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Cannabinoids As A Potential Therapeutic Agent: A Comprehensive Review

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Abstract

The discovery of cannabinoid receptors has aided in our knowledge of the endocannabinoid system and its constituents. Cannabinoid receptors (CB1 and CB2) cannabinoid receptors (anandamide and 2-arachidonoylglycerol) are endogenous agonists generated when arachidonic acid is conjugated with ethanolamine (anandamide) or glycerol, which serves as a lipid signalling mediator through cannabinoid receptors. The development of particular CB antagonists, inhibitors of eCB transport and metabolism, cannabinoid receptor impaired animals, and increased awareness of amidohydrolase has aided significantly in the subsequent research of the eCB system. Anxiety, depression, neuropathic pain, multiple sclerosis, neurodegenerative diseases, obesity, and cancer are just a few of the diseases that may benefit from excitatory cholinergic system modulation (eCB). This portion of the book will provide an in-depth examination of the signalling and metabolic pathways, physiological roles, therapeutic potential, and pharmacology of endocannabinoids.

Keywords: cannabinoids, nervous system, cancer, endocannabinoids

1. Introduction

Cannabis sativa (marijuana), a member of the Cannabinaceae family, has a long and illustrious history in traditional Chinese medicine dating all the way back to the sixth century B.C. It was originally utilised in nineteenth-century western medicine. Cannabis cultivation began in western Asia and Egypt and expanded to Europe and North America as the first source of textile fibres. Federal law imposes no prohibitions on the cultivation, use, or possession of marijuana in the United States. Numerous countries, including the United States, support cannabis decriminalisation for medical and recreational uses.

Cannabis sativa is a member of the Cannabiaceae family and is a dioecious species, which means that each plant contains distinct male and female flowers. The sticky resins secreted by glandular hairs on female flowers and adjacent leaves are usually thought to be responsible for cannabis' psychoactive

qualities. Numerous plant components have been demonstrated to have a crucial role in a variety of ailments, with THC (the most active element) being the most essential. Cannabis sativa seeds contain a fixed oil generated from hempseed, which is found naturally in the plant(1-3).

Among the ailments for which this plant may be used therapeutically are nausea, pain, glaucoma, neuralgia, cardiovascular problems, epilepsy, inflammation, cancer, cognitive dysfunction, neurodegenerative disorders, addiction, arthritis, depression, and headache. According to recently uncovered research, phytocannabinoids may help relieve symptoms of multiple sclerosis (MS) and HIV/AIDS.

The number of compounds extracted from the plant is steadily increasing; C. sativa has been reported to have 565 substances, about 120 of which are classified as cannabinoids. Cannabinoids are compounds that contain the C21 terpenophenolic ring or its derivatives/transformation products (CBs). CBs may be classified into two broad categories according on their location. The phytocannabinoids (pCBs) found in Cannabis sativa are referred to as phytocannabinoids (pCBs), whilst the endocannabinoids (ECBs) found in animals are referred to as endocannabinoids (ECBs) (eCBs). Phytocannabinoids are found in both the cannabis and cultivated hemp plants. Due to the lipophilic nature of CBs, it was formerly considered that medicine directly disrupts the cellular membrane. When phytocannabinoids were found, it was revealed that CB receptors were present. CBs bind to a specific receptor in the animal body to display their pharmacological actions(4-6). The terms cannabinoid 1 receptor (CB1R) and cannabinoid 2 receptor (CB2R) refer to receptors that bind to cannabinoids (CB2R). These cannabinoid receptors are G-protein-coupled receptors (GPCRs). Endocannabinoids are made up of lipid-based endogenous cannabimimetic neurotransmitters that link to the CB receptor and CB receptor protein in the neurological system" (both in CNS and PNS). The endocannabinoid system (eCS) is made up of eCBs and is critical for maintaining and restoring human health. Consumption of nutritional and dietary cofactors is required for the endocannabinoid system's development. Following their formation by the body, eCBs may bind to receptors and have an effect on the body's physiology. The two endocannabinoids found in the human body are N-arachidonoyl-ethanolamine (AEA; anandamide) and 2-arachidonoylglycerol (AG) (2-AG). Endogenous CBR agonists regulate the central and peripheral neural systems, affecting a broad variety of body activities(7, 8). Homeostasis is maintained by the eCBs. This indicates that alterations to the endocannabinoid system may result in a variety of illnesses ranging from neurological disease to rheumatoid arthritis. Enzymatic degradation of eCBs maintains the homeostatic balance. Despite this, anandamide binds to the CB1 receptor more strongly than tetrahydrocannabinol (THC). In comparison, 2-arachidonoylglycerol has a lesser affinity for both receptors but remains quite efficient. Due to their hydrophobic nature, eCBs diffuse more slowly. eCBs are degraded in the cell by oxidation or hydrolysis. Arachidonic acid and ethanolamine are generated when anandamide is hydrolyzed by fatty acid amide hydrolase, while 2-arachidonoylglycerol is hydrolyzed by monoacylglycerol lipase to create arachidonic acid and glycerol (MAGL). The eCBs are oxidised by cyclooxygenase-2 and a variety of lipoxygenases. Not only are the eCBs responsible for maintaining homeostasis, but also for healing and mending injured cells. Anxiety and sadness may be eased, as well as a variety of other maladies, including cancer prevention, nausea alleviation, and a variety of other health advantages. Additionally, the body has endogenous fatty acid derivatives, referred to as eCB-like compounds(9-11). When these compounds are present, the entourage effect has been found to boost the action of classical eCBs. Three other eCBs have been discovered: noladin ether (2-arachidonylglyceryl ether), arachidonoyl dopamine, and

virodhamine. As a result, it is currently impossible to identify their biochemical or pharmacological characteristics (Figure 1)(12, 13)

Figure 1: Cannabis sativa Plant.

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2. Cannabinoid receptors: signaling pathway and distribution

Cannabinoid receptors are members of the rhodopsin-like receptor family of G protein-coupled cell membrane receptors (GPCR). Two cannabinoid receptor subtypes, CB1 and CB2, have been found; both are negatively and positively coupled to the Gi or Go protein through adenylyl cyclase and mitogen-activated protein (MAP) kinase families. Additionally, the Gi/o proteins connect CB1 receptors to ion channels. When connected to A-type inwardly rectifier potassium channels, there is an identical positive coupling to potassium channels and a negative coupling to voltage-gated calcium channels of the N and P/Q kinds. CB1 via Gs is also expected to activate adenylate cyclase types II, IV, and VIII. Both receptors, which are presynaptically located, govern neurotransmitter release. The CB receptor seems to be responsible for activating the PI3K/AKT pathway. By stimulating the anandamide/CB/PI3K pathway, rodent brains protected against cocaine-induced neurodegeneration(14, 15).

CB1 is expressed presynaptically on peripheral and central nerve terminals, as well as in peripheral organs, while CB2 is expressed exclusively in the central nervous system. The cerebellum (motor control and cognitive function), the cerebral cortex (information processing and cognitive function), the hippocampus (short and long term memory), the hypothalamus (hormone release, metabolic process, and sexual orientation), the basal ganglia (voluntary movement control, learning, and emotion), the amygdala (memory of and emotions), and the nucleus accumbens (memory of and emotions), and the nucleus accumbens (nucleus accumbens). The placement of CB1 receptors in the central nervous system explains why (-)9-THC has such potent effects. These effects are shown in rats as catalepsy and hypokinesia, as well as enhanced food intake and analgesia(16, 17).

CB2 receptor expression is mostly seen in peripheral immune system cells. This gene transcript was discovered in the thymus, mast cells, spleen, and tonsils, as well as blood cells, where it modulates inflammatory and immunosuppressive activity as well as cytokine release (Figure 2)(18-20).

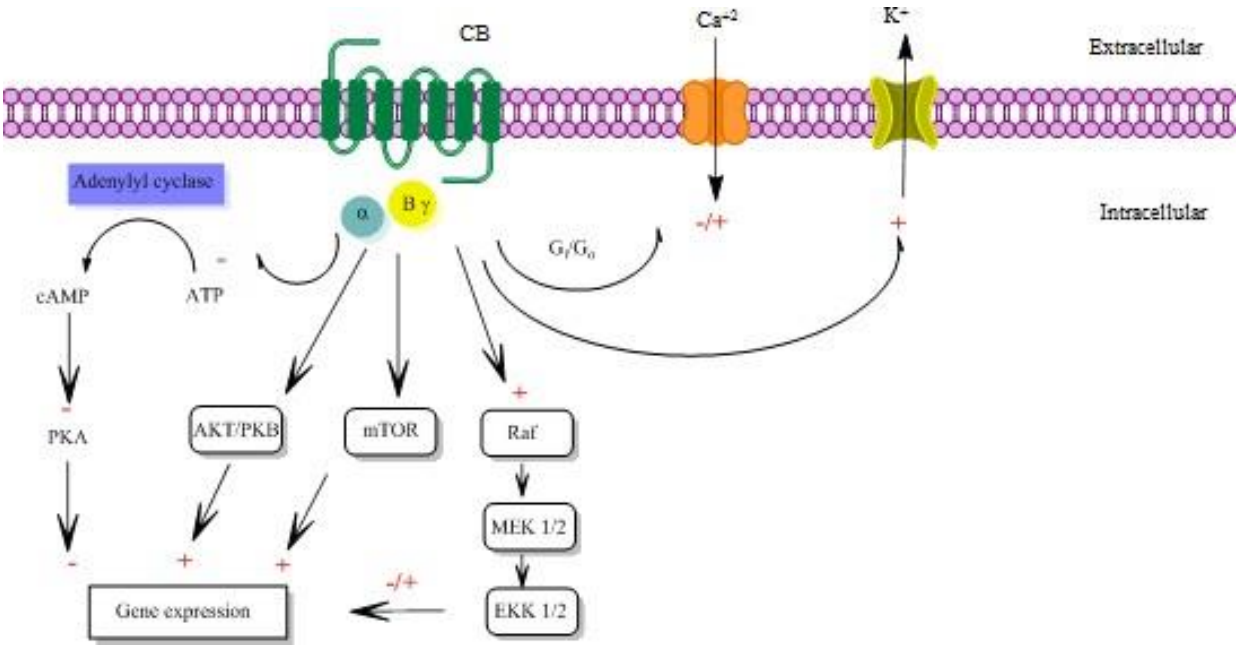

Figure 2. Cannabinoid receptor signalling. CB, Cannabinoid receptor ; mTOR, mechanistic target of rapamycin; Akt, protein kinase B; PI3K, Phosphatidylinositol-3-kinase; PKA, Protein kinase A; ERK, Extracellular signal-regulated kinase.

While this is true for a large number of organs and systems across the body, CB1 was detected in just a handful of these tissues. According to a research published in the journal Neuron, microglial cells, for example, possess CB2. According to the results, healthy individuals have less CB2 receptors in their cerebrum than those who have CB1 receptors. The CB2A transcript is predominant in the brain, whereas peripheral tissues such as the spleen, bones, heart, thymus, and kidneys, as well as immune cells such as macrophages, lineage thymus, tonsils, T lymphocytes, monocytes, natural killer cells, polymorphonuclear cells, and b lymphocytes, have higher levels of CB2A and CB2B transcripts. The fact that cannabinoid receptors are located in practically every system in the body explains why this chemical has such a broad therapeutic potential(21, 22).

It has been shown that humans, amphibians, and fish all have the CB1 receptor. On the other hand, cannabinoid CB2 receptors appear in a greater diversity of types. Bingham (2007) discovered that, despite the fact that all three are CB2 receptors, rat CB2, mouse CB2, and human CB2 receptors have unique pharmacological properties. Although rat and human CB2 receptors share 81 percent of their amino acid sequence, rodent and mouse CB2 receptors share 93 percent. Contrary to common assumption, pharmacological studies indicate that cannabis' effects may be mitigated by non-CB1 and non-CB2 receptors. Although this "CB3" receptor may exist in specific proteins, its presence is still debatable and has not been verified(23, 24).

3. Cannabinoid receptors agonist and antagonist

A. Endocannabinoids

Anandamide and 2-Arachidonoylglycerol have been extensively studied as endocannabinoid (eCB) candidates (2-AG). Anandamide was called after the sanskrit word for pleasure, Ananda, due to its amide bond in its structure. It was identified in pig brains and is the first putative endocannabinoid to be discovered.

Due to the fact that this ligand functions as a partial agonist on both CB1 and CB2 receptors, it has a higher affinity for CB1 than for CB2. Gonsiorek and associates demonstrated that anandamide, not arachidonic acid, reduced 2-AG activation of hCB2 in CHO-hCB2, indicating that anandamide may serve as a peripheral antagonist at cannabinoid receptors. According to this study, it is now more plausible that 2-AG or other cannabinoids exert immunosuppressive effects in vivo through anandamide and 2-AG concentrations in the nearby vicinity(25-27).

Following the discovery of anandamide, 2-AG was discovered as the second endogenous cannabinoid receptor ligand and shown a stronger affinity for the cannabinoid receptor CB1 than for the cannabinoid receptor CB2. The affinity of 2-AG and anandamide for hCB2 is similar. The endocannabinoid characteristics of other medicines have been verified. These include N-dihomo-linoleoylethanolamine, N-docosatetraenoylethanolamine, arachidonoylethanolamine (virodhamine), oleamide, N-arachidonoyl dopamine (NADA), arachidonoyl serine (ARA S), Noladin ether, and N-Oleoyl Dopamine (Figure 3)(28, 29).

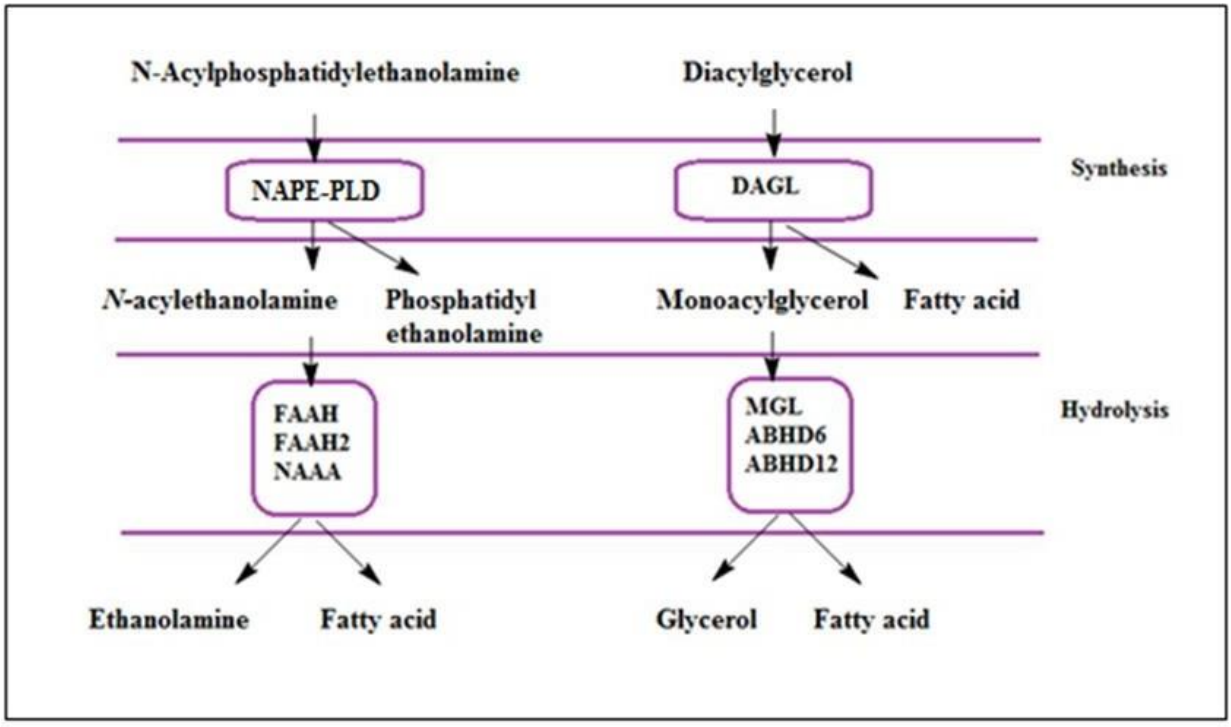

Figure 3. Schematic representation of the endocannabinoid synthesis and hydrolysis.DAGL, diacylglycerol lipase; NAPE-PLD, N-acylphosphatidylethanolamine phospholipase D; FAAH, fatty acid

amide hydrolase; NAAA, N-acylethanolamine-hydrolyzing acid amidase; MGL, monoacylglycerol lipase; ABHD6, α,β-hydrolase 6; ABHD12, α,β-hydrolase 12.

a. Biosynthesis of endocannabinoids

There have been two main forms of eCB discovered and extensively explored. Both 2 -AG and anandamide are bioactive lipids classified as monoacylglycerols and N-acylethanolamines.

When it comes to intercellular signalling, endocannabinoids do not need storage in vesicles since they are synthesised and used immediately. A stimulus-dependent process synthesises endocannabinoids on demand, activating cannabinoid receptors when they are required. Cannabinoids lose their effectiveness as soon as they enter cells, when they are degraded by enzymatic hydrolysis(30, 31).

Numerous ideas have been advanced on the synthesis of AEA from NAPE. The most extensively studied method is the one involving NAPE and phospholipase D (PLD). Despite this, two additional alternative routes have been proposed recently. In a second pathway, ABHD4 deacylates NAPE and cleaves glycerolphosphate to form anandamide. Phospholipase C hydrolysis of NAPE results in the formation of phosphoanandamide through the second pathway. The latter is dephosphorylated by the tyrosine phosphatases PTPN22 and SHIP1, and is then dephosphorylated by phosphatases such as SHIP1. In terms of AEA synthesis, the functional significance of these varied pathways has not been determined, but there is some certainty that the tissues in which it is produced may have an effect on its creation. The first stage in the production of 2-AG occurs when phosphatidylinositol is transformed to diacylglycerol (DAG) through PLC activity, and the second step involves the hydrolysis of 1-acyl-2-arachidonoylglycerol (DAG) by diacylglycerol(32, 33).

b. Hydrolysis of endocannabinoids

The hydrolase and oxygenase pathways are the most significant in terms of endocannabinoid metabolism. The hydrolytic dissociation of the amide bond that results in arachidonic acid and ethanolamine is mediated predominantly by fatty acid amide hydrolase (FAAH). Additionally, the FAAH2 and N-acylethanolamine-hydrolyzing acid amidase have been identified (NAAA). The major enzyme responsible for 2-AG hydrolysis is monoacylglycerol lipase (MGL). Two more 2-AG hydrolases, AbHD12 and Abhd6, have been found. Additionally, cyclooxygenase type-2 (COX-2) converts AEA to prostamides (prostaglandin-ethanolamides), while COX-2
converts 2-AG to prostaglandin glycerol esters(34, 35).

c. Pharmacodynamics of endocannabinoids

Anandamide and 2-AG are well-known endogenous agonists of CB receptors. Retrograde signs at the neuronal connection show that 2-AG is more physiologically significant than anandamide, which is a partial agonist for both the CB1 and CB2 receptors but has a higher affinity for the CB1 receptor. Calcium channel (N- and P/Q-type) blockade and potassium channel opening in the cell membrane are likely associated to synaptic discharge regulation for both eCBs that initiate biological activity through Gi/o G protein initiation (either restraint of glutamate or GABA). eCB has the ability to prolong the activities of cells by blocking adenyl cyclase and reducing cAMP or by activating MAP kinase pathways(36, 37).

d. Physiological role of endocannabinoids

The eCBrevolutionised the treatment of pain, obesity, neurological diseases such as multiple sclerosis, and other mental problems such as drug addiction. Motor control and tremor control, psychological capacity (such as learning and memory), thermogenesis, sleep/wake cycle regulation, adult neurogenesis, stress response via regulation of the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal pivot (HPG), and sexual behaviour, retinal neurotransmission from the retina to the primary visual cortex. Thermogenesis CB1 receptor agonists' anxiolytic effects on GABA, glutamate, acetate, and noradrenaline arrival have been widely established in a variety of preclinical and clinical investigations(38, 39).

e. Pharmacology of endocannabinoids

Indian experts identified both the therapeutic and hallucinogenic qualities of Cannabis sativa as long back as 4000 years ago. The eCB system is comprised of eCB receptors and ligands. Several research have investigated the use of CB receptor antagonists to treat obesity and to control eating behaviour, food intake, and energy metabolism. There was unquestionably insufficient proof of marijuana's widespread medicinal, religious, and recreational applications across all age groups to justify the meticulous and lengthy CB studies done until the late twentieth century. The majority of the endocannabinoid system's activities are associated with stress recovery and homeostasis maintenance, however there are several more. Endocannabinoids have a number of roles, including protecting the brain from oxidative stress, regulating motor activity, and regulating certain stages of the memory process. Additionally, it is related to the endocannabinoid system's function in balancing resistive and provocative reactions. It has an effect on the pulse, pressure, and bronchial capacity, as well as the cardiovascular and respiratory systems as a whole. It is well established that tumour cells are susceptible to the antiproliferative actions of endocannabinoids(40-42).

On this day in 1992, scientists found the first endogenous CB, also known as anandamide and abbreviated as AEA. This approach resulted in the discovery of 2-arachidonoyl glycerol (2-AG). Both are derived from arachidonic acid and bind to CB1 and CB2 receptors, but their binding affinities and initiating efficacies are significantly different. CB type-1 and type-2 receptors, as well as their endogenous ligands, have been proven to play a substantial role in the function of the eCB system through neuropsychopharmacology. The nerve centres, amygdaloid complex, hippocampus, mesencephalic structures (such as the substantia nigra), periaqueductal grey, superior colliculus, and inferior colliculus are responsible for fear and resistance responses. The substantia nigra pass reticulate circuit functions as a modulator circuit for anxiety and delirium. The eCB system in the brain has emerged as a key focus of stress-related research in recent years. Endocannabinoids have a profound effect on brain responses ranging from perception to suffering to fear and anxiety. The majority of research has been on N-arachidonoylethanolamide and 2-arachidonyl glycerol as possible eCBs for binding to CB receptors. CB receptor-1 and CB receptor-2 are two CB receptors with a similar signalling mechanism. CB receptor-2 regulates constrained restriction in the brain, as well as functions that are separate from those regulated by CB receptor-1(43-45). CB receptor-1 is associated with glutamatergic excitatory pathways as well as inhibitory GABA neurons. The CB receptor is referred to as a "cerebrum type" because it is concentrated in the cerebrum, while CB receptor-2 is distributed throughout the

body in immune and blood cells, as well as other organs. Numerous studies on striatonigral neurons and the nigrostriatal pathway have identified presynaptic CB receptors.

In well-evolved species, the ECS has the potential to influence a broad variety of physiological processes at both the central and peripheral levels. In any case, the ECS's involvement in skeletal muscle illness is unknown. 2-AG has been found to diminish muscle dimensions during myotube production in vitro from C2C12 myoblasts and mouse muscle development in vivo. As previously documented, stimulation of CB1 in primary human myoblasts with endogenous 2-AG or synthetic agonists such as arachidonoyl-2-chloroethylamide (ACEA) promotes cell proliferation while inhibiting myoblast separation. Rimonabant (SR141716) and AM251, two CB1 antagonists/reverse agonists, showed detrimental consequences. When CB1 is active, a typical G protein-coupled receptor signalling component, 4,5-bisphosphate hydrolysis, occurs. According to a limited number of studies, this suppresses the function of myogenesis-promoting voltage-gated potassium Kv7.4 channels. PIP2 hydrolysis is inhibited by protein Gq, resulting in the production of diacylglycerols and inositol trisphosphate. GPR55, a novel G protein-coupled receptor, binds CB ligands, indicating that this receptor may represent a novel site of CB activity. CB receptor-1 is one of the most abundant G-protein-coupled receptors identified in the human brain. Vesicles can store a variety of neurotransmitters, but not ECB(46-48).

As a result, the ability to modulate endocannabinoid signalling through their creation, release, absorption, and degradation is severely constrained. There are many possible triggers for the complex enzymatic machinery that results in the cleavage of membrane phospholipids and the formation of eCB, including layer depolarization, increased intracellular calcium, and receptor activation. The interaction of unique proteins with the formation of particular eCB demonstrates an independent inclusion of eCB under diverse conditions. Following synthesis, eCB may activate CB receptors by either discharging into the extracellular space or directly entering the cell membrane and activating the receptors. Flagging endocannabinoids is complicated by very effective breakdown processes such as enzymatic catabolism interleaved with intracellular compounds that promote endocannabinoid external absorption. The transporter protein(s) responsible for endocannabinoid absorption remain unknown at the molecular level. However, the compound's capacity to degrade eCB is widely documented. The enzymes FAAH and monoglycerollipase are responsible for the breakdown of anandamide and related eCBs, as well as 2-AG, although other substances may also be involved. The creation, activation, and breakdown of endocannabinoids are all intriguing elements of their action. According to this idea, there exist endocannabinoid frameworks that may act on the basis of interest, with a controlled spatial and temporal selectivity. The framework's modulatory operations are triggered only when they are required. Exogenous CB receptor agonists, which need such selectivity, have tremendously profited from this refinement of the endocannabinoid system's physiological characteristics(49, 50). The creation of eCB by glucocorticoids in the nerve centre may be activated by quick nongenomic pathways, which is interesting in terms of endocrine system management. As a follow-up research demonstrated, phospholipase C interacts with an intracellular signal transducer to initiate membrane depolarization and receptor activation in the hippocampus, activating eCBsignalling. We've learnt something about the endocannabinoid system as a result of these studies, which may be utilised to modulate other endocrine systems. Depletion of endocannabinoids has a significant effect on the mobility and control of endocannabinoids(51, 52).

B. Phytocannabinoids

Cannabis sativa contains both phytocannabinoids and non-phytocannabinoids, totaling more than 500 different compounds. During their investigation, they uncovered the following 11 distinct chemical types of phytocannabinoids: These include (–)-delta-9 trans-tetrahydrocannabinol, (–)-delta-8 trans-tetrahydrocannabinol (8-THC), cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG), and cannabinol (CBN). Additionally, cannabinoids of the cannabinoid type and cannabinoids of the terpene type are included. The term "miscellaneous cannabinoids" refers to cannabinoids with a variety of chemical structures and psychoactive properties. Since Ganoi and Mechoulam's 1964 discovery of 9-THC and later discovery of CBD by other researchers, these two cannabinoids have been assigned the psychoactive properties of cannabis. Since 2005, eight distinct chemical classes of non-cannabinoids have been found in cannabis: steroids, flavonoids, fatty acids, phenanthrenes, spiroindans, xanthones, biphenyls, and nitrogenous compounds(53, 54).

C. Examples of cannabinoids

a. Δ^9-tetrahydrocannabinol (THC)

Cannabis sativa is one of the most misunderstood substances in the world today, having been used by man in the past and continuing to be widely misunderstood. 9-THC, the major psychoactive component of cannabis, is a partial agonist for both CB1 and CB2 receptors. Gaoni and Mechoulam discovered and characterised 9-THC in 1964. It has a variety of effects, including an increase in desire, a reduction in sickness intensity, and a rise in intraocular tension, euphoria, and dyspnea. It has a rising number of adverse effects, including respiratory issues (tachycardia), chest discomfort (muscle jerks), severe renal failure (nodules), anxiousness (agitation), psychosis (self-destructive ideas), and intellectual impedance. Recently, it was shown that purified active molecules of 9-THC (dronabinol) are beneficial in the treatment of chronic pain, nausea, and vomiting associated with chemotherapy. Nabilone, a well-established commercial 9-THC, is used to relieve nausea and vomiting associated with chemotherapy.

b. Cannabidiol (CBD)

According to fresh data, CBD may be beneficial in the treatment of a number of neuropsychiatric disorders. Cannabidiol was shown to have no sedative effect in a mouse testing. Cannabidiol (CBD), the second most abundant component of cannabis, was shown to have a decreased risk of misuse(55).

c. GW405833

Depending on the kind of neurosis, different regions of the brain express varying levels of CB receptors, most notably the cerebrum's CB2 receptor. On the other hand, preclinical tests on the GW405833 sub-atomic molecule reveal that it acts as an agonist for the CB2R. A current research indicates that the CB2R agonist GW405833 protects liver cells and has a therapeutic effect by decreasing serum aminotransferase levels and inhibiting hepatocyte apoptosis in response to severe concanavalin A-induced toxicity(56).

d. URB597 ([3-(3-carbamoylphenyl) phenyl]-N-cyclohexylcarbamate)

URB597 is an FAAH inhibitor that inhibits the breakdown of anandamide, increasing its availability to the CB1 receptor for natural movement. Additionally, it has been shown that URB597 is beneficial in alleviating inflammation, nerve discomfort, and anxiety in people diagnosed with these illnesses(57).

D. CB Receptor Blockers

Numerous neuropsychiatric and weight-related disorders may benefit from medicines that disrupt regulatory signalling and modify endogenous eCB levels through CB receptor inhibition. As receptor blockers, Rimonabant, Taranabent, AM4113SR141716A, and SR144528 have all been widely researched.

a. Rimonabant and Taranabent

Both Rimonabant from Sanofi-Aventis and Taranabant from Merk pharmaceuticals suppress cannabinoid CB1 receptor activation induced by agonists, although Taranabant has a far higher affinity for cannabinoid CB1 receptors than Rimonabant.

It has been shown in some CB1 receptor-containing tissues that these mixtures may elicit responses that are diametrically opposed to those elicited by CB1 receptor agonists. Despite this, these combinations lack the capacity to activate CB1 receptors on their own. It has been claimed that it might be used to treat obesity by activating CB1 receptors in the central nervous system. Other probable components include activities on GIT receptors that may change appetite, or on fat tissue receptors that may alleviate metabolic confusions such as insulin resistance, coronary artery disease, and dyslipidemia, all of which are prevalent in the obese population. A recent research provided new data on Rimonabant's tumor-fighting capacity, suggesting that it may be a potential new treatment option for colorectal cancer. Rimonabant has also been researched clinically as a prospective treatment for a range of conditions, including diabetes, atherosclerosis, and smoking cessation. Rimonabant (20 mg/day) was shown to produce an increased number of mental adverse effects, such as sorrow and anxiety, in exploratory trials conducted by the US Food and Drug Administration. Additionally, two suicides among Rimonabant patients have been documented. Sicknesses and infections of the upper respiratory tract were the most common negative effects (over 10% of people); gastroenteritis, stress, sleep disorders, heaviness and dry or itchy skin, tendonitis and muscle issues, fatigue and flu-like symptoms, as well as an increased risk of falling, were the most common negative effects (between 1% and 10% of people)(58, 59).

The drug was never licenced in the United States for obesity treatment. Rimonabant's marketing has been restricted by European regulatory authorities since 2009.

E. Therapeutic Potential of Targeting cannabinoid receptors

The unwanted psychoactive effects of cannabis agonists are a concern when used medicinally. On the other hand, activating CB2 receptors has no psychotropic side effects such as hypolocomotion or catalepsy. Drugs that activate CB2 receptors at low or no activation of CB1 receptors are now being investigated as a technique of doing this. Given the overwhelming evidence that CB1 activation, rather than CB2 activation, is responsible for the adverse effects produced by CB1/CB2 receptor agonists, this technique seems to be attractive. This indicates that selective CB2 agonists may have significant

therapeutic advantages. For instance, agonists targeting the CB2 receptor have been proposed for a wide range of medical conditions(60, 61).

a. Pain

CB2 receptor-targeting medicines have been proposed for a number of painful conditions. This category of illness includes acute pain, nociceptive pain, neuropathic pain, and chronic inflammatory pain. All animal models of neuropathic pain, including partial sciatic nerve ligation, spinal nerve ligation, and chemotherapy-induced neuropathy, reacted well to analgesics including CB2 agonists. Cannabis was also shown to have analgesic properties in a range of chronic inflammatory pain models, including carrageenan, capsaicin, the complete Freund's adjuvant, formalin, and arachidonic acid. Cannabis works by decreasing the sensitivity of the transient receptor potential channel vanilloid 1 (TRPV1) to painful stimuli. Additionally, suppression of NF-B activity and microglial production of IL-1, IL-6, and TNF- are possible causes.

Cannabis is not more effective than codeine in treating pain, and the risks associated with its use outweigh the benefits due to its depressive effects, according to some qualitative systematic studies.

b. Metabolic disorders

According to one idea, CB1 receptors decrease POMC neurons, which are involved in the sense of fullness and create beta-endorphins, in mice exposed to marijuana. According to the first human experiment on the effects of cannabis on appetite, there was a reported increase in food intake after the use of Cannabis in 1971. Additionally, another study discovered that oral 9-THC doses of up to 15 mg/day enhanced appetite and led in significant weight gain in advanced cancer patients. Further study established unequivocally that smoking cannabis results in a large increase in calorie intake. The CB1 receptor, MAGL, and FAAH have been identified in the human pancreas, and it has been proven that CB1 suppresses -cell proliferation by interfering with insulin synthesis. CB1 receptor blockade increases -cell mass and improves insulin sensitivity in diabetic mice. Additionally, cannabinoids have been implicated in the development of diabetic neuropathy, retinopathy, and nephropathy.

Activating CB2 receptors resulted in a rise in insulin resistance and fatty liver in rats missing CB2 receptors, indicating that suppressing CB2 may be beneficial in treating insulin resistance and fatty liver.

c. Asthma

According to a number of studies, asthmatics may benefit by targeting cannabinoid receptors. Cannabinoids' immunosuppressive, anti-inflammatory, and bronchodilator effects are widely known. According to the results, cannabinoids suppressed mast cells and eosinophils in lung tissue and decreased the levels of cytokines involved in the immune response to an allergen in vivo models. Cannabis was also demonstrated to be bactericidal against Staphylococci and Streptococci in broth. CB2 receptors inhibit the production of cytokines by natural killer cells in an asthma murine model.

Unlike opiates, cannabis smoke did not promote cerebral respiratory depression in humans, although cigarette smoke did. Another study discovered that aerosolized doses of THC induced bronchodilation, as seen by enhanced lung function(62).

d. Glaucoma

According to study, marijuana's neuroprotective and vasorelaxant properties may help lower intraocular pressure. By increasing p42/44 MAP kinase activity, stimulation of the CB2 receptor increased aqueous humour outflow in cultured porcine trabecular meshwork cells. The American Glaucoma Society promotes cannabinoids, which are produced from the cannabis plant, for lowering eye pressure and minimising the risk of optic nerve damage(63).

e. Autoimmune diseases

Cannabis has been shown to have immunosuppressive properties, suggesting that it may be beneficial in the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. By increasing the quantities of anti-inflammatory mediators while decreasing the levels of pro-inflammatory cytokines, the immunological balance may be altered. THC's ability to alter epigenetic regulation via histone modification has been recently linked to its immunomodulatory effect.

When cannabis was utilised in animal experiments, there was a significant decrease in beta cell damage in autoimmune diabetes. As a consequence, normoglycemia is preserved. Additionally, as previously noted, cannabinoids have been found to decrease inflammation in rheumatoid arthritis and to prevent neurodegeneration in multiple sclerosis. Cannabis has been demonstrated to aid patients with Crohn's disease, fibromyalgia, and multiple sclerosis in clinical studies. According to this research, cannabinoids exert immunosuppressive effects without eliciting psychotropic effects by adversely modulating the cAMP signalling pathway, resulting in decreased cAMP response element-binding protein (CREB)-mediated gene expression(64).

f. Bone diseases

Due to the fact that osteoblasts, osteoclasts, and osteocytes all express CB receptors, several studies have connected marijuana use to an increased risk of osteoporosis. Human postmenopausal osteoporosis has been related to bone density and a variation in the gene encoding the CB2 receptor, and stimulation of CB2 inhibits osteoclast formation. Cannabis has been demonstrated in vivo to aid in the healing of fractures and reduce the progression of arthritis.

g. cardiovascular disease coronary artery

CBD has been proven to have anti-arrhythmic, vasodilator, antioxidant, and anti-inflammatory activities in both animal and human study. Acute THC administration prior to ischemia also shown cardioprotective effects by minimising myocardial damage.

CB2 receptor activation has been found to minimise myocardial infarct size after I/R injury by decreasing apoptosis and increasing Akt activity(65).

h. Gastrointestinal disorders

Because prior studies established that THC and its analogues were useful in treating chemotherapy-induced nausea and vomiting, nausea and vomiting are the most often used indications for cannabis. Chronic cannabis use has been associated with a number of uncommon but dangerous adverse effects, including cannabinoid hyperemesis syndrome. It has been shown that activating CB1 receptors decreases both stomach acid production and intestinal secretion.

CB2 receptors have also been demonstrated to have a role in regulating intestinal inflammation by inhibiting the production of proinflammatory cytokines. By targeting cannabinoid receptors, it has been demonstrated to be effective in a variety of conditions, including stomach ulcers, GERD (gastro-esophageal reflux disease), IBS, Crohn's disease, and hepatitis C(66).

i. Anxiety and mood disorders

Numerous studies have advised the use of CB2 agonists in the treatment of bipolar disease, personality disorders, and drug addiction. According to recent studies, cannabinoids may also aid with the symptoms of post-traumatic stress disorder. CB2 receptors have been demonstrated to impact dopamine activity in the midbrain and ventral tegmental area, which is necessary for both rewarding behaviour and addiction.

j. Nervous system disorders

The disadvantage in medication development is that CB1 receptor agonists might cause mental adverse effects. On the other hand, hypolocomotion and catalepsy are not related with CB2 receptor activation. Due to the minimal number of CB2 receptors found in the brain, addressing these receptors may be useful in treating neuroinflammatory and neurodegenerative disorders. Examples of this kind include inflammatory peripheral disorders, Parkinson's disease, amyotrophic lateral sclerosis, and other neurodegenerative diseases. Minocycline-induced neuroprotection against edoema, microglial activation, and neurological impairment after traumatic brain injury (TBI) in mice has been shown to include the endocannabinoid system.

Parkinson's disease patients exhibit a reduction in CB2 receptors. Thus, activating CB2 receptors has been hypothesised to decrease the progression of the sickness(67).

THC has been demonstrated to reduce hyperactivity in patients with ADHD due to its affinity for CB1 receptors and the resulting improvement of retrograde signalling inhibition at brain synapses. In a scientific research conducted in Germany, patients with attention deficit hyperactivity disorder (ADHD) were able to improve their cognitive capacities with the use of THC and CBD. According to a new research, inhibiting mTOR signalling may be a viable therapeutic option for autism spectrum disorders since it suppresses autophagy, which results in autistic-like behaviours.

k. Cancers

Cannabis has been proven in preclinical studies to have anticancer, proliferative, and proapoptotic effects in vitro and in vivo against a variety of different types of cancers. Among the illnesses connected with the brain include glioblastoma, glioma, pancreatic cancer, oral cancer, breast cancer, prostate cancer, lung cancer, blood cancer, liver cancer, colorectal cancer, thyroid cancer, ovarian cancer, cervical cancer, gastric cancer, and skin cancer.

Cannabis may promote apoptosis and autophagy in breast cancer cells by downregulating the Id-1 gene and boosting the generation of reactive oxygen species. Cannabinoids and phytocannabidiols, as well as synthetic and endogenous ligands, have been demonstrated to inhibit tumour growth in a range of breast cancer cell lines, both hormone-dependent and hormone-independent. On the anticancer front, this involves inducing apoptosis (cell death) by blocking pro-caspase-3 cleavage into caspase-3 and cell

cycle progression, lowering pro-angiogenic factors (VEGF), and suppressing angiogenesis (cell proliferation).

Two critical advantages of cannabis in cancer treatment are its selectivity and cytotoxicity to normal cells. This is despite the fact that comparable effects have been seen in cultured cells derived from human, mouse, and rat tumour models. Cannabis' effectiveness and safety in cancer patients must be established via clinical study(68).

Cannabinoids and the hazards associated with their abuse.

According to the National Institute on Drug Abuse, marijuana (cannabis) is the most extensively used illicit drug. Psychological effects are one of the key concerns associated with cannabis use. According to Moreau's earlier clinical studies on marijuana's effects, chronic usage results in personality changes and hallucinations.

CB1 has been implicated in the subjective effects of marijuana use. Cannabinoids may have a variety of effects depending on the product, its route of administration, dose form, duration of usage, and drug-cannabis interaction, as well as its pharmacokinetics and pharmacogenetic characteristics. Marijuana's short-term, dose-dependent effects may have physiological and psychological consequences on the body. Cannabis use, even at low doses, may impair coordination, induce dizziness, agitation, and memory loss, as well as tachycardia and a spike in blood pressure. Large doses, on the other hand, may result in anxiety, visual hallucinations, paranoia, and sensory distortion. THC, cannabis's primary psychoactive component, is responsible for these effects. CBD (cannabidiol), the nonpsychoactive component of cannabis, has the opposite effect: it is anti-anxiety, anti-psychotic, neuroprotective, and bradycardic(56).

Cannabis has a long half-life due to its lipophilic and protein-bound nature, and THC retention may last several days to several weeks depending on the amount consumed and the mode of administration. As a result, rapid cannabis withdrawal is often acceptable. The withdrawal syndrome associated with marijuana use often starts within 48 hours after cessation and may last up to two weeks. It manifests itself via longing, fury, aggression, and irritability, as well as through tiredness, worry, and shakiness. Cannabis use's safety and efficacy must yet be shown via substantial clinical study(48).

Conclusion

The endocannabinoid system has been the topic of intensive research over the past three decades, revealing what is perhaps the most significant retrograde neurotransmission channel yet found. CB1R has garnered considerable interest in recent years due to its involvement in THC's psychotropic effects. Its widespread expression and diverse range of activities not only contribute to its intriguing potential as a therapy target for a broad variety of illnesses, but also virtually exclude unwanted reactions. Due to this issue, CB2R and other endo/phytocannabinoids have been disregarded for a lengthy period of time. Crosstalk between the endocannabinoid and other synaptic systems has also been promoted as a neuromodulator through neighbouring neural circuits, receptor heteromerization, or a downstream pathway. Successful study has shown the intricacy of the whole endocannabinoid system. It is critical to remember that research on the endocannabinoid system should include other neurotransmission systems, as well as geographic locations and situations.Although cannabis has been around for over 5,000 years, anecdotal evidence shows that marijuana may aid in the treatment of a variety of human

disorders. Numerous therapeutic conditions for which cannabis may or may not be useful are unknown at the moment. The majority of data is derived from case reports and small retrospective investigations, rather than from randomised controlled trials. Numerous cannabis products, doses, and delivery techniques make it difficult to draw conclusions from study.

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