabivarin (Δ^9-THCV) a non-psychoactive cannabinoid, have been shown to play a role in lipid and glucose metabolism in animal models, and may be opportunities for glycaemic control in the case of patients with type 2 diabetes mellitus (T2DM) [99]. The CB_1R has also been implicated as a therapeutic target for the treatment of T2DM, as the ECS has demonstrated a role in insulin resistance characteristic of T2DM [100]. Δ^9-THCV has been implicated in the clinical management of type 2 diabetes as it has demonstrated the ability to decrease appetite, up-regulate energy metabolism, and increase satiety [101].

CBD also seems to have therapeutic activity against endothelial dysfunction [93]. The endothelium is a layer of single-celled tissue which lines organs, in this case the heart. Endothelial dysfunction is characterized by inflammation, blood clotting (thrombosis), and impaired vasodilation. High glucose intake, as in cases of diabetes, is a cause of endothelial dysfunction. Another proposed mechanism of action of CBD on diabetes is through the upkeeping of the blood–retinal barrier. Disruption of the blood–retinal barrier is characteristic of diabetes [93].

2.5.2. Stroke

The wide distribution of the components of the ECS makes it a promising target in the treatment of CNS diseases/neurological disorders such as strokes [7]. A stroke is a type of cardiovascular disease that is characterized by brain damage and other possible signs and symptoms such as severe headache, loss of coordination, dizziness, confusion, blurred vision and even temporary blindness, slurred speech, and numbness/paralysis of face or limbs [102]. Strokes are the result of a lack of oxygen and nutrients to the brain due to interruption or restriction of blood supply to brain [102]. Types of strokes include: (1) ischemic stroke due to a blocked artery, and (2) haemorrhagic stroke due to a leaking or burst blood vessel [102].

Δ^9-THC has demonstrated positive effects on brain oxygenation and increased hemodynamic blood flow to the prefrontal cortex, and may possibly be beneficial in the treatment of (frontal lobe) strokes [103]. The anti-spastic properties of CBD may also be beneficial for patients with post-stroke spasticity [103].

In in vivo and in vitro animal models, CBD plays a neuroprotective role in the pathophysiology of ischaemic stroke–the most common type of stroke—characterized by blockage of blood vessels in the brain by blood clots. Studies show that CBD increases cerebral blood flow (CBF), thereby reducing the risk of ischaemic strokes [93]. HU-211 has also demonstrated therapeutic promise against CNS diseases [104].

Another proposed mechanism of action of CBD on CBF is through antagonism of the serotonin ($5HT_3$) receptor ($5\text{-}HT_{1A}R$) [93]. CBD facilitates $5\text{-}HT_{1A}R$ signalling in animal models. Yet, another proposed mechanism of action of CBD on strokes is through the upkeeping of the blood–brain barrier [93]. Disruption of the blood–brain barrier is one proposed cause of ischaemic stroke.

An increased infarct size is characteristic of heart attacks (myocardial infarction). Studies have shown that CBD reduces infarct size by reducing inflammation [93][105][106]. There is also evidence that CBD influences blood cell function, including promoting the survival and migration of white blood cells, mediating programmed cell deaths, and regulating platelet aggregation [93].

2.6. Cancer

Cannabinoids have demonstrated well established analgesic, antinauseant, antidepressant, antiemetic, anti-nociceptive, and orexigenic properties and, as a result, they have been studied and utilized in the treatment of cancer patients receiving chemotherapy or radiotherapy, and in AIDS/HIV patients [107][108][109][110]. In addition to the well-established palliative properties that Δ^9-THC and CBD exert on cancer-related symptomology, several phyto-, endo-, and synthetic cannabinoids all exert their anti-cancer properties via several different proposed mechanisms of action including, but not limited to: induction of apoptosis, autophagy and cell-cycle arrest, inhibition of cancer cell migration, metastasis, angiogenesis, neovascularization, adhesion, and/or invasion [111][112][113][114][115][116][117]. These properties are likely attributed to their role in endocannabinoid signalling pathways involved in cancer processes such as the MEK-extracellular signal-regulated kinase signalling cascade, and the adenylyl cyclase, cyclic AMP-protein kinase-A pathway [113][118]. Ultimately, the use of cannabinoids to target the ECS-signalling involved in the pathogenesis of these cancers, is a very promising target that is currently being given increasing attention in the medical landscape.

Multiple studies also confirm the direct correlation between the upregulation of said cannabinoid receptors, endocannabinoid metabolic enzymes, and endogenous ligands in cancerous tissue [119][120][121][122][123][124][125].]. Signalling between cancer cells is also shown to be mediated by cannabinoids [119]. One study suggests that the ECS may play a role in tumour suppression [126]. Multiple studies have also demonstrated the apoptotic, anti-metastatic, anti-angiogenic, anti-inflammatory properties of cannabinoid and non-cannabinoid secondary metabolites of *C. sativa* L. This suggests that cannabinoid-based therapeutics may be promising in the treatment of many different types of cancers, in addition to the aforementioned diseases.

Cannabinoids such as AEA, Met-F-AEA, 2-AG, Δ^9-THC, CBD, CBDA, HU120, WIN-552122, JWH-133, AME121, and R-(+)-MET have all demonstrated anti-cancer properties in various cancer models such as breast-, lung-, prostate-, testicular-, gastric-, skin-, colon-, bone cancers, and glioblastomas, lymphomas, leukaemias, and neuroblastomas. Mechanisms of action of these cannabinoids in these cancers range from induction of apoptosis and cell cycle arrest, inhibition of DNA synthesis, inhibition of various signalling pathways such as the PI3K/AKT/mTOR/AMPK or the EGF/EGFR, inhibition of angiogenesis, inhibition of tumour growth, tumour regression, and inhibition of metastasis.

3. Neurological/Neurodegenerative Diseases

Neurodegenerative diseases are characterized by inflammation and dysregulation of the function of neurons, and in some cases death, resulting from an ongoing/progressive degeneration of neurons [127]. This category of diseases includes amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, Huntington's, Batten disease, fatal familial insomnia, and, by some hypotheses, schizophrenia. These diseases are incurable, but cannabinoids have been shown to provide relief to some symptoms associated with said diseases. Cannabinoids are known to play a role in the modulation of inflammation (neuroinflammation), along with providing and enhancing neuroprotection [95][127][128]. In addition, cannabinoids such as CBD have shown analgesic, anxiolytic, and immunosuppressive properties that may help to combat certain neurological disorders [129].

Cannabinoids have been implicated in the modulation of adult neurogenesis in the hippocampus and the lateral ventricles [130][131]. Chronic treatment of the synthetic cannabinoid HU-210 has been shown to enhance the survival and proliferation of cells in murine models of hippocampal neurogenesis while exerting anxiolytic and anti-depressant properties [132]. Other synthetic cannabinoids, such as JWH-133, AM1241, JWH-056, AM251, WIN55,212-2, and URB597, have also demonstrated pro-neurogenic properties [130]. Neurogenesis is the process by which neural stem cells (NSCs) produce neurons (nerve cells). Neurogenesis in the hippocampus influences our capacity to learn and retain memory. Neuroplasticity is the brains capacity for synaptogenesis, which is the structural change/re-wiring of said connections between neurons. Studies show that schizophrenia and other psychiatric disorders physically alter the brain, as

characterized by a reduction in the volume of the hippocampus, along with other areas [40]. This is typically as a result of an inhibition of neurogenesis in the hippocampus.

In one study, prolonged CBD administration demonstrated a neuroprotective role against neuroanatomical alterations in the hippocampus, hippocampal volume loss, and even ameliorated brain damage [133]. In murine models, CBD promoted hippocampal neurogenesis, synaptic- and dendritic-remodelling, and prevented autophagy, neurogenic disruption, stress-induced anxiogenesis, THC-induced neurotoxicity, oxidative damage/ROS production, and neuronal damage [40].

Cannabinoids may also have potential in the treatment of mood instability associated with neurological disorders, as the ECS has been implicated in pathophysiology of neurological disorders [134]. Although some studies suggest that cannabinoids in general may be promising in the treatment of neurological disorders, others suggest a link between high consumption of recreational cannabis and an increased risk of mental health disorders such as substance dependence—though this is controversial [120][135]. This is, however, likely due to the presence of THC. Further studies are required to clearly elucidate the pro-neurogenic effects of CBD and other cannabinoids in humans.

Scientific evidence suggests that cannabinoids such as Δ^9-THC, CBD, WIN55212-2, and CP-55940 may be used to treat various forms of substance abuse such as heroin-, cocaine-, nicotine- and alcohol-abuse and their symptomologies thereof [136].

3.1. Schizophrenia

While some studies suggest that *C. sativa* L. use may increase the risk of developing psychotic disorders and even worsen prognosis and disease burden, likely due to psychoactive compounds [134][137], others suggest non-psychoactive compounds in the plant may have therapeutic efficacy.

The anti-psychotic, anti-inflammatory, and neuroprotective properties of CBD make it a safer, more tolerable, and promising alternative treatment for psychotic disorders such as schizophrenia [134][138][139]. Δ^9-tetrahydrocannabivarin (Δ^9-THCV) is another cannabinoid that has gained interest due to its anti-convulsant and non-psychoactive properties [134]. On this same tangent, whole-cannabis extract, or pure Δ^9-THC, on the other hand, may be less effective due to the psychoactive properties of Δ^9-THC and possibly other psychoactive cannabinoids present in the whole-cannabis extract mixture, and may even increase the risk of psychosis [140][141]. In some studies, CBD has demonstrated the ability to attenuate Δ^9-THC-induced psychotic symptoms in healthy patients and symptoms of schizophrenia in schizophrenics [139].

Both SR141716A and CBD have demonstrated antipsychotic properties in dopamine- and glutamate-based models of schizophrenia [142][143][144].

3.2. Epilepsy

Epilepsy is a neurological/central nervous system disorder that is characterized by frequency seizures. Multiple anecdotal and scientific evidence confirm the success of medical cannabis in reducing the frequency of seizure episodes with the use of CBD—this being after the end-of-the-road, i.e., failing therapy with traditional AEDs [145].

In recent years, there has been scientific interest in cannabinoid-based drugs for the treatment of epilepsy, particularly treatment-resistant epilepsy (TRE) and paediatric-onset drug-resistant epilepsy. Phytocannabinoids such as CBD, cannabigerol (CBG), cannabidavarin (CBDV), and Δ^9-THCV have demonstrated anti-convulsant properties and may be promising opportunities to develop safer alternatives (and even adjuncts) to traditional antiepileptic drugs (AEDs) [146][147][148]. Of these cannabinoids, Δ^9-THC and CBD have been given the most attention for their anti-convulsant properties [149]. CBD, in particular, is of particular interest as it has it circumvents the psychotropic effects resulting from the activation of CB_1R [150]. CBD has demonstrated efficacy as an adjunct treatment option in the clinical management of Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) as, in multiple studies, it has reduced the frequency of epileptic seizures [149][151][152][153][154][155].

Charlotte Figi, a SCNIA-confirmed Dravet syndrome patient, is the most famous cases of medical cannabis being used to treat epilepsy—likely as, at one point, she was the youngest medical marijuana patient, and this caused of a lot of controversy [156]. Charlotte Figi began having seizures at the age of 3 months [156]. By the age of 5 years, she was having up to 300 generalized chronic-tonic seizures (GCTs) seizures per week (50/day), and facing a failing therapy of a cocktail of antiepileptic drugs and a ketogenic diet [156]. She had to be fed through a tube, had motor impairment and cognitive delay and, as a result, had to be assisted with every activity.

Charlotte began receiving sublingual doses of *C. sativa* L. plant extract—starting with low doses (2 mg CBD/lb per day) and increasing up to 4 mg CBD/lb per day [156]. This extract, made from the Charlotte's Web strain, had 0.3% Δ^9-THC, sufficient to avoid psychosis, and high content of CBD. Twenty months later, Charlotte's seizures were reduced by 90% to 2–3 per month, and she could now walk, talk, and do activities unassisted [156]. Upon the success of her treatment with CBD, Charlotte no longer had to take the antiepileptic drug Clobazam®. The preparation also began to improve her autistic behaviour. A reduction in dosages of this preparation resulted in a return of seizures, clearly indicating that the preparation had therapeutic effects.

In 2018, Epidiolex® became the first and currently the only US Food and Drug Administration (FDA)-approved plant-derived CBD-based pharmaceutical preparation developed for the treatment of Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS).

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