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Review Article

Neurological and Health Benefits of Cannabidiol (CBD)

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Abstract

The differences between the hemp and cannabis plants are briefly described together with the biosynthesis of THC and CBD by the two plants and their chemical make-ups. The bioactivity of CBD oil, notably its importance in pain relief, dermatology and neurology, is reviewed. The mechanisms involved in the bioactivity of CBD are discussed in relation to its interaction with the endocannabinoid system and its three major components, namely endocannabinoid receptors, endocannabinoids and enzymes.

Keywords: Cannabidiol (CBD); *Cannabis sativa L; Dermatology and Neurology*

Introduction

The hemp plant, *Cannabis sativa L.* [1], is commonly confused with what is known as the marijuana (cannabis) plant because they belong to the same genus although the two plants are quite different. The generally accepted nomenclature that distinguishes between the two most common varieties of *Cannabis sativa* are *sativas* and *indicas*. Sativas have long thin leaves, grow best in humid climates, and have a slow growth cycle whereas indicas have short, fat leaves, grow best in mild climates, and have a fast growth cycle.

The hemp plant will only be a sativa whereas the cannabis plant can be a sativa, indica or a hybrid, the latter being a mixture of the two. The greatest difference between sativas and indicas is their levels of the psychoactive drug Δ^9-THC (Delta-nine-tetrahydrocannabinol). Hemp usually contains ≤ 0.3% whereas marijuana contains ≥ 16% THC. In this review, and in concert with common parlance in blogs and the popular media, Δ^9-tetrahydrocannabinol will be referred to simply as THC for convenience.

The biosynthetic pathways of sativas and indicas are initially the same up to the formation of cannabigerolic acid (CBGA) but then diverge (Figure 1) [2]. Enzymatic action converts CBGA into tetrahydrocannabinolic acid (THCA) within the cannabis plant whereas hemp produces cannabidiolic acid (CBDA). Thereafter, when heated, these two acids decarboxylate to form Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) respectively.

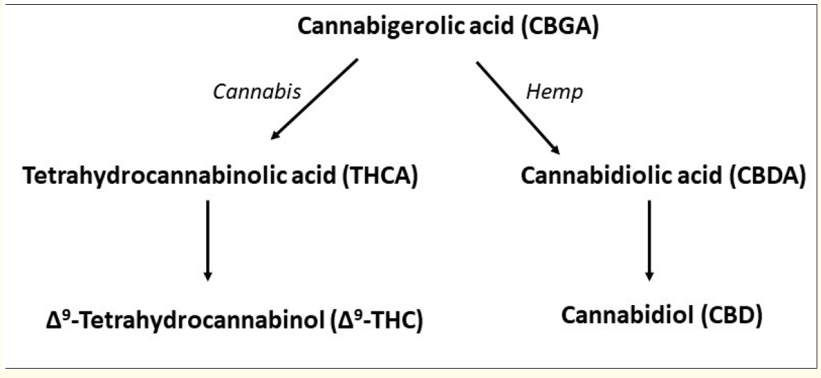

Figure 1: *Biosynthesis of THC and CBD.*

Whereas Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have quite similar chemical structures (Figure 2a and 2b), THC (and therefore marijuana) is a federally listed Schedule I drug under the Controlled Substances Act in the U.S.A., but CBD is legal and not a Schedule I drug.

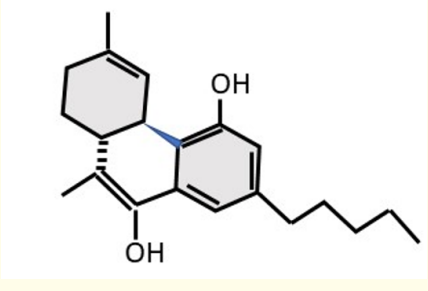

Figure 2a: *Chemical structure of cannabidiol (CBD).*

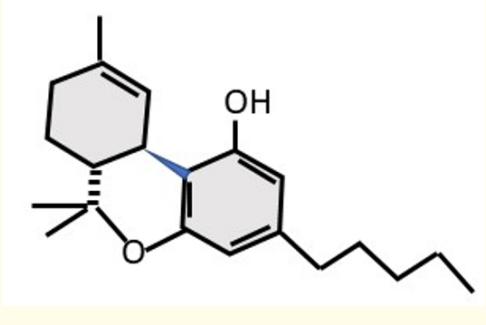

Figure 2b: *Chemical structure of Δ9-tetrahydrocannabinol (THC).*

Cannabidiol, commonly known as CBD, is the most abundant of about 113 cannabinoids[1] found in hemp plant extracts and constitutes some 40% of those extracts. It should be mentioned that the terms hemp oil and CBD (cannabidiol) are sometimes but incorrectly used interchangeably, as will be seen below. Likewise, and also misleadingly, it is not uncommon to see references to the hemp plant, *Cannabis sativa L.*, as the *cannabis* plant. Hemp seed oil, commonly referred to as hemp oil, is obtained by cold-pressing hemp seeds and is often used unrefined but, as stated, usually contains very low levels of psychoactive compounds.

Varieties of hemp plant that are cultivated specifically to contain higher levels of CBD will inevitably have elevated THC contents, i.e. they are not considered to be hemp and exceed the USDA mandated limits on THC content necessary to conform with the Controlled Substances Act of the United States.

CBD oil

Cannabidiol (CBD) is usually extracted from the whole hemp plant. Typically, the plant is allowed to dry naturally or is dried by heat, ground up and extracted using either supercritical CO_2 or hydrocarbon solvents (butane, pentane, hexane, ethanol, etc.). If the flowers or the extracts are distilled, then CBDA and THCA will undergo decarboxylation, losing the extra carboxyl group to form THC. This is why CBD, unlike essential oils, is not distilled from its plant source, thereby minimizing and/or preventing formation of THC.

Refluxing CBD with a solvent such as toluene or heptane together with an acid, typically *p*-toluenesulfonic acid or other acid that can function as a catalyst, will convert it into Delta-8-THC together with small amounts of the isomers Delta-9-tetrahydrocannabinol and Delta-10-tetrahydrocanabinol and the additional by-product olivetol [3]. The latter is a precursor of THC although it apparently inhibits cannabis intoxication [3]. Although the Delta-8 and Delta-10 tetrahydrocannabinols are psychoactive, they are apparently less "potent" than THC and, apparently, are not regulated in many states of the U.S.A. It should be mentioned that whereas tetrahydrocannabinolic acid (THCA), the biosynthesis precursor of THC, is known to possess anti-inflammatory and neuroprotective effects, it is not psychoactive.

Commercially, CBD tends to be purer and subject to controlled manufacturing standards when intended for healthcare or personal use products and although having no psychoactive properties, it is sometimes, and confusingly, referred to as "*Medical Marijuana".* This term is also used for marijuana when prescribed (or not) for various conditions such as multiple sclerosis, chronic pain, recovery from chemotherapy, etc.

However, CBD is known to exert metabolic effects and its bioactive properties include soothing/calming and anti-inflammatory effects. In fact, both topical application and ingestion of CBD has now grown into one of the fastest growing modern health and wellness trends, and CBD is the active ingredient in a wide variety of tinctures, oils, creams, cosmetics and dietary supplements.

Although current FDA guidelines indicate that CBD may not be used in food or dietary supplements, topical products and cosmetics are compliant with regulations. However, the FDA has approved a CBD-based medication, Epidiolex®, for the treatment of two forms of severe childhood epilepsy, namely Dravet syndrome and Lennox-Gastaut syndrome [4]. A mouth spray containing THC and CBD, nabiximols (Sativex®), has been approved in the U.K., Canada, and several European countries as a treatment for alleviating neuropathic pain, spasticity[2], overactive bladder and other symptoms of multiple sclerosis. With regard to the efficacy and safety of Sativex® (nabiximols) for treating spasticity in people with multiple sclerosis, research work, notably a meta-analysis, a double-blind, placebo-controlled study

[1]Cannabinoids are a group of chemicals found in cannabis. The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis.

[2]Spasticity is abnormal muscle tightness due to prolonged muscle contraction. It is associated with damage to the brain, spinal cord or motor nerves, and is seen in individuals with neurological conditions, such as cerebral palsy, multiple sclerosis, stroke (cerebral hemorrhage) and traumatic brain or spinal cord injury

and other studies, indicated that the drug is well tolerated and does reduce spasticity [5]. These neurological benefits have been ascribed to the unique interactions of CBD and THC with the endocannabinoid system (ECS) [6], a subject discussed later in this review. Despite the association between CBD and THC, there is no evidence of addiction associated with CBD and even the World Health Organization (WHO) has issued a report that CBD does not appear to have the potential for abuse or cause harm.

Finally, manufacturers of cannabidiol products expend efforts to ensure that their products have CBD contents within certain limits. Nevertheless, the scientific literature indicates that there can be marked variations between the claimed and actual CBD contents of various products [7], especially in a variety of merchandise available online, many of which are obtained from questionable sources.

Medicinal benefits of CBD

The medicinal properties of THC have been recognized for centuries, and THC has been used by many civilizations to treat joint pain and muscle spasms as well as for conditions such as gout and malaria [8-10]. In contrast, cannabidiol is a relative newcomer on the health and wellness scene and research studies are ongoing to determine the full medicinal benefits of CBD as well as test for potential side-effects.

Blogs, CBD web-sites and a host of commercial sources of CBD oils and products not only extol the virtues of CBD but also make some extraordinary, and often unconfirmed, claims for its health benefits. The purported health benefits of CBD are indicated in table 1.

Pain relief
Reduced anxiety and depression
Neuroprotective Properties
Anti-inflammatory
Potential cardiac benefits
Dermatological applications
Skin treatments
Diabetes treatment and control
Menstrual cramps alleviation
Reduced spasticity with neurological conditions
Potential antipsychotic effects
Potential substance abuse treatment
Potential alleviation of cancer-related symptoms
Potential anti-tumor effects

Table 1: *Purported health benefits of cannabidiol (CBD).*

Many of these health benefits have not been validated by clinical research studies and, for example, the FDA has issued warnings against various CBD products that promise unrealistic results, including claims that it can cure cancer.

Confounding and confusing the issue with such health claims is that there are wide variations between the claimed and actual CBD contents of various extracts and CBD-containing products, especially those available online. Further, there is a paucity of data on what the optimum CBD content should be in the commercial creams and oils advocated for a variety of health/medical conditions.

Another consideration, as previously stated, is that the variety of commercially-available CBD products are unregulated, so potential users are not always aware of the purity of the oils and creams that they are using. It follows from this that CBD users should be cautious regarding what they are using and confine their purchases and use to products and oils to those obtained from trusted and reliable sources. There also is concern that the myriad of CBD products on the market have not been evaluated by the FDA, were not determined to be safe, or that their use "cannot hurt". Aside from the one prescription drug approved to treat two rare and severe pediatric epilepsy disorders, no other CBD products have been evaluated or approved by the FDA. Further, the agency recently issued a statement updating the public on concerns about potential harm from CBD products. These concerns include potential liver injury, interactions with other drugs and male reproductive toxicity, as well as side effects such as drowsiness. In particular, other than the approved prescription drugs, little is known about the potential effects of sustained and/or cumulative use of CBD, co-administration with other medicines, or the risks to vulnerable populations like children, pregnant and lactating women, the elderly, unborn children and certain animal populations. In other words, the FDA concluded that unapproved CBD products may not be safe for use, and they encourage Americans to consult with their health care providers before using CBD products.

The other problem with using CBD products is that little validated clinical data are available on their health benefits and, for example, pediatricians appear to actively discourage their use with children [11]. In fact, the available information in the literature does not wholly support the popular use of CBD for chronic pain, depression, anxiety disorder, insomnia, and inflammation or for treating Parkinson's disease, schizophrenia, cancer palliation and treatment, and spasticity. In other words, science and clinical studies do not, as yet, support the largely anecdotal health claims made for CBD. Nevertheless, for completeness, these various claims will be briefly reviewed here.

Pain relief

Numerous CBD-containing creams are now available for topical treatment of arthritis, muscle, joint and neuropathic pain but, as indicated above, the actual content of CBD of these products may be questionable. Further, there is limited clinical data supporting the various pain-relieving claims, in part because, historically, greater attention has been paid to the psychoactive component of the cannabis plant, Δ^9-tetrahydrocannabinol (THC) [12,13]. Consequently, there have been fewer scientific studies on the medical use of cannabidiol (CBD) as a single component of pain medications.

A recent but very limited study reported on two patients treated with transdermal CBD cream for the symptomatic relief of a lumbar compression fracture and to mitigate thoracic discomfort and dysesthesia[3] secondary to a surgically resected meningioma [14]. It was found that topical CBD application provided significant symptom and pain relief, appearing to have anti-nociceptive[4] and anti-inflammatory effects on patients with neuropathic and radicular pain. This finding that CBD may offer effective treatment of acute and chronic pain supports earlier preclinical and clinical studies that suggested cannabis extracts and synthetic cannabinoids have application in treating acute or chronic pain [15]. The study also supports a more recent finding that topical CBD application has therapeutic potential for relief of arthritis pain-related behavior and inflammation in a rat model study and without evident side-effects [16].

[3]The term dysesthesia can have 3 different but related meanings: 1. an impaired sensation short of anesthesia, 2. a condition caused by lesions of the peripheral or central sensory pathways in which an unpleasant sensation is produced by ordinary stimuli; or 3. abnormal sensations that are experienced even in the absence of stimulation.

[4]Nociceptive pain is the most common type of pain, caused by potentially harmful stimuli being detected by nociceptors around the body. They will detect injury caused by bruising, skin damage, overuse or muscle damage, joint damage (e.g. arthritis or sprains), burns and fractures.

Cannabidiol (CBD) also is a popular supplement used for its ergogenic[5] benefits by high intensity-training athletes. This use may be based on various preclinical studies which suggest that its anti-inflammatory, analgesic, anxiolytic and neuroprotective properties could be useful to athletes [17]. These effects are ascribed to CBD's interactions with the ECS and other body systems, as discussed below. However, a recent clinical trial involving 13 participants evaluated the effect of topically-applied CBD cream on delayed onset muscle soreness at 24 and 48 hours after severe exercise. No significant differences were found between CBD cream-treated and placebo-treated legs, and the data suggested that the CBD cream had no effect on delayed onset muscle soreness [18]. It would seem therefore, that the literature overall provides limited support for the potential analgesic action of topically-applied CBD.

Nevertheless, it does appear that creams containing approximately equal amounts of CBD and THC are effective in providing pain relief. In one reported study, three patients suffering from pyoderma gangrenosum[6] were treated with CBD/THC creams [19]. The patients reported analgesia within 3 - 5 minutes of applying the topical treatment and that not only was there a statistically highly significant drop in pain score ratings but also a large decrease in the need for opioid medications. It was concluded that the anti-inflammatory and analgesic effects were due to an interaction between CBD and THC acting on the human endocannabinoid system (see below). Other reports indicate a combination of CBD and THC, notably the oral spray called Sativex® (nabiximols), is effective in treating pain related to multiple sclerosis and arthritis [20]. Another systematic literature review also suggested that CBD and THC might be effective for chronic pain treatment for neuropathic pain patients although this conclusion was admittedly based on limited evidence [21].

The role of CBD in pain management is clearly a complex issue and there are numerous, usually anecdotal, reports that consumers have claimed complete independence from analgesics with prolonged use of CBD. It appears that these promising analgesic effects as well as the causes of pain may be directly correlated with the endocannabinoid system [22]. In particular, CBD may help reduce chronic pain by impacting endocannabinoid receptor activity, thereby reducing inflammation and interacting with certain neurotransmitters.

Dermatology and skin care

There is a growing awareness that CBD may be effective in dermatology and skin care but much of the scientific data come from preclinical studies with few reported high-quality clinical trials evaluating these effects. Nevertheless, there are increasing numbers of studies devoted to the therapeutic potential of CBD and cannabinoids against different skin diseases [23]. An overview of the dermatological applications of CBD are indicated in table 2, and a few of these purported benefits are discussed here.

Anti-aging
Anti-allergenic
Anti-bacterial
Anti-inflammatory
Anti-oxidant
Anti-pruritic
Hydrating and moisturizing
Scar resolution
Topical analgesia
Treatment for acne, eczema and psoriasis
Wrinkle-reducing

Table 2: *Purported skin care benefits of CBD.*

[5]Ergogenic is the term for a performance-enhancing substance, also known as a performance-enhancing drug (PED).

[6]Pyoderma gangrenosum (PG) is a rare inflammatory skin disorder that causes large, and very painful ulcers to develop on the skin, commonly on the legs. The exact cause of PG is unknown, but it appears to be a disorder of the immune system.

Anti-aging

The antioxidant activity of topically-applied CBD-containing creams etc. in protecting the skin and possibly ameliorating the ravages of oxidative stress, suggests that these emollients may have an "anti-aging" effect. If the claims that CBD has anti-inflammatory, analgesic, hydrating, moisturizing and wrinkle-reducing properties as well as being able to treat skin aging, acne, eczema, psoriasis and pruritus are accurate or can be validated, then topical CBD would certainly appear to be an "anti-aging" agent.

Anti-acne treatment

Acne is one of the most common chronic skin disorders**,** caused by *Propionibacterium acnes* infection and subsequent inflammation of the hair follicles and oil-producing (sebaceous) glands of the skin. Commonly, development of acne is characterized by the overproduction of sebum.

Research studies indicate that CBD helps control the overproduction of lipids (including sebum) in skin cells [24] as well as showing some potential as an antibacterial agent [25]. These findings suggest that CBD may be effective in preventing acne as well as reducing bacterial proliferation, and consequent irritation, around hair follicles.

Research studies indicate that topically-applied CBD does activate the endocannabinoid system, the latter being central to homeostasis of the skin and is involved in, and regulates, the production of new keratinocytes[7] [26]. Once activated, the ECS could provide therapeutic support for a range of skin conditions such as inflammation, redness and psoriasis as well as offering protection from environmental assaults and oxidative stress [27]. Since the body must maintain its ability to grow new dermal cells (keratinocytes) while discarding the old ones, efficient functioning of the ECS is necessary for the skin to maintain a "radiant" and well-moisturized appearance, and CBD appears to facilitate activation of the dermal endocannabinoid system.

Neurology

The scientific literature and various anecdotal reports indicate that CBD, often in conjunction with Δ^9-tetrahydrocannabinol (THC), possesses numerous therapeutic benefits in neurology, including anxiolytic, antidepressant, neuroprotective, anti-inflammatory and immunomodulatory properties [6,28]. However, most of the literature on the neurological benefits of CBD is not based on human studies, although there are a few major exceptions.

In addition to the treatment of Dravet and Lennox-Gastaut syndromes with the CBD-based medication, Epidiolex®**,** it has been suggested [6] that CBD has been successful as an adjunctive treatment for malignant brain tumors, Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS) and neuropathic pain.

It should be mentioned that there is some evidence for the use of CBD in treating anxiety disorders. There are, for example, limited studies using patients in simulated public-speaking tests that provided some support for the successful application of CBD in treating social anxiety disorders and social phobias [29]. Likewise, CBD is often used in the alleviation of insomnia, often in combination with melatonin but little data exist regarding its effectiveness although at least one study has been reported [30]. In this study, the effectiveness

[7]Keratinocytes are the primary cell type of cell in the outermost layer of the skin or epidermis, constituting some 90% of epidermal skin cells.

of CBD was compared with placebo for insomnia in 15 patients and it was found that 160 mg of CBD improved sleep duration without concomitant next-day sedation. Support for CBD's potential applicability in insomnia also comes from the comment that patients taking Epidiolex® in clinical trials experienced somnolence and others have noted that somnolence is an adverse effect associated with CBD [31].

Another interesting study involving an experimental model of autoimmune encephalomyelitis (EAE)[8] in mice showed that topical administration of a 1% CBD-cream, given at the time of symptomatic disease onset and then daily, exerted neuroprotective effects against EAE [32]. In particular, the treatment regimen affected progression of the EAE, diminished clinical disease scores, assisted in recovery of paralysis of hind limbs and ameliorated histological indications typical of the disease in spinal cord tissues. It was concluded that CBD could be introduced into the clinical management of MS and its associated symptoms, at least in association with current conventional therapy [32].

Other neurologically-important effects of CBD include inhibition of calcium ion (Ca^{2+}) transport across membranes and reduced anandamide[9] uptake, as well as increasing brain adenosine levels by reducing adenosine[10] reuptake [33]. The latter effect is associated with neuroprotection and lowered inflammation following brain trauma [34]. Interestingly, the inability of CBD to produce a "high" may possibly be because it interacts with anandamide rather than binding directly to cannabinoid receptors.

Regarding brain trauma, it has also been noted that CBD exerts vascular effects, notably vasodilation and hypotension, suggesting that cannabinoids like CBD may provide protection against cerebrovascular damage following a stroke.

The various neurological therapeutic benefits of CBD have been ascribed to the unique interactions of CBD (and THC) with the endocannabinoid system (ECS) and influencing endogenous cannabinoids [6]. Other workers indicate that these benefits are due to the ability of CBD to decrease the production of inflammatory cytokines, assist microglial[11] cells to return to a ramified or "resting" state, preserve cerebral circulation during ischemic events, and reduce vascular changes and neuroinflammation [35].

The potential application of CBD in treating Alzheimer's disease may possibly be due to its ability to prevent glutamate-induced excitotoxicity[12], reduce pro-inflammatory cytokines[13] and also its reactive oxygen species (ROS) scavenging capability. Further research in this area is clearly imperative.

[8]Autoimmune encephalomyelitis (EAE) in mice is the one of the most used models for studies of multiple sclerosis (MS).

[9]Anandamide is a fatty acid neurotransmitter or endocannabinoid produced in the brain. It binds to CB1 and CB2 cannabinoid receptors in the endocannabinoid system (ECS) and is involved in a variety of physiological processes.

[10]Adenosine is a naturally occurring nucleoside that is formed through the breakdown of adenosine triphosphate (ATP), the primary energy source in cells for transport systems and many enzymes.

[11]Microglial cells are a specialized macrophages that are found in the central nervous system (CNS). They are important for maintaining the health of the CNS, remove damaged neurons and infectious organisms. Macrophages are a type of white blood cell that surround and kill microorganisms, removes dead cells, and stimulate the action of other immune system cells.

[12]Excitotoxicity is the term for when nerve cells suffer damage or death due the levels of otherwise necessary and safe neurotransmitters such as glutamate or N-methyl-D-aspartic acid (NMDA) becoming pathologically high and causing excessive stimulation of receptors.

[13]Cytokines such as TNF-α, IL-1 β and IL-6 are important initiators of the inflammatory response.

Mechanism of action and the endocannabinoid system

The promising health benefits of CBD regarding pain treatment, dermatology and neurology as well as certain other conditions may be directly correlated with the endocannabinoid system (ECS). This is because the biochemical and physiological effects of CBD are the result of its interactions with the receptors and enzymes in the ECS.

The term endocannabinoid originates from the mid-1990s following the discovery of membrane receptors for Δ^9-tetrahydrocannabinol in humans [36] and these receptors and their endogenous ligands are now known as the endocannabinoid system. This relatively newly discovered system comprises three core components, namely endocannabinoid receptors, endocannabinoids, and enzymes.

Endocannabinoid receptors: are specific G-protein-coupled receptors that are involved in regulating such functions as sleep, appetite, pain and the response of the immune system to pathogens. There are two main endocannabinoid receptors:

- CB1 receptors are mainly found in the central nervous system and the brain, lungs, liver and kidneys.
- CB2 receptors are primarily found in the peripheral nervous system, especially immune cells and in hematopoietic cells.

Endocannabinoids (also called endogenous cannabinoids) are molecules similar to cannabinoids, but which are made within the body. Two key endocannabinoids have been identified: anandamide (AEA) and 2-arachidonoylglyerol (2-AG). These molecules are synthesized from membrane lipids in neurons after calcium ion (Ca^{++}) levels increase in the synapses between nerve cells and are produced within the body as needed. Endocannabinoids diffuse, bind to endogenous agonists and activate CB1 receptors, initiating signaling to and from the ECS. This process induces intracellular cascades which inhibit neural activity and neurotransmitter release in neurons, thereby maintaining smooth operation of internal functions. Because they produce an inhibitory effect, endocannabinoids are referred to as "retrograde neurotransmitters".

Enzymes: are responsible for de-activating the endocannabinoids anandamide (AEA) and 2-arachidonoylglyerol (2-AG) once they have performed their required function of initiating signaling to and from the ECS. The two enzymes primarily responsible for this are fatty acid amide hydrolase (FAAH), which breaks down anandamide (AEA), and monoacylglycerol acid lipase (MGL or MGAL), which typically breaks down 2-arachidonoylglyerol (2-AG.).

The ECS is ubiquitous in animal species and its cell-signaling activity is modulated by numerous factors, including diet, sleep, exercise, stress and exposure to phytocannabinoids like CBD [37]. Further, there are indications that the ECS is involved in regulating physiological and cognitive processes and, possibly, in mediating the pharmacological effects of cannabis.

Although the ECS is still not fully understood, pathological alteration of cannabinoid signaling occurs in numerous disorders (Table 3) [28].

Cancer
Cardiovascular issues
Gastrointestinal problems
Multiple Sclerosis
Neurodegenerative conditions (Parkinson's and Alzheimer's diseases)
Psychiatric disorders
Reproductive issues
Stroke (Cerebral hemorrhage)

Table 3: *Pathological conditions associated with impaired cannabinoid signaling [28].*

A review of 10 years of research on the subject led to the suggestion that low endocannabinoid levels in the body or dysfunction within the ECS, often referred to as clinical endocannabinoid deficiency (CECD), can contribute to the development of certain conditions [38]. This theory suggests that low endocannabinoid levels account for why some people develop such conditions as migraine, fibromyalgia and irritable bowel syndrome [38]. Deciding whether CBD deficiency and/or impaired cannabinoid signaling are the actual cause of, or at least contribute to, the above pathological conditions likely depend on the findings of clinical trials, but it is obvious that the ECS is of major physiological significance. It may also be involved in the development of psychosis.

The potential effectiveness of CBD in neuropsychiatric disorders has been discussed by various researchers [39]. Clinical and pre-clinical studies indicate that CBD possesses anti-epileptic, anti-oxidant, anti-inflammatory, anti-psychotic, anxiolytic and anti-depressant properties as well as, apparently, exhibiting an ability to reduce the addictive effects of some drugs of abuse. Further, whereas cannabis use is associated with an increased risk of developing psychosis, CBD appears to display antipsychotic properties based upon its interactions with the ECS.

CBD and endocannabinoid receptors

The ability of CBD (and THC) to influence anxiety and cognition as well as the body's response to pain arise through binding to cannabinoid receptors and consequently these phytocannabinoids can participate in multiple metabolic mechanisms. In fact, the "high" associated with marijuana (cannabis) results from THC being a partial agonist on the cannabinoid CB1 receptor and causing central nervous system (CNS) effects but also through having CB2 agonist activity in the immune system. Although CBD has minimal activity with CB receptors, it does affect the ECS [40]. In fact, various studies have shown that the action of CBD in reducing chronic pain and inflammation results from its interaction with, and impact on, endocannabinoid receptor activity. However, various mechanisms proposed to account for the analgesic, anti-inflammatory, anxiolytic, and anti-epileptic effects of CBD also include agonist activity at several different receptors, as noted above.

It has been suggested that CBD acts indirectly as an endogenous cannabinoid receptor agonist when exerting its neuroprotective effects but also through different signal transduction pathways mediated indirectly by cannabinoid receptors. Furthermore, CBD prevents $A\beta$[14] interacting with, and activating, the pivotal kinase GSK-3β which is thought to be responsible for the memory deficits seen in both advanced age and Alzheimer's disease.

Stimulation of the vanilloid receptor TRPV-1 receptor by CBD influences a variety of processes including body temperature, inflammation and pain perception, and is one of the reasons why CBD may be an effective remedy for neuropathic pain. This agonist activity with TRPV-1 receptors is the basis for CBD's action in reducing feelings of pain, heat and itching (pruritis) as well as localized inflammation. Studies on components of the GI system of mice indicate that cannabinoids like CBD can affect both the activity and the expression of TRPV1-4 channels, suggesting various potential therapeutic applications, including within the gastrointestinal tract [41].

CBD exerts its anti-anxiety effects through activation of adenosine receptors, the latter being important in cardiovascular function, regulation of myocardial oxygen consumption and coronary blood low. The adenosine (A2A) receptor, for example, helps regulate myocardial oxygen consumption, coronary blood flow and CNS neurotransmitters and has broad anti-inflammatory effects throughout the body. In fact, adenosine receptors are a major target of caffeine and have a significant role in the brain in that they down-regulate the release of other neurotransmitters such as dopamine and glutamate.

[14]Aβ is the main component of the extracellular amyloid plaque deposits found in the brains of patients with Alzheimer's disease.

The family of 5-HT receptors, activated by serotonin, are involved in a range of biological and neurological processes, including anxiety, addiction, appetite, sleep, pain perception, nausea and vomiting. The 5-HT1A (hydroxytryptamine) serotonin receptor is directly activated by CBD [42], thereby achieving an anti-depressant effect. The latter is the result of CBD triggering an inhibitory response that slows down 5-HT1A signaling. The CBD inhibition of neuropathic pain also operates through 5-HT1A receptors. In contrast, psychoactive/psychedelic drugs such as LSD, mescaline, "magic mushrooms" and various other "reality-altering drugs" activate a different type of 5-HT receptor to produce an excitatory response, the "hallucinogenic high".

In contrast to its agonist activity with other receptors, CBD functions as an antagonist that blocks or deactivates the GPR55 receptor, now considered to be a third cannabinoid receptor [43]. GPR55 is widely expressed in the brain, notably in the cerebellum, and is involved in modulating blood pressure and bone density. It also promotes osteoclast cell function, facilitating bone remodeling and reabsorption but overactive GPR55 receptor signaling is associated with osteoporosis. It has also been suggested that, when activated, GPR55 also promotes cancer cell proliferation [44] and has been associated with obesity, diabetes, epileptic disorders as well as inflammatory and neuropathic pain in addition to cancer. Other studies suggest that CBD also reduces the proliferation of aggressive breast cancer cells as well as their invasion and metastasis by a different molecular pathway, namely inhibiting Id-1 gene expression. Optimal results, however, appear to be achieved when CBD was administered in combination with THC.

CBD and enzymes

The endocannabinoid system has been the focus of intense scientific study for the past decade or so. These studies were not only directed at the CB1 and CB2 receptors but also on the endocannabinoid deactivating enzymes, notably fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) [45].

The FAAH enzyme is responsible for degrading the fatty acid amide family of signaling lipids**,** notably the endocannabinoid anandamide (AEA) which activates the CB1 receptor. It follows from this that by degrading AEA and activating CB1, FAAH is one of the factors responsible for THC achieving its psychoactive effects. FAAH also appears to be involved in pain and nervous system disorders. Interestingly, CBD is reported to bind to fatty acid-binding proteins (FABPs) and reduce endocannabinoid metabolization, indirectly inhibiting FAAH activity and preventing metabolization of anandamide (AEA). In suppressing the functioning of the FAAH enzyme, CBD helps stimulate endogenous cannabinoid signaling and enhances the body's innate protective endocannabinoid response. As a result, CBD strongly diminishes the action of THC at the CB1 receptor, muting its psychoactive effects. This is the reason why the clinical use of combinations of THC and CBD does not evince neurological effects. CBD also stimulates the release of 2-AG, a major endogenous cannabinoid compound that activates both CB1 and CB2 receptors.

Monoacylglycerol lipase (MGL) enzyme is a hydrolase involved in endocannabinoid and triglyceride hydrolysis and is the primary enzyme responsible for the metabolization of 2-arachidonylglycerol (2-AG) in the brain as well as being involved in lipid signaling. Whereas degradation of AEA is facilitated mainly by fatty acid amide hydrolase (FAAH), 2-AG is degraded mostly by MGL. MGL in astrocytes[15] is an important regulator of 2-AG levels, neuroinflammation and arachidonic acid (AA) availability. Since the levels of fatty acids such as AA in the brain correlate with serotonin transport and the severity of depression, inhibition of MGL by CBD may account for its anti-depressive effects.

[15]Astrocytes are star-shaped glial (non-neuronal) cells in the brain and spinal cord that perform many functions, including biochemical support of endothelial cells that form the blood–brain barrier, provide nutrients to the nervous tissue, maintain extracellular ion balance and regulate cerebral blood flow. They also have a role in the repair and scarring process of the brain and spinal cord following infection and traumatic injuries.

Safety of CBD

There is a paucity of information on the long-term effects of sustained and/or cumulative use of CBD or the potential risks to vulnerable populations. Likewise, minimal information is available on possible interactions between CBD and hormones. The reason for concern regarding the ingestion of CBD is because it is metabolized in the body first through the stomach and then through the liver before being distributed throughout the body. This is the same pathway followed by most pharmaceutical drugs as well as opioids and ingested THC. As a result, CBD may either increase or decrease the potency of many drugs, including common analgesics, even causing adverse reactions. Other interactions could include affecting the half-life of pharmaceuticals in the body and it is unknown whether CBD might influence the metabolization of drugs within the body. On the other hand, it is also possible that while CBD may not affect the potency of pharmaceutical drugs, it could potentially counteract some of the side effects of these medications, notably those administered in the control of nausea, sleeplessness and pruritis, and consequently be beneficial.

Data from both animal and human studies have shown that CBD absorption depends on the product formulation and, overall, orally administered CBD is poorly absorbed, having a bioavailability of only 13% - 19% [46]. This low bioavailability is due to the first-pass metabolization of CBD on passage through the liver although there is ongoing research to develop alternative formulations that may increase CBD's oral bioavailability.

In contrast, when inhaled, the average bioavailability of CBD is about 31% and, depending upon the type of inhaler, can be much higher. At this time, based on animal studies, transdermal CBD absorption is variable and is not yet fully elucidated in humans or in animals [47].

Absorption of CBD may also be altered by food intake and, for example, when Epidiolex® is administered with a high-fat, high-calorie meal, plasma levels of CBD increased four to fivefold compared with administration on an empty stomach.

At this time, the optimal administration of CBD is unknown and, unfortunately, nor is there sufficient information available on where, how and for what conditions it should or can be used. No doubt the FDA or other regulatory bodies will eventually step in to ensure that the proper levels of purity and cannabidiol content are maintained in all CBD products. Until such time as adequate regulations are in place, caution should be exercised by all consumers.

Conclusion

Although CBD-based products appear to have burst suddenly upon the home health care markets in the past few years, in fact extensive research studies have been undertaken on CBD and other cannabinoids since the turn of the 21st Century. It is also somewhat ironic that all the research and clinical studies on what appears to be a major health care advance apparently stem from investigations of the hallucinogenic activity of what was once an illegal drug, namely THC (delta-9-tetrahydrocannabinol). The popularity and widespread use of THC is evident from the 550 existing nicknames for cannabis, including marijuana, weed, 420, Ace, Kush, MJ and airplane, and many, many more. Now, it appears that the use of CBD as well as the cannabis isomers, delta-8 and delta-10-tetarhydrocannbinols, may be subject to a comparable growth. Although in the case of CBD, the escalating use will be for medicinal purposes.

This review clearly indicates the scope and complexity of CBD and its associated health benefits, and there is a rapidly growing scientific literature on almost every imaginable aspect of cannabidiol. Despite the extraordinary number of apocryphal, anecdotal and some often-downright impossible claims associated with CBD, it is increasingly obvious, and now scientifically validated, that many of these health benefits are extraordinary. Whereas it is true that there have been far too few high-quality controlled clinical trials on CBD, that situation is slowly changing, and CBD may eventually become as a great a boon to mankind as have other plant derived formulations and essential oils for millennia.

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