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A Desktop Primer and Practical Review of Cannabis-Containing Compounds and Their Entourage Effects

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Abstract

Cannabis sativa is one of the first domesticated plants known to humankind for its numerous psychological, physical, and emotional benefits. Its first use was reported in 2600 BCE in Chinese Pharmacopoeias. Cannabis subspecies hemp and marijuana are widely studied extracts. It is a complex plant with specific constituents acting synergistically. The discovery of the plant's numerous compounds led to another discovery—that of the endocannabinoid system (ECS), which is widely distributed in the human brain and body. The ECS is responsible for various physiological and psychological effects. However, an increase in epidemiological studies is associated with dose-increasing psychotic disorders, raising significant concern among researchers and physicians. Research began on hundreds of cannabinoids contained in the cannabis plant, leading to the detection of CB1 and CB2 receptors—following the characterization of the ECS in the human body. Specific chemicals express synergistic effects, known particularly as "entourage effects". The concerted effect of chemical constituents of cannabis enhance the overall pharmacological properties of the plant. This entourage effect has been supported by various studies. However, a few studies debunk the construct of cannabis' entourage effects. Recent changes in the US FDA Legalization and Scheduled Drug Act are facilitating research on the cannabis plant and compounds to explore therapeutic potential.

Keywords: *Cannabidiol; Cannabinol; GABA; Phytocannabinoids; Sativa; Sleep Disorder; Terpenes; Tetrahydrocannabinol*

Abbreviations

2-AG: 2-Arachidonoylglycerol; cAMP: Cyclic Adenosine Monophosphate; CBC: Cannabichromene; CBD: Cannabidiol; CBE: Cannabielsoin; CBG: Cannabigerol; CBL: Cannabicyclol; CBND: Cannabidiol; CBT: Cannabitriol; GABA: Gamma-Aminobutyric Acid; GPCR: G-Protein Cou-

pled Receptors; IBD: Inflammatory Bowel Disease; MAPK: Mitogen-Activated Protein Kinase; QoL: Quality of LIfe; RCT: Randomized Controlled Trial; THC: Tetrahydrocannabinol

Introduction

Cannabis sativa is the oldest human-cultivated plant that is widely present around the world [1]. Archaeobotanical investigations traced the evidence of cannabis remains to 800 BCE. Cannabis was reported to be a source of fiber, food, and seed oil. Historical evidence also shows that human ancestors ingested or inhaled cannabis for its euphoriant properties [2,3]. Cultivation transitioned to being a commissary project approximately 12,000 years ago after the culmination of the glacial period, which led to an evolutionary symbiotic relationship between humankind and plant propagation that assisted in colonization [4].

The book *Ebers Papyrus*, written in Egypt in 1500 BCE, mentions the topical application of cannabis for treating of inflammation. The mention of cannabis first appeared in Asian countries in the Indian Vedas, referring to cannabis as a religious and divine agent. It has been used in Ayurvedic medicine for thousands of years to treat pain, nausea, anxiety, sleep disorders, and induce euphoria. The classic *Odyssey—a book* written in the seventh or eighth century mentions using cannabis with wine to provide relief from pain and strife [4].

Cannabis came to the attention of Western medicine in the 1890s when Russel Reynolds summarized the years of investigation in *The Lancet* [5]. In the nineteenth and twentieth centuries, it was reported to be used by females for dysmenorrhea. Cannabis became a globally popular recreational drug throughout the 1900s, considered the golden era of cannabis consumption [4]. However, in 1961, cannabis was listed as a controlled drug by the United Nations' Single Convention on Narcotic Drugs, making its use illegal in most countries [6]. It was also designated as a Schedule I drug in the USA, prohibiting all possible research on the drug molecule [4].

Discussion

Cannabis is a generic term mainly used for the drugs extracted or prepared from the genus *cannabis* [7]. The cannabis plant contains more than 400 botanical compounds. The term medical cannabis is used when cannabis and its related compounds—such as cannabinoids—are applied in the treatment of disease or to alleviate particular symptoms. Cannabis constituents have various modes of administration, such as topical, sublingual, and oral. Also, specific plant parts can be smoked, inhaled, or mixed with food or tea. Extracts can be manufactured synthetically, in addition to the isolation of naturally occurring compounds from cannabis itself [8].

Cannabinol was the first compound extracted from the plant—reported in 1899—and was considered responsible for the psychoactive effects [9]. This assumption was reconfirmed in 2000 [10]. Cannabidiol (CBD) was the second compound to be isolated—noted in 1963 by Mechoulam and Shvo [11]. In 1964, tetrahydrocannabinol (THC) was isolated and labeled the main component responsible for the psychoactive effect of the cannabis plant [12]. Both CBD and THC have the same chemical scaffold with 21 carbon atoms, 30 hydrogen atoms, and two oxygen atoms; however, there is a difference in the rearrangement of these atoms. THC has a tricyclic structure, whereas CBD has a bicyclic structure [13]. The graphic structure below represents CBD and THC with a cyclic ring and a hydroxyl group (Figure 1). Thus, the cannabis plant contains major cannabinoids, such as intoxicating THC and non-intoxicating CBD, along with more than 100 other trace cannabinoids, collectively known as phytocannabinoids [9].

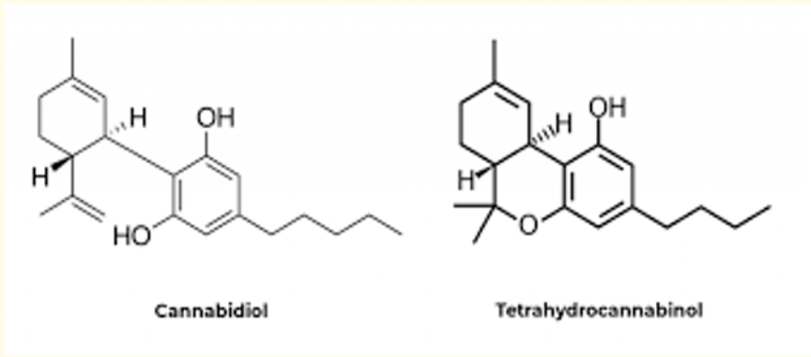

Figure 1: *Chemical structure of CBD and THC.*

The plant contains terpenes, called terpenoids, such as limonene, myrcene, linalool, and beta-caryophyllene. In addition, vitamins, minerals, fibers, proteins, flavonoids, omega fatty acids, phenols, and chlorophyll are present in the plant [14].

Cannabis is a complex dioecious plant, with and female flower parts occurring in separate plants [15]. It has numerous properties and functions—and each individual reacts differently—making it a complicated plant to investigate [15,16]. CBD and THC are two phytocannabinoids that have been extensively studied for their medicinal properties in pain relief, anxiety, and inflammation-related issues. CBD has also been widely used for sleep benefits, seizure reduction, and autism treatment.

Other plant chemicals identified in cannabis are flavonoids, terpenes, and alkaloids.These compounds are non-phytocannabinoids; however, they have been identified as having therapeutic potential. In addition to anti-inflammatory and antioxidant effects, flavonoids are responsible for the pigmentation of the cannabis plant [16]. Terpenes (terpenoids) make up the majority of phytochemicals and are responsible for the odor and flavor of the different strains of cannabis plants [17].

Ben-Shabat S., et al. (1998) proposed the entourage effect for the first time while studying the 2-arachidonoylglycerol (2-AG) molecule that binds to CB1 and CB2 cannabinoid receptors. Two other compounds, 2-linoleoylglycerol and 2-palmitoylglycerol, were also found to improve the binding ability of 2-AG to receptors [18,19].

The cannabis-producing, enhanced, combined effect of these phytochemical compounds is termed the entourage effect [3]. The percentage of this synergistic effect increases when the entire spectrum of cannabinoids, terpenes, and all other naturally-occurring botanical compounds in cannabis act together upon ingestion-known as the full spectrum entourage effect.

A full spectrum contains CBD and a small amount of all other constituents, including THC, whereas the broad spectrum contains CBD and other constituents except THC. The CBD isolate is the pure form and does not contain any other constituents of the cannabis plant. Clinical benefits were observed historically with full-spectrum and broad-spectrum CBD [20].

THC is a psychoactive metabolite in the cannabis strain of *Sativa*, whereas the nonpsychoactive metabolite is CBD. Therapeutic purposes include the treatment of spasms, pain, insomnia, and depression. Legalization has made researchers, physicians, and the public more aware of the beneficial and adverse effects of both short- and long-term use.

Few studies have identified any significant adverse effects when the compound is dosed properly. However, poor judgement, paranoia, and impaired motor coordination can occur with excessive consumption. In some instances, addiction or long-term or heavy use of the drug can lead to cognitive impairment, altered brain functioning, and an increased schizophrenia risk [21].

In addition to CBD and THC, several other compounds benefit the human body. Cannabigerol (CBG) is a CB1 and CB2 receptor agonist, acting alternatively as a gamma-aminobutyric acid (GABA) receptor reuptake inhibitor. CBG is not known to cause any intoxicating effects—and is helpful in treating several conditions, such as gastrointestinal disorder, pain, and inflammation.

Cannabinol (CBN) is a product of the chemical conversion of CBD. CBN is structurally similar to THC; however, it lacks psychoactive properties. CBN helps treat bacterial infections, sleep disorders, and eating disorders.

Cannabichromene (CBC) is a relatively new development in cannabis compound research that has significant potential as a medical supplement. Some of the therapeutic benefits are similar to CBD; however, research on cancer benefits, neuroregeneration, and analgesics expands the horizon [22,23].

Essential oils from terpenes or terpenoids are extracted using a distillation procedure. There may be variations in essential oils, depending on the plant's environment and harvesting conditions [3]. D-limonene is an example of a monoterpenoid, but its role in the

activity of the cannabis entourage has not been extensively studied. On the other hand, Phytol has a diterpene structure and has been accounted for the observed relaxing effect [24].

Other phytocannabinoids are present in cannabis in less quantity and, therefore, have not been explored or studied for their pharmacological effects in therapeutic use. These less abundant constituents are cannabidiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), and cannabitriol (CBT) [23].

CBD is a THC isomer lacking any psychoactive properties, but modulates the overall effects of the plant. It improves the tolerability and safety of THC by suppressing the undesirable side effects of THC, such as intoxication, anxiety, tachycardia, and sedation—while attenuating analgesic and anticarcinogenic effects [25,26]. The effects of the most researched and consequential cannabinoids are noted in Table 1 (below).

Name	Effects
Cannabidiol (CBD)	Used to treat psychotic disorders and used as an analgesic, anxiolytic, anti-inflammatory, anticonvulsant
Tetrahydrocannabinol (THC)	Euphoric, analgesic, anti-inflammatory, anticonvulsant
Cannabinol (CBN)	Anti-inflammatory, anticonvulsant, antibiotic, sedative
Cannabigerol (CBG)	Antifungal, anti-inflammatory, analgesic
Cannabichromene (CBC)	Antifungal, anti-inflammatory, analgesic
Flavonoids	Antioxidative, anti-inflammatory
Terpenes (Terpenoids)	Aroma

Table 1: *Functions of various cannabinoids.*

The CB1 and CB2 cannabinoid receptors belong to the rho family class of G-protein coupled receptors (GPCR). Both receptors are part of the endocannabinoid signaling pathway [27]. The CB1 and CB2 signal transduction pathways involve adenylyl cyclase inhibition—decreasing cyclic adenosine monophosphate (cAMP) formation and increasing mitogen-activated protein kinases (MAPK) [26]. Research regarding the different ligand activities and differential pathway activation have led to the understanding of biased signaling via the cannabinoid receptors CB1 and CB2 [28]. The structure of the CB1 receptor includes an allosteric site that binds to CBD and an orthosteric site that binds to THC. Both sites are close to each other and form an overlapping matrix.

The presence of CBD at the allosteric site influences the binding of THC at its orthosteric site. The results of the binding analysis have shown that CBD reduces the binding affinity of THC by modulating the CB1 receptors. Furthermore, the results of the stability complex of the N-terminal of the CB1 receptor have also supported the mechanism of CBD-THC compared to THC alone [25].

Specific meta-analyses support cannabinoid use as adjuvant therapy for the treatment of chronic pain and spasticity related to cancer, due to multiple sclerosis, and paraplegia. There is evidence of improvements in nausea and vomiting caused by chemotherapy, appetite regulation in HIV infection, treatment of psychosis, mood, and sleep disorders [29,30]. Also, a topical cannabis-based medicine has been reported as a helpful adjuvant therapy to treat venous leg ulcers. These studies observed a healing trend in patients with no significant adverse reactions [31].

Furthermore, doctors have reported certain case studies for the use of cannabis as adjuvant therapy to manage pain-related symptoms in patients with inflammatory bowel disease (IBD). Both CBD and THC have been shown to alleviate intestinal pain, joint pain, diarrhea,

and nausea with an overall improvement in quality of life (QoL) in the IBD population. Several studies have focused on IBD as a target population to generate more evidence, exploring varying doses and administration modes. Nevertheless, studies have yet to describe any attempt to discontinue traditional medical therapy, and whether cannabis therapy would replace it in such a patient population [32].

THC's psychoactive effects are attributed to the activation of the CB1 cannabinoid receptor, which is abundant in brain cells. Activation of CB1 signalling pathways release receptors at the presynaptic terminal, with subsequent stimulation of CB1 receptors and inhibition of neurotransmission. However, the CB2 receptor is not highly expressed in the nervous system; instead, THC binds to the CB2 receptors predominantly found in immune cells, in the spleen, and the liver. The interaction of CBD with receptors is complex compared to THC. However, it also suppresses the inflammatory response similar to that of THC.

Instead of modulating GPCR activity, CBD acts as a partial agonist and antagonizes THC, implying that CBD may counteract the psychoactive effects of THC to some extent [14]. Compared to other cannabinoids, including THC, CBD shows a better safety profile. Both animals and humans have been reported to tolerate higher doses of CBD, up to 1500 mg/day. With increasing doses, CBD does not change any psychomotor or psychological functions, contrasting with THC [33], which may be due to the lack of direct agonist properties of CBD in cannabinoid receptors [34].

Ethan Russo (2011) supported the pioneering research of Raphael Mechoulam by deciphering the entourage effect. He reported the finding that THC is not the only pharmacological component of cannabis. He started looking at the anecdotal data of other strains of cannabis that supported the treatment of sleep disorders and pain relief [24].

According to Worth (2019), Russo suggested that essential oil compounds, such as lavender and peppermint, which can be extracted from plants, also aid in healing properties by enhancing the effect of THC [18]. CBD research was extended in a clinical trial with Sativex (nabiximols) as an experimental intervention—containing a mixture of cannabis extracts of THC and CBD. Approximately 40% of the enrolled subjects treated with Sativex reported twice the pain relief score compared to THC alone or placebo [35].

Worth (2019) cited another meta-analysis study in a patient population with treatment-resistant epilepsy, and reported that 71% of the subjects who received the extracts showed improvement in seizures compared to only 46% who received purified CBD extracts [18]. Evidence suggests that of terpenoids enhance the effect of THC while reducing psychosis and memory-related issues [36].

Other examples include the use of myrcene to improve sleep disorders with chronic pain conditions in patients with arthritis and migraine headaches [37] and the extensive use of limonene in anxiety and psychological stress [38].

The entourage effect can be considered an orchestra of all compounds in cannabis—with THC being the primary component—contributing to heightened therapeutic benefits. Although extensive research is still in the early stages, the concept of the synergistic effect of cannabis beyond the pharmacological effects of THC remains unexplained and a plausible topic of controversy [39].

An *in vitro* study of the cancer cell line model to validate the efficacy of the entourage effect found a decrease in cell viability in 3 of 6 cancer cell lines tested. The findings concluded that pure CBD shows potency in reducing viability in cancer cells, while no entourage effect was observed [40].

With recent developments in cannabis terpenoids research showing no involvement in activating CB1 or CB2 receptors or modulating signaling pathways through the THC agonist, molecular analysis and clinical trials are of utmost importance to support the supposition of an entourage effect [41].

Summary

The cannabis genome and transcriptome sequencing was completed in 2011, opening new speculation about cannabis' application in medicine [42]. However, the existing cannabis genome sequences are not fully annotated, which is required to further acquire empirical data in comprehending the genetic function in cannabis [43]. Understanding the regulation of biosynthetic pathways, especially terpenoids, has begun, and is an open field for additional research [44].

Appropriate counseling of cannabis use in patients needs to be evidence-based regarding their pharmacokinetics and pharmacodynamics, along with an understanding of individual biosynthetic pathways—and should be supported by regulations and guidelines for research. There remains much more to know about the efficacy of the constituents, the response to treatment by the patients, therapeutic dosing, appropriate and effective modes of administration, and the management and monitoring of side effects. Understanding the individual component's pathways may help in effectively combining various cannabis chemical constituents regarding an entourage effect.

In 1999, the Institute of Medicine in the United States evaluated cannabis to demystify the prospective use of medicinal cannabis in healthcare. The extraction of raw materials from the plant and their combination in different percentages to achieve any therapeutic effect is complex. However, this challenge should drive and direct researchers to create biosynthetic versions of the compounds, accelerating research and application [45].

Conclusion

Over the years, public and research interests have continually expanded regarding the potential health benefits of various extracts and strains of the cannabis plant. There are arguments in favor, based on anecdotal evidence; however, the science in support of the chemical constituents of the cannabis plant is limited. Moreover, many scientists consider the entourage effect wishful thinking.

Understanding the medicinal chemistry of hundreds of cannabis compounds is essential to determine via clinical trials. Individual randomized controlled trials are necessary to identify various constituents, and their relationship to patient characteristics and any underlying medical disease.

Future studies will also help weigh the potential benefits against any risks, especially concerning side effects, short-term or long-term.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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